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Water-loss (intracellular) dehydration assessed using urinary tests: how well do they work? Diagnostic accuracy in older people[1–3]

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ABSTRACT

Background: Water-loss dehydration (hypertonic, hyperosmotic, or intracellular dehydration) is due to insufficient fluid intake and is distinct from hypovolemia due to excess fluid losses. Water-loss dehydration is associated with poor health outcomes such as disability and mortality in older people. Urine specific gravity (USG), urine color, and urine osmolality have been widely advocated for screening for dehydration in older adults.

Objective: We assessed the diagnostic accuracy of urinary measures to screen for water-loss dehydration in older people.

Design: This was a diagnostic accuracy study of people aged ≥65 y taking part in the DRIE (Dehydration Recognition In our Elders; living in long-term care) or NU-AGE (Dietary Strategies for Healthy Ageing in Europe; living in the community) studies. The reference standard was serum osmolality, and index tests included USG, urine color, urine osmolality, urine cloudiness, additional dipstick measures, ability to provide a urine sample, and the volume of a random urine sample. Minimum useful diagnostic accuracy was set at sensitivity and specificity ≥70% or a receiver operating characteristic plot area under the curve ≥0.70.

Results: DRIE participants (women: 67%; mean age: 86 y; n = 162) had more limited cognitive and functional abilities than did NU-AGE participants (women: 64%; mean age: 70 y; n = 151). Nineteen percent of DRIE participants and 22% of NU-AGE participants were dehydrated (serum osmolality >300 mOsm/kg). Neither USG nor any other potential urinary tests were usefully diagnostic for water-loss dehydration.

Conclusions: Although USG, urine color, and urinary osmolality have been widely advocated for screening for dehydration in older adults, we show, in the largest study to date to our knowledge, that their diagnostic accuracy is too low to be useful, and these measures should not be used to indicate hydration status in older people (either alone or as part of a wider tranche of tests). There is a need to develop simple, inexpensive, and noninvasive tools for the assessment of dehydration in older people. The DRIE study was registered at www.researchregister.org.uk as 122273. The NU-AGE trial was registered at clinicialtrials.gov as NCT01754012.

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Keywords: aged, dehydration, osmolar concentration, sensitivity and specificity, specific gravity, urinalysis

INTRODUCTION

Water-loss dehydration [or hypertonic, hyperosmotic, or intracellular dehydration due to insufficient fluid intake, which is referred to as dehydration in this article and is not to be confused with volume depletion or hypovolemia (1–4) (**Text Box 1**)] is common in older people and associated with increased risks of adverse health outcomes and death. Dehydrated older people (serum osmolarity ≥300 mOsmol/L) had 40% increased risk of 8-y mortality and doubled risk of new disability over 4 y (after multivariate adjustment) compared with well-hydrated older people (5). Dehydration (as assessed by serum or plasma osmolality) is associated with longer hospital stays and higher mortality (6, 7). Nineteen percent of older people in long-term care, and 40% of older people at admission to United Kingdom hospitals, were dehydrated with serum osmolality >300 mOsm/kg (6, 8).

Water-loss dehydration results from deficient fluid intake and is characterized by raised directly measured serum osmolality. Although disputed, directly measured serum osmolality is the reference standard for water-loss dehydration in older people (1, 9, 10); serum osmolality can be measured at a single assessment, is associated with important adverse health outcomes, is used

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[3] Supplemental Figures 1 and 2 and Supplemental Tables 1–4 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Text Box 1 Key definitions

Dehydration: Also referred to as water-loss, hypertonic, hyperosmotic, or intracellular dehydration. The result of insufficient fluid intake, which leads to an elevation of directly measured serum osmolality and a drop in extracellular fluid volume. Fluid intake is insufficient to replace normal fluid losses through urine, feces, breath, and sweat. In dehydration, body fluids become more concentrated.

Osmolality: Osmotic concentration, expressed as the number of milliosmoles of solute per kilogram of water. Assessed by the degree of freezing point depression, which directly measures the concentration of effective solute.

Directly measured serum osmolality: Normal values for directly measured serum osmolality, indicating euhydration, are 275 to <295 mOsm/kg, whereas 295–300 mOsm/kg is classified as impending dehydration, and >300 mOsm/kg is classified as current dehydration.

Hypovolemia: Decreased blood or plasma volume due to excessive bleeding, loss of plasma, diarrhea, or vomiting. In hypovolemia, the quantity of body fluids decreases, and serum osmolality may remain stable or decrease slightly. Sometimes referred to as extracellular or salt-loss dehydration or volume depletion.

Urinary osmolality: Normal values for urinary osmolality vary with the concentration of urine (higher in more-concentrated urine).

Urine specific gravity: A measure of the density of urine relative to the density of water.

physiologically to trigger thirst and renal concentrating capacity, thereby increasing fluid intake and reducing losses, is not affected by failing renal function (common in older people), and directly measures amounts of effective solute in serum or plasma (3, 9, 10). Other proposed reference standards for water-loss dehydration do not work in older adults. In older adults, a sudden weight change is unhelpful because the dehydration development timescale is slow, and weight can be altered for many other reasons (11–13). In the absence of renal dysfunction, plasma blood urea nitrogen:creatinine ratio indexes hydration status relative to protein metabolism, but renal dysfunction is common in older adults (1, 14). Fluid intake can be assessed, but individual fluid needs are unclear and fluid-assessment methods are unreliable (15, 16), and physician assessments may not be reproducible (17). These characteristics make directly measured serum or plasma osmolality the clear reference standard for the assessment of hydration in older people. The US Institute of Medicine stated that "The primary indicator of hydration status is plasma or serum osmolality" (9), and other dehydration authorities concur (1, 10). Although clinicians may not be aware of the importance of directly measured serum osmolality in dehydration, they commonly rely on osmolarity equations, which estimate directly measured serum osmolality, to assess patients.

The early identification, prevention, and treatment of dehydration would likely improve the health of older people and reduce healthcare costs. Serum osmolality, although the reference standard, requires phlebotomy skills and is too invasive for day-to-day monitoring outside of the hospital (18). Urinary markers, particularly specific gravity, urinary osmolality, and color have long been described as clinical indicators of dehydration, with nursing and medical text books, reviews, guidelines and websites aimed at the public advocating their use (19–31). Urinary markers can be assessed with minimal training and expense. However, although urinary tests appear justified in younger adults (12, 32–36), evidence supporting their use in older adults has been weak (37–44). We aimed to assess the diagnostic accuracy of urinary measures in screening for water-loss dehydration in older people by using serum osmolality as the reference standard.

METHODS

Baseline (cross-sectional) data from 2 prospective cohorts were analyzed: the DRIE (Dehydration in our Elders)[6] study (www.researchregister.org.uk; 122273) and the Dietary Strategies for Healthy Ageing in Europe (NU-AGE) study (clinicialtrials.gov; NCT01754012).

The DRIE study aimed to quantify the diagnostic accuracy of clinical and physical signs of water-loss dehydration in frail older people. Its research methods and ethical procedures have been reported in full (8, 45) and are summarized in the current article. Recruitment and interviews were carried out by LH and DKB from April 2012 to August 2013.

Men and women aged ≥65 y who were living in residential care, nursing homes, specialist dementia care, or mixed homes in Norfolk and Suffolk, United Kingdom, were eligible. We worked with all care homes that agreed to participate. Within each home, we sent written information and a DRIE general meeting invitation to all residents, relatives, and staff. Residents were asked whether they would like to participate (≥24 h later), and all residents who fulfilled the inclusion criteria and wished to participate were accepted. Individuals were excluded if they had renal or heart failure, received palliative care, were unlikely to survive ≥3 mo, had a care home manager who reported that the resident did not wish to participate, or were too anxious or unwell to be approached.

Participants signed informed consent if willing to participate and able to demonstrate capacity by answering questions about the study (after discussion of the participant-information sheet). Individuals willing to take part but unable to demonstrate capacity were included when their consultees provided written declaration that the participants would have chosen to take part if they still had capacity. Interviews were only conducted when informed

[6] Abbreviations used: DRIE, Dehydration Recognition In our Elders; MMSE, Mini-Mental State Examination; NNUH, Norfolk & Norwich University Hospital NHS Trust; NU-AGE, Dietary Strategies for Healthy Ageing in Europe; ROC, receiver operating characteristic; USG, urine specific gravity.

consent or consultee agreement was documented and when participants were happy to take part at the time of interview. Participants could withdraw consent, without reasons, at any point verbally or through their behavior.

Interview times were agreed with participants (75 min from 0800 to 2000 in their residential home, usually in their own bedroom). Venepuncture was conducted by LH or DKB [both of whom completed approved training at the Norfolk & Norwich University Hospital NHS Trust (NNUH)]. During the interview, nonfasting venous blood was collected (from an antecubital vein or back of the hand) using needle and syringe after participants had rested while sitting (or occasionally lying) ≥5 min. If a sample was not obtained at the second attempt, venepuncture was abandoned and the participant excluded. Samples were transferred to BD vacutainer SST Advance tubes inverted several times, transported to the Department of Laboratory Medicine, NNUH, in a temperature-controlled box, delivered within 4 h of collection, and analyzed on arrival. The laboratory was fully accredited with Clinical Pathology Accreditation (United Kingdom) Ltd., had daily internal quality control run with calibrators, and was judged fortnightly against its peers. Directly measured serum osmolality [measured by depression of freezing point using Advance Instruments Model 2020 with a repeatability of ±3 mOsm/kg (1 SD) in the 0–400-mOsm region] was assessed in all samples.

Classification of hydration status was based on serum osmolality. Participants were categorized as normally hydrated (serum osmolality 275 to <295 mOsm/kg), having impending dehydration (295–300 mOsm/kg), or current dehydration (>300 mOsm/kg) (1, 12). Seven participants with serum osmolality <275 mOsm/kg were included in this analysis as being adequately hydrated (although they may have been overhydrated).

Participants were asked to provide a urine sample in a nonsterile container within 120 min of phlebotomy. Urinalysis was conducted with noncontaminated fresh urine. Urine measures included urine specific gravity (USG), determined by dipstick and refractometer (46); urine color; cloudiness; volume; other dipstick tests including glucose, ketones, blood, pH, protein, nitrite, and leukocytes; and reasons for lack of a sample. Training in urinary assessment was conducted within the DRIE study according to the procedures described for the equipment used. Some samples were assessed by both researchers who were blinded to each other's readings; all urinalysis was conducted while blinded to serum osmolality. Blood and urine results were shared with the resident's care home manager and general practitioner.

Serum osmolality measurement was by experienced laboratory staff blind to index test data (with access only to the participant number, birth date, and sex). Birth date, sex, comorbidities (including diabetes), height, weight history, and current medication use were obtained from home records. All diabetes diagnoses were double checked against urine and serum glucose results and medication records, but no additional participants with diabetes were identified. The Barthel Index [used to determined functional status with a scores from 0, implying very limited functional abilities, to 100, indicating functional independence (47)] was assessed using information from staff. The Mini-Mental State Examination (MMSE) (used to assess cognitive function with scores from 0 to 30 with 30 indicating normal cognition) was assessed during the participant interview (48). Weight was measured during the interview using the care home's scales or the most recent weight obtained from home records.

NU-AGE was a randomized controlled trial that aimed to assess the effects of a year's dietary intervention based on recommendations, specifically developed for the elderly, on markers of inflammation and a series of related health outcomes including cognitive function, physical ability, bone mineral density, body composition, and cardiovascular markers (3, 49, 50). The study was carried out in 5 European centers; the current analysis only includes the 271 participants recruited in Norfolk (United Kingdom) from September 2012 to July 2013.

Recruitment and selection criteria have been reported (50), and Norfolk cohort details are summarized here. Participants were aged 65–79 y; were recruited through local advertisements, publicity, and general practitioner surgeries; were free from frailty (51) and current or recent chronic diseases; were able and willing to provide informed consent; and were free living and responsible for their own shopping, cooking, meal choices, and preparation. At baseline (before the dietary intervention), all participants provided a 24-h urine collection. The final (early morning) collection of this 24-h sample was made on the morning (0730–0930) of the Norwich Clinical Research Trials Unit (CRTU) study day; participants fasted overnight but were encouraged to drink water in the morning. On arrival at the Norwich Clinical Research Trials Unit, participants were weighed and measured, had vascular health measurements (taking 30–60 min) then venepuncture (100 mL by a single venepuncture draw) after which they had breakfast before completing assessments on general health (including age, sex, and diabetes status), cognitive status (MMSE), and physical functioning (using Katz's Activities of Daily Living scale [scores ranging from 0, implying very limited functional abilities, to 6, implying a high degree of independence (52)] and the Instrumental Activities of Daily Living scale (scores ranging from 1 to 8, higher scores indicating better functional ability (53)]). Whole blood was processed immediately (using tubes with clot activator) to give serum samples that were stored at −80°C until serum osmolality assessment.

A standard 24-h urine-collection protocol was followed and included one first morning sample (1% sodium azide solution in a collection bottle). A 1-mL subsample was stored at −80°C until assessed for urine osmolality. When sufficient urine had been frozen and stored, USG by refractometer and dipstick (Multistix; Siemens) and additional dipstick measures (once the sample was fully defrosted and mixed) were assessed by LH, AA or SM, using the same techniques and equipment used in DRIE. Some samples were assessed by several raters for an interrater reliability assessment. Stored samples were too small for assessment of urine color. Serum and urinary osmolalities were assessed in the same laboratory as DRIE serum samples, using the same methods. Index tests were carried out with researchers blind to serum osmolality (reference standard) results.

Ethics approval

DRIE was approved by the United Kingdom National Research Ethics Service Committee London–East Research Ethics Committee (11/LO/1997). The NU-AGE protocol was approved by the National Research Ethics Committee–East of England (12/EE/0109). All study procedures for both studies were in

accordance with the ethical standards of the Helsinki Declaration. All NU-AGE participants gave informed consent before participating, whereas DRIE included participants who gave their own informed consent and also some who were unable to give informed consent (the process of inclusion of these participants, as previously described, was approved by our ethics committee).

Statistical analyses

Data were entered into a Microsoft Access database, cleaned, and transferred to SPSS software (version 22; IBM) and STATA software (IC 11.2; StataCorp) for analysis. All statistical analyses, including cleaning of the dataset, descriptive statistics, and assessment of diagnostic accuracy, were duplicated by different people to ensure analytic accuracy. Primary tests of interest were USG (assessed using a refractometer and dipstick in both data sets), urine color (assessed in DRIE only), urinary osmolality (assessed in NU-AGE only), and the ability to provide a urine sample (assessed in DRIE only, including inability for any reason, because of incontinence, or despite attempting to provide a sample). Other potentially useful tests were analyzed when available including additional dipstick measures (of glucose, ketones, blood, pH, protein, nitrite, and leukocytes) and volume of a single urine sample. We assessed the utility of these tests in screening for current dehydration (directly measured serum osmolality >300 mOsm/kg) and impending and current dehydration (serum osmolality ≥295 mOsm/kg). We used κ (weighted when there were ≥3 ordered categorical choices) to assess the interrater agreement.

We created receiver operating characteristic (ROC) curves for all tests and for both current and impending and current dehydration to assess the AUC (with 95% CIs). To have a reasonable diagnostic accuracy, ROC_{AUC} ≥0.70 was required. For each test, we also checked whether there was any cutoff at which sensitivity and specificity were both ≥70% and calculated the relevant positive and negative likelihood ratios. We intended to calculate positive and negative predictive values, diagnostic ORs, pretest and positive and negative posttest probabilities for potentially useful tests (ROC_{AUC} ≥0.70 or sensitivity and specificity ≥70%). Analysis and reporting of the study was in accordance with the standards for reporting of diagnostic accuracy (54).

RESULTS

Study flows

DRIE

A total of 365 residents expressed interest in taking part in DRIE of whom 160 provided informed consent. Consultees of the remaining 205 residents were asked for their agreement, which was obtained for 96 (**Figure 1**). Of these 256 residents with written consent or agreement, interviews were initiated with 232 (24 residents changed their mind, their health worsened, or they died between consent and interview), and venepuncture failed in 31, which left 201 participants with directly measured serum osmolality. Of these, 3 results were incorrect (caused by malfunction in semiautomatic sample handling), and 3 participants were later shown to have had heart failure, which left 195 participants included in this analysis of whom 162 provided urine samples. Reasons for noncollection of urine samples included inability to produce a urine specimen in an appropriate container or while researchers were on site or inability to produce a specimen uncontaminated with feces.

NU-AGE

Of 301 participants screened, 14 did not meet the inclusion criteria. Of the 287 eligible volunteers, 12 withdrew, blood samples could not be obtained for 3, and one participant was undergoing hospital tests. A total of 271 participants took part in baseline interviews and were randomly assigned. Serum osmolality was measured for 238 participants (for logistic reasons, serum osmolality was analyzed before the final 21 participants were recruited, and 12 samples appeared hemolyzed and, thus, were not analyzed). Of these, 221 had samples available for assessment of urine osmolality (urinary hydration measures were not primary NU-AGE outcomes and, thus, were measured when backup urine samples were available), and 151 had enough additional urine for USG analysis.

Participant characteristics

DRIE participants (**Table 1**) were 67% women, aged 65–105 y (mean ± SD age: 85.8 ± 7.9 y) with the full range of cognitive and functional status. BMI (in kg/m^2) ranged from 15.5 to 44.4, and 17% of participants had diagnosed diabetes. Nineteen percent had current dehydration, and a further 27% impending dehydration, which left 54% normally hydrated.

NU-AGE participants (**Table 2**) were also predominantly women (64%) and younger (aged 65–79 y; mean ± SD age: 70.1 ± 4.0 y). NU-AGE participants were more cognitively able than DRIE participants (mean ± SD MMSE score: 28.4 ± 1.5 in NU-AGE compared with 21.8 ± 5.7 in DRIE). Functionally, NU-AGE participants were also more able [Activities of Daily Living score: 4–6; median, 6.0 (the top score); Instrumental Activities of Daily Living score: 4–8; mean: 6.9] with low levels of diabetes (3%). Mean BMI was higher with fewer outliers (mean ± SD: 26.8 ± 4.0 in NU-AGE compared with 25.6 ± 5.6 in DRIE). A total of 22% of participants had current dehydration, an additional 41% had impending dehydration, and only 37% were normally hydrated. NU-AGE subgroups in whom we were able to assess the diagnostic accuracy of urinary measures were similar to the main population in age, sex, and cognitive, functional, and nutritional status, but more of those who had USG measured had current or impending dehydration than in the total cohort. No adverse events were reported in either study, although participants occasionally suffered bruising as a result of the blood draw.

CVs and interrater reliability

We sent 19 disguised, duplicate serum osmolality samples to the NNUH laboratory (from June 2014 to January 2015, duplicates were taken from the same blood draw in separate tubes with different sample numbers, dates of birth, and collection times among other samples). The laboratory quote their CV for serum osmolality analysis (at all levels) as 0.9%, whereas the mean CV for these 19 duplications was better at 0.58%.

In the 16 mo of DRIE, LH and DKB assessed 11 urinary samples in duplicate. During NU-AGE urinary analyses (which occurred over 10 h), LH and AA assessed 13 samples in duplicate.

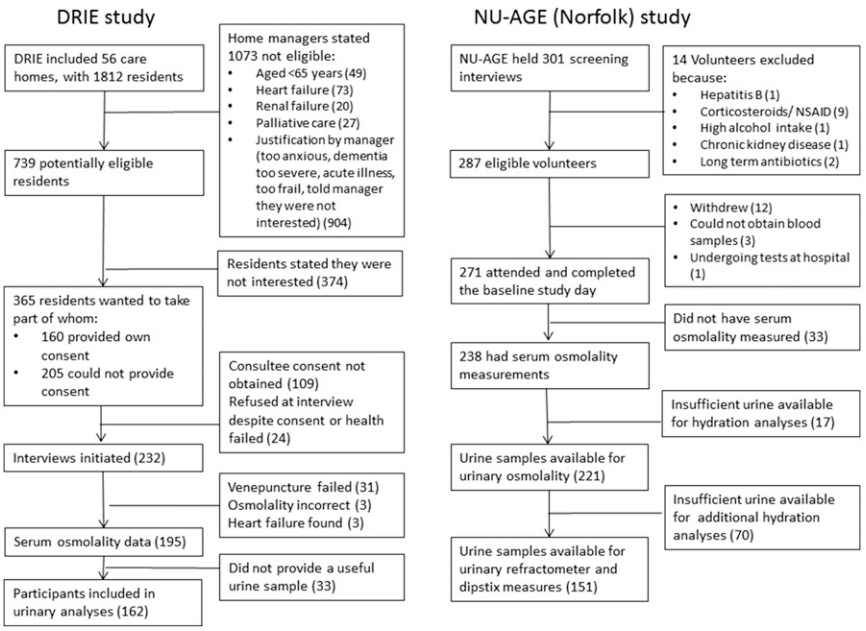

FIGURE 1 Flow charts for DRIE and NU-AGE (Norfolk cohort) studies in relation to urinary analyses (54). dis, disease; DRIE, Dehydration Recognition In our Elders; NSAID, nonsteroidal anti-inflammatory drug; NU-AGE, Dietary Strategies for Healthy Ageing in Europe study.

The interrater agreement was >0.60 (classified as substantial or almost perfect) for urine cloudiness (in DRIE), glucose, USG by dipstick and refractometer, blood, nitrite, and leukocytes (**Supplemental Table 1**). In both studies the reproducibility of the assessment of urine color, pH, and protein was low. For protein analyses, assessors showed that negative and trace readings were interchangeable, and if we assumed negative and trace readings were equivalent, we had perfect agreement.

Diagnostic accuracy of urinary tests

None of the urinary measures had an ROC_{AUC} >0.7 in diagnosis of current dehydration [>300 mOsm/kg (**Table 3**); ROC plots for USG, urine osmolality, and urine color are shown in **Figure 2**, and all urinary measures are shown in **Supplemental Figure 1**] or impending and current dehydration (≥295 mOsm/kg) (**Supplemental Table 2**, **Supplemental Figure 2**) in either data set. USG assessed by both refractometer and dipstick did have limited diagnostic utility (ROC_{AUC} statistically significantly >0.5) in diagnosing impending and current dehydration but not current dehydration as did urinary osmolality, glucose, and pH in some analyses but not in others. Urine color, the lack of provision of a urine sample (for any reason, for incontinence, or despite trying), and other dipstick tests did not appear to have any useful diagnostic characteristics for dehydration.

None of the potential tests at any cutoff and for either current dehydration or impending and current dehydration had both sensitivity and specificity ≥70% (**Supplemental Tables 3** and **4**). Because there were no potentially useful tests, we did not calculate additional diagnostic variables.

TABLE 1
Baseline characteristics of the whole DRIE cohort (all participants were living in residential care) and for participants who did and did not provide urine samples[1]

	Full DRIE population (n = 195)	DRIE participants with urine samples (n = 162)	DRIE participants without urine samples (n = 33)
Age, y	85.8 ± 7.9 (65–105)[2]	86.3 ± 7.8 (65.0–105.5)	83.4 ± 7.9 (69.4–100.5)
Women, n (%)	130 (67)	109 (67)	21 (64)
MMSE	21.8 ± 5.7 (0–30) [187][3]	22.4 ± 5.5 (0–30) [160]	18.6 ± 5.9 (7–28) [27]
Barthel Index	67.1 ± 26.4 (0–100)	70.6 ± 24.9 (5–100)	49.8 ± 26.9 (0–100)
Weight, kg	68.5 ± 17.0 (38.8–123.4)	68.0 ± 17.0 (38.8–123.4)	71.2 ± 17.5 (40.7–110.5)
BMI, kg/m^2	25.6 ± 5.6 (15.5–44.4)	25.2 ± 5.4 (15.5–44.4)	27.1 ± 6.8 (17.4–42.0)
Diabetes, n (%)	34 (17)	29 (18)	5 (15)
Directly measured serum osmolality, mOsm/kg	292.5 ± 9.3 (265–314)	292.3 ± 9.1 (266–314)	293.1 ± 10.1 (265–307)
Serum osmolality, mOsm/kg, n (%)			
<295	105 (53.8)	88 (54.3)	17 (51.5)
295–300	52 (26.7)	44 (27.2)	8 (24.2)
>300	38 (19.5)	30 (18.5)	8 (24.2)

[1]Data include all relevant participants unless otherwise noted. DRIE, Dehydration Recognition In our Elders; MMSE, Mini-Mental State Examination.
[2]Mean ± SD; range in parentheses (all such values).
[3]n values in brackets.

TABLE 2
Baseline characteristics of whole NU-AGE Norwich cohort (all participants were free living)[1]

	Full NU-AGE population (n = 271)	NU-AGE participants with serum osmolality and urine dipstick / refractometer (n = 151)	NU-AGE participants with serum and urine osmolality (n = 221)
Age, y	70.1 ± 4.0 (65–79)[2]	70.2 ± 4.0 (65–79)	70.1 ± 4.0 (65–79)
Women, n (%)	173 (64)	94 (62)	138 (62)
MMSE	28.4 ± 1.5 (17–30)	28.4 ± 1.7 (17–30)	28.4 ± 1.6 (17–30)
ADL	5.9 ± 0.2 (4–6)	6.0 ± 0.2 (4–6)	6.0 ± 0.2 (5–6)
Weight, kg	74.0 ± 13.7 (47.6–128.5)	73.1 ± 13.4 (47.6–109.1)	74.0 ± 14.0 (47.6–128.5)
BMI, kg/m^2	26.8 ± 4.0 (18.4–42.9)	26.6 ± 3.8 (19.7–42.9)	26.7 ± 4.1 (18.9–42.9)
Diabetes, n (%)	7 (3)	2 (1)	6 (3)
Directly measured serum osmolality, mOsm/kg	296.0 ± 7.0 (269–323) [238][3]	296.9 ± 7.2 (269–323)	295.4 ± 6.2 (269–311)
Serum osmolality, mOsm/kg, n (%)			
<295	88 (37.0)	43 (28.5)	83 (37.6)
295–300	97 (40.8)	70 (46.4)	96 (43.4)
>300	53 (22.3)	38 (25.2)	42 (19)

[1]Data include all relevant participants unless otherwise noted. ADL, Activities of Daily Living; MMSE, Mini-Mental State Examination; NU-AGE, Dietary Strategies for Healthy Ageing in Europe.
[2]Mean ± SD; range in parentheses (all such values).
[3]n in brackets.

DISCUSSION

In the largest study to date, to our knowledge, that assessed the diagnostic accuracy of urinary analyses as markers of dehydration in older people living in the community and long-term care, we found that urinalyses had little diagnostic value. Although USG (by refractometer or dipstick) was better than chance at diagnosing impending and current (but not current) dehydration in both DRIE and NU-AGE participants, neither USG nor any of the other potential tests had an ROC_{AUC} ≥70% or sensitivity and specificity ≥70% at any cutoff and for either current dehydration or impending and current dehydration.

Strengths and weaknesses of the study

We assessed urinary measures in 2 cohorts of older people with different characteristics and with urine collected in different ways (24-h samples taken over the day before the blood sample and frozen; and urine samples taken from 30 min before to 120 min after phlebotomy and analyzed fresh). The stability of urine samples to freezing, thaw cycles, and the speed of freezing have been studied, and urinary characteristics appeared to be stable in the handling of both DRIE and NU-AGE samples (55, 56). The reproducibility of serum osmolality, which was our reference standard, was high with an experimental CV of 0.58%. The interrater reliability was high for most urinary tests with exceptions being urinary color, pH, and protein. Protein readings were all either negative or trace, and we had already decided, as raters, that negative and trace readings could not be distinguished. Other researchers have described difficulties in duplicating the assessment of urinary color despite training and repeated checks. However, if a measure is not reproducible between 2 trained researchers in standardized conditions, it is unlikely to be useful as an assessment tool in community and long-term care settings. Urine color may be altered by medications (including senna, warfarin, amitriptyline, indomethacin, and vitamins B and C), foods (beet, blackberries, rhubarb, fava beans, carrots, and asparagus), and medical conditions, which could alter any relation between urine color and hydration status.

We used serum osmolality as the reference standard for water-loss dehydration (1, 3, 9, 10), but its use has been disputed (24), and the debate has not yet been fully resolved (57, 58). Our physiologic model (1, 3, 10, 59) is that, when humans drink too-little fluid, their extracellular fluid volume drops while the amount of solute (mainly electrolytes) remains constant, and thus, the serum solute concentration (osmolality) rises. Because osmolality must equalize through body fluids (and thus, the measurement of serum osmolality effectively measures the osmolality of all body fluids), and because most osmotically active solutes cannot easily pass across cell membranes, water flows from inside cells into extracellular fluid. This process moderates the serum osmolality rise, thereby increasing the osmolality within cells (hence, intracellular dehydration) and causes cells to shrink as water migrates. The overall effect of drinking too little fluid is a rise in the osmolality of all intracellular and extracellular body fluids and a decrease in the volumes of both intracellular fluid and extracellular fluid (12, 35). Both shrinking and concentration within cells and the reduction in extracellular volume may have health consequences.

In young, healthy humans, the rise in osmolality is corrected quickly as cellular osmoreceptors detect raised osmolality, signifying limited fluid intake, triggering both thirst and vasopressin (or antidiuretic hormone) release. Vasopressin acts locally and as a diffusible signal across neurosecretory and presympathetic neuronal populations, leading to integrated volume regulation via renal fluid conservation, which results in more-concentrated urine, darker color, raised urinary osmolality and specific gravity, and lower urine volume (60). This protective response to dehydration appears to work well in young adults (12, 32–36), but our data suggest it works less well in older adults.

In hypovolemia, the main cause of fluid shortage is increased fluid loss (e.g., due to secretory diarrhea or vomiting), and serum is depleted of both fluid and electrolytes. Because serum

TABLE 3
ROC_{AUC} for urinary measures, assessing diagnostic accuracy of assessment of current dehydration (directly measured serum osmolality >300 mOsm/kg)[1]

	DRIE data		NU-AGE data	
Test	ROC_{AUC} (95% CI)	Any cutoff with sensitivity and specificity ≥70%?	ROC_{AUC} (95% CI)	Any cutoff with sensitivity and specificity ≥70%?
USG via refractometer	0.59 (0.48–0.71)	No	0.53 (0.41–0.64)	No
USG via dipstick	0.58 (0.48–0.69)	No	0.55 (0.46–0.65)	No
Urinary osmolality	Not assessed	—	0.56 (0.46–0.66)	No
Urine color	0.51 (0.39–0.62)	No	Not assessed	—
Urine volume	0.54 (0.41–0.67)	No	Not assessed	—
Urinary cloudiness	0.47 (0.38–0.56)	No	Not assessed	—
Urinary glucose	0.59 (0.51–0.66)	No	0.51 (0.49–0.54)	No
Urinary ketones	0.51 (0.46–0.56)	No	No data	No data
Urinary blood	0.50 (0.41–0.58)	No	0.49 (0.46–0.52)	No
Urinary pH	0.61 (0.51–0.70)	No	0.58 (0.48–0.68)	No
Urinary protein	0.47 (0.36–0.58)	No	0.49 (0.40–0.59)	No
Urinary nitrite	0.46 (0.40–0.53)	No	0.51 (0.47–0.55)	No
Urinary leukocytes	0.42 (0.33–0.51)	No	0.53 (0.43–0.63)	No
No urine sample provided (any reason)	0.53 (0.45–0.60)	No	Not assessed	—
No urine sample as incontinent	0.51 (0.46–0.56)	No	Not assessed	—
No urine sample although tried	0.53 (0.48–0.57)	No	Not assessed	—

[1]No data denotes that none of the participants had a nonnegative finding. Not assessed denotes that this measure was not assessed in this cohort. USG assessed with the use of refractometer (Atago manual Master-URC/NM clinical refractometer) was calibrated from 1.000 to 1.050 in units of 0.001, read by eye, and calibrated against distilled water daily (46). USG assessed with the use of a dipstick (Siemens Multistik 8SG dipstick) was read by eye with options of 1.000, 1.005, 1.010, 1.015, 1.020, 1.025, and 1.030. Urine color (range: 1–8) was assessed with the use of color charts (Human Hydration LLC; www.hydrationcheck.com) with urine decanted into a 30-mL clear container held up in the light against a white background. Urine volume was assessed with the use of a random urine sample. Urine cloudiness was defined as clear, partially cloudy, or cloudy. The following variables were determined with the use of a dipstick (Siemens Multistik 8SG dipstick): glucose [negative or 5.5 (trace), 14, 28, 55, or ≥111 mmol/L]; ketones [negative or 0.5 (trace), 1.5, 4, 8, or ≥16 mmol/L]; blood [negative or 10 (trace), 80 (nonhemolyzed), 10 (trace), 25, 80, or 200 (hemolyzed) erythrocytes/μL]; pH (5.0, 6.0, 6.5, 7.0, 7.5, 8.0, or 8.5); protein (negative, trace, or 0.3, 1, 3, or ≥20 g/L); nitrite (negative or positive); and leukocytes [negative or 15 (trace), 70, 125, or 500 leukocytes/μL]. DRIE, Dehydration Recognition In our Elders; NU-AGE, Dietary Strategies for Healthy Ageing in Europe; ROC, receiver operating characteristic; USG, urine specific gravity.

osmolality does not alter greatly, fluid is not moved from the cells and, thus, does not compensate for the reduced serum volume, resulting in greater serum volume depletion, whereas cells are less affected. A 1-L fluid shortage would lead to ~1-L serum or plasma fluid depletion in hypovolemia or to a ~0.33-L serum or plasma fluid depletion in dehydration (the additional 0.67 L is lost from within cells) (10, 59). Although plasma volume reduction is clearly part of the pathogenesis of the effects of dehydration, measuring the reduction would not have added much value to our research. Measurement of the plasma volume reduction, instead of osmolality, would lead to confusion about whether a drop in extracellular fluid volume was due to a small excess loss (hypovolemia) or a relatively much larger fluid-intake deficit (dehydration). A mixed model of dehydration in which fluid is limited in young adults exercising in heat (sweating heavily such that electrolytes are modestly reduced, a common model for dehydration) would lead to smaller rises in serum osmolality and, thus, a greater relative volume depletion than would fluid restriction alone. However, it is doubtful that this mixed model is particularly relevant to the elderly population in whom the primary driver is inadequate fluid intake. Although this physiologic model of dehydration suggests that serum osmolality is the appropriate reference standard for water-loss dehydration, this is not completely certain. If another reference standard is shown to better diagnose insufficient drinking in older adults, the diagnostic accuracy of urinary indexes in older adults will need to be retested against this new standard.

A strength of this study is the clarity over the type of dehydration being discussed. There has often been confusion when the term dehydration is used between what the authors of this article would term dehydration (also called water loss and hypertonic or intracellular dehydration) and hypovolemia (also called salt loss, extracellular dehydration, or volume depletion) (1–4). We separated out these 2 related but distinct conditions and reported the results on dehydration but not on hypovolemia, believing that, to make progress in research on dehydration, we need to be specific. Dehydration as a result of low fluid intake in older adults is very common, is linked to poor outcomes, needs to be identified to prevent these poor outcomes, but is poorly characterized in older adults. Reduced fluid intake is common in older adults for a variety of physiologic and social reasons, but the remedy for dehydration is increased fluid intake (i.e., drinking more). Increasing fluid intake in older adults, in itself, is not simple (61) but also is not medical (although dehydration can lead to medical problems); dehydration ranks with other nutritional deficiencies. Dehydration is a common nutritional deficiency in older adults. In contrast, hypovolemia is a medical

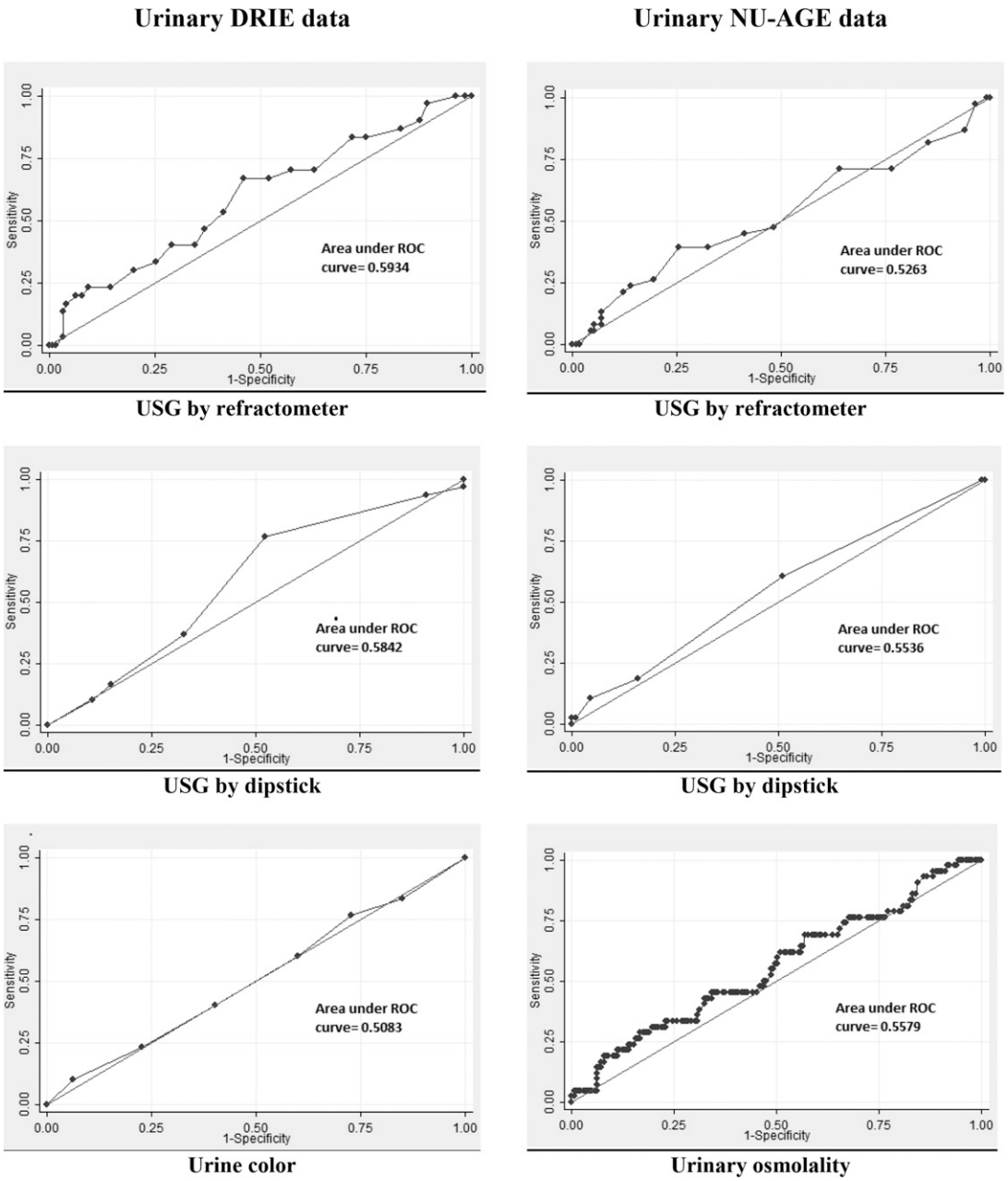

FIGURE 2 ROC plots for USG, urine osmolality, and urine color for DRIE and NU-AGE data, current dehydration (>300 mOsm/kg). Numbers of participants for each analysis were as follows: for DRIE USG assessed with the use of both a refractometer and dipstick, n = 162; for DRIE urine color, n = 162; for NU-AGE USG assessed with the use of both a refractometer and dipstick, n = 151; and for NU-AGE urine osmolality: n = 221. DRIE, Dehydration Recognition In our Elders; NU-AGE, Dietary Strategies for Healthy Ageing in Europe; ROC, receiver operating characteristic; USG, urine specific gravity.

condition that is often due to excessive loss of body fluids such as blood or diarrhea.

Strengths and weaknesses in relation to other studies and their findings

These findings are consistent with the findings from previous small studies on the utility of urinary measures in screening for dehydration. A recent systematic review assessed the diagnostic accuracy of signs and tests compared with hydration status in older people and collated published studies and data sets for the assessment of diagnostic accuracy (62). Within the review, 2 small studies (21 and 13 participants) assessed USG against serum osmolality (62–64), and urinary color was assessed in 3 small studies (17, 40, and 13 participants) (62, 64, 65) without diagnostic utility. Urine osmolality was assessed against directly measured serum osmolality in 5 small studies, and only one of these studies, in 13 healthy older people, suggested potentially useful sensitivity of 80% and specificity of 67% but with very wide CIs (64). The other studies, with sample sizes between 17 and 43 participants, did not suggest useful diagnostic utility (65–67). Similarly, urine-volume measures were not diagnostically helpful in 4 small studies (63, 65–67) of 17–43 participants. Several studies have also assessed urinary measures against

calculated serum osmolarity, which is a less-good reference standard but, again, none of the studies showed that USG (2 studies), urinary osmolality, or urinary color (one study each) was useful (38, 62, 68, 69). More recently, Fortes et al. (44) used a combined reference standard of directly measured plasma osmolality and blood urea nitrogen in 130 patients (mean age: 78 y) who were admitted to an acute hospital care ward or emergency department and showed little value of urine color or USG. The current analyses, with much larger numbers of participants and a strong reference standard, confirm and extend the findings of these small studies that urinary measures are not helpful in screening for dehydration in older people.

Meaning of the study: possible explanations and implications for clinicians and policymakers

The research that suggests that urinary tests can be used to diagnose dehydration in young, healthy populations (12, 25, 32–36, 70) is in accordance with our understanding of the physiology of the body's response to dehydration (discussed above). It may seem surprising that urinary indexes do not work well in older adults. However, both thirst and the body's ability to concentrate urine decrease with age (70), and no relation was found between serum osmolality and expressed thirst in the DRIE population (14). Effective renal blood flow has been shown to decrease from 1077 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} in 20–29-y-old men to 475 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} in 80–89-y-olds (71), whereas 60–79-y-olds had a 20% reduction in maximum urine osmolality and a 100% increase in the minimum urine flow rate compared with 20–39-y-olds (72). Because urinary tests to detect dehydration rely on normal kidney function, and ageing is associated with impaired kidney function (73, 74), it is perhaps not surprising that the ability of urinary measures to accurately reflect hydration status in older people is limited. Urine color, USG, urine osmolality, urine volume, and urinary measures such as pH, glucose, and protein should not be used to screen for dehydration, or as part of wider screens for dehydration, in older people because these measures are not sensitive or specific enough.

Unanswered questions and future research

Although we could screen older people for dehydration using blood tests [for serum or plasma osmolality or, pragmatically, using serum osmolarity equations from blood tests carried out for other reasons (75)], there is a need for simple, noninvasive dehydration-screening tests that work well in older people. Future research should investigate potentially useful index tests for dehydration as well as combinations of index tests with the aim of creating and validating a useful screening test for dehydration in older people. Better understanding of the relations between changes in fluid intake, serum osmolality, and hypovolemia in older adults and, similarly, between serum osmolality, hypovolemia, and the hormones vasopressin, angiotensin II, and aldosterone involved in fluid conservation would be helpful to address relations between dehydration and other health states in older age.

The authors' responsibilities were as follows—LH: conceived the DRIE study; LH and DKB: wrote the first draft of the manuscript; LH, DKB, AA, RG, AJ, KM, SM, ET, and LS: carried out the data collection and analysis; LH, DKB, PRH, LS, JFP, and SJF-T: developed the research; SJF-T: conceived the NU-AGE study; and all authors: were accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved, critically revised the manuscript for important intellectual content, and agreed on the final draft of the manuscript. LH was supplied with plane tickets and had hotel accommodation paid for 2 nights by the European Hydration Institute (EHI) for LH to give a talk on dehydration in older people at the European Hydration Institute's symposium at the International Congress of Nutrition, Granada, Spain, 16–18 September 2013. None of the other authors reported any conflicts of interest related to the study.

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