A randomized trial to assess the potential of different beverages to affect hydration status: development of a beverage hydration index*1

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ABSTRACT
Background: The identification of beverages that promote longer-term fluid retention and maintenance of fluid balance is of real clinical and practical benefit in situations in which free access to fluids is limited or when frequent breaks for urination are not desirable. The post-ingestion diuretic response is likely to be influenced by several beverage characteristics, including the volume ingested, energy density, electrolyte content, and the presence of diuretic agents.

Objective: This study investigated the effects of 13 different commonly consumed drinks on urine output and fluid balance when ingested in a euhydrated state, with a view to establishing a beverage hydration index (BHI), i.e., the volume of urine produced after drinking expressed relative to a standard treatment (still water) for each beverage.

Design: Each subject (n = 72, euhydrated and fasted male subjects) ingested 1 L still water or 1 of 3 other commercially available beverages over a period of 30 min. Urine output was then collected for the subsequent 4 h. The BHI was corrected for the water content of drinks and was calculated as the amount of water retained at 2 h after ingestion relative to that observed after the ingestion of still water.

Results: Total urine masses (mean ± SD) over 4 h were smaller than the still-water control (1337 ± 330 g) after an oral rehydration solution (ORS) (1038 ± 333 g, P < 0.001), full-fat milk (1052 ± 267 g, P < 0.001), and skimmed milk (1049 ± 334 g, P < 0.001). Cumulative urine output at 4 h after ingestion of cola, diet cola, hot tea, iced tea, coffee, lager, orange juice, sparkling water, and a sports drink were not different from the response to water ingestion. The mean BHI at 2 h was 1.54 ± 0.74 for the ORS, 1.50 ± 0.58 for full-fat milk, and 1.58 ± 0.60 for skimmed milk.

Conclusions: BHI may be a useful measure to identify the short-term hydration potential of different beverages when ingested in a euhydrated state. This trial was registered at www.isrctn.com as ISRCTN13014105. Am J Clin Nutr 2016;103:717–23.

Keywords: fluid balance, dehydration, rehydration, euhydration, electrolytes, macronutrients, gastric emptying, intestinal absorption, renal excretion, urine

INTRODUCTION

Water intake is episodic, whereas losses are continuous. Under normal free-living conditions, homeostatic mechanisms mean that body water balance fluctuates over the course of a normal day, but generally returns to the same point over a 24-h cycle (1). Consequently, large fluid deficits are uncommon for the majority of the population, but knowledge of beverages that can maintain hydration status over a longer period may be of interest to those who wish to stay hydrated in situations in which free access to fluid is limited or when frequent breaks for urination are not desirable (2–5). Although several studies have examined the effectiveness of beverages for postexercise rehydration (6), the protocols employed do not represent a common situation for the majority of the population. Thus identification of beverages that promote longer-term fluid retention and maintenance of fluid balance for prolonged periods under euhydrated conditions would be of real clinical and practical benefit.

Adequate daily water intake is defined in the United States by the Institute of Medicine (7) at 3.7 L for men and 3.0 L for women and in Europe by the European Food Safety Authority (8) as 2.5 L for men and 2.0 L for women. The distribution of fluids over the course of the day and their composition, however, also may be important in determining how well an individual is able to maintain an adequate hydration status. The volume and composition of ingested drinks have a strong influence on the rates at which they empty from the stomach and are absorbed in the small intestine, thus affecting their entry into the body water pool (9). Beverage components are also metabolized and excreted on different time scales (9). These various factors are likely to result in different hydration status profiles in the first few hours after ingestion of different beverages. It should therefore be possible to assign a beverage hydration index (BHI) to each drink that will define the hydration response to any particular drink, in much the same way as the glycemic index defines the blood glucose response to ingestion of foods (10). In the case of a BHI, the cumulative volume of urine passed over a fixed period of time is in effect the AUC for renal water excretion. The urine volume passed relative to a standard treatment (still water) can therefore be calculated as the BHI of a beverage.

1Supported by a grant from the European Hydration Institute.
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Received May 12, 2015. Accepted for publication November 24, 2015.
First published online December 23, 2015; doi: 10.3945/ajcn.115.114769.
Therefore, the aim of the present study was to assess fluid balance responses to the ingestion of a fixed volume of commonly consumed beverages ingested when in a euhydrated state, with a view to establishing the feasibility of a BHI. We hypothesized that drinks containing a high electrolyte content or high energy content would have greater fluid retention and thus a higher BHI than plain water. Conversely, drinks containing nutrients with known diuretic actions, such as alcohol and caffeine, may have lower BHI values.

METHODS

General study design

Three separate laboratories (Loughborough, Bangor, and Stirling) collaborated to test 72 recreationally active, healthy male subjects. Ethics approval for the study was obtained separately from the ethics committees of the 3 institutions involved.

A randomization table was generated based on each participant undertaking a maximum of 4 experimental trials, which included water plus 3 other test drinks administered in a randomized fashion, and was based on each experimental site’s assessing all available test drinks (www.randomization.com). Rehydration study data (11, 12) informed the sample size estimates and indicated a minimum sample size for each test drink of \( n = 12 \). Although not a cluster randomized trial, we factored in an additional sample size weighting to account for possible increased variance because of data collection across 3 different sites. The final sample size estimate based on 80% power with mean total difference of 220 mL, detectable at an alpha level of 0.05, required a total of \( n = 15 \) observations per drink. We therefore aimed to recruit \( n = 30 \) at each site; allowing for loss to follow-up, this ensured completion of \( n = 24 \) at each site, giving \( n = 17 \) observations on any given test drink.

Pretrial standardization/exclusion criteria

At each site, 24 healthy, physically active men between 18 and 35 y of age were recruited. For the total sample of \( n = 72 \) the mean ± SD characteristics were the following: age 24 ± 4 y, height 178 ± 6 cm, body mass 77.3 ± 9.9 kg, and water intake 2.0 ± 0.8 L/d (Table 1). Those with a history of cardiovascular, renal, musculoskeletal, or metabolic diseases, as determined from a preparticipation health screen questionnaire, were excluded. Because body mass was used as an index of euhydration, those currently undertaking an energy-restricted diet and/or exercise plan also were excluded. Participants were asked to record their diet, including their fluid intake (household measures technique), as well as any exercise performed, in a diary over the 2 d before the first trial and asked to replicate this before their subsequent visits. Participants also were asked not to perform any strenuous exercise or consume alcoholic beverages in the 24 h preceding all trials.

Experimental procedures

After an overnight fast of at least 8 h, participants emptied their bladder on waking, retaining an aliquot in a sterile collection tube. One hour before arriving at the laboratory, volunteers were instructed to consume 500 mL still water (Highland Spring) over the course of 15 min. On arrival in the laboratory, volunteers remained seated in a comfortable environment for 10 min. A single 5-mL blood sample was collected via venipuncture from an antecubital vein, and blood was dispensed into a serum tube. Participants were then asked to void their bowels and bladder before measurement of near-nude body mass (underwear only) to the nearest 50 g behind a screen. Approximately 30 min after arrival at the laboratory, participants then ingested 1 L of the assigned test drink over a period of 30 min (4 equal volumes administered 7.5 min apart). A fixed volume, rather than a volume relative to body mass, was chosen, because most drinks are served and ingested in containers of a standard volume. Participants were asked to empty their bladder at the end of the drinking period and again at the end of each hour of the study period. If a participant requested to pass urine before the hour was complete, this was collected and then added to any further urine produced at the end of the corresponding hour. After the final urine sample was collected, near-nude body mass was recorded once again.

Drinks and drink preparation

Each participant consumed still water (Highland Spring) and 3 of the following drinks in a randomized, counter-balanced order: sparkling water (Highland Spring), cola (Coca-Cola), diet cola (Diet Coke), sports drink (Powerade; Coca-Cola), oral rehydration solution (ORS) (Dioralyte; Sanoﬁ), orange juice (Tesco Everyday Value), Lager beer (Carling), hot black coffee (Nescafe Original), hot black tea (PG tips), cold black tea (PG tips), full-fat milk (3.6% fat; Tesco) or skimmed milk (0.1% fat; Tesco). The nutrient composition of the test drinks is presented in Table 2.

All cold drinks were stored at a standard refrigerated temperature (4–6°C) until serving. Tea, coffee, and ORS were prepared according to the manufacturer’s instructions and were prepared with still water (Highland Spring still water). Hot black coffee and black tea were brewed with freshly boiled still water (Highland Spring) and served at 60°C, with the temperature being maintained in a hot water bath. Cold black tea was brewed in the same manner, then stored and served at 4–6°C. The ORS was prepared and served and also served at 4–6°C. A 5-mL sample of each drink preparation was portioned into aliquots in plain tubes. All drinks were tested for osmolality, sodium, and potassium after preparation within 48 h and 5 d after collection, respectively.

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**Table 1**

Participant physical characteristics and daily water intake at each of the 3 study sites and for combined data (all sites)

<table>
<thead>
<tr>
<th></th>
<th>Bangor (n = 24)</th>
<th>Loughborough (n = 24)</th>
<th>Stirling (n = 24)</th>
<th>All sites (n = 72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>24 ± 4</td>
<td>26 ± 3</td>
<td>25 ± 5</td>
<td>25 ± 4</td>
<td>0.05</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177 ± 7</td>
<td>180 ± 6</td>
<td>179 ± 7</td>
<td>178 ± 6</td>
<td>0.48</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>76.2 ± 12.3</td>
<td>77.4 ± 7.3</td>
<td>78.3 ± 9.8</td>
<td>77.3 ± 9.9</td>
<td>0.77</td>
</tr>
<tr>
<td>Water intake, L/d</td>
<td>2.0 ± 0.9</td>
<td>2.0 ± 0.6</td>
<td>2.1 ± 0.8</td>
<td>2.0 ± 0.8</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Values are means ± SDs. P values shown were obtained from an ordinary 1-factor ANOVA.
Urine and serum analysis

All urine collected during the study was passed into a 1-L plastic container. The volume of each urine pass was determined by measuring the mass on an electronic balance (to the nearest 0.1 g), with the mass of the empty plastic container subtracted to enable the estimation of urine volume. From each urine sample, a 5-mL aliquot was dispensed into a plain screw-capped tube. This was stored at 4°C for the analysis of urine osmolality and sodium and potassium concentrations. Urine and serum osmolality was measured in duplicate with the use of the freezing-point depression method (either Gonotec Osmomat or Advanced Instruments) within 48 h of collection. Urine sodium and potassium concentrations were measured in duplicate with the use of flame photometry (Corning Flame Photometer) within 5 d of collection. Collection, handling, and storage of urine and serum were in accordance with the Human Tissues Act. Stored samples were discarded once satisfied analysis was completed.

Whole blood in the serum tube was allowed to stand for 1 h at room temperature to clot before centrifugation (10 min; 4°C for measurement of osmolality. To help ensure consistency in the data analyzed across sites, 7 independently prepared quality control solutions were also analyzed in replicates of 10 by each research group. These contained undisclosed concentrations of sodium and potassium and a measured osmolality. Two-way random-effects intraclass correlation coefficient analysis suggested good agreement between the different institutions for osmolality, sodium, and potassium analysis in which the intraclass correlation coefficients were all ≥0.999. In addition, Bland-Altman limits of agreement analysis indicated that bias between any 2 institutions was <2% for osmolality, <1% for sodium, and <2% for potassium.

Data and statistical analysis

Participant characteristics, pretrial participant preparation, and urine responses to the still water trial from each institution were initially compared by an ordinary 1-factor ANOVA. To confirm that hydration status was similar before each trial, serum and urine osmolality were compared between drinks by repeated-measures ANOVA.

The main outcome measure was cumulative urine mass after ingestion of each drink. This was also expressed as a BHI for each beverage by dividing each individual’s cumulative urine mass after still water with cumulative urine mass for each other test drink consumed. Individual hour cumulative urine mass and BHI of each drink was compared by paired t test to determine which drinks differed from still water.

To assess the practical meaning of the BHI differences observed between still water and each of the test drinks, the difference was compared with the normal variation determined from a separate repeatability analysis. For this purpose 12 participants ingested the same drink on 2 occasions. The drinks used for this repeatability analysis were the same as those used in the present study. The repeatability of the BHI was equal to a CV of 18% (~180 mL). In addition, the meaningfulness of group differences was also calculated with the use of Cohen’s d effect size (13) and 95% CI of differences between means.

Although a fixed volume of each of the test drinks was consumed, the presence of other components in some of these drinks means the water content of drinks varied from 88% to 100% (Table 2). It might therefore be argued that the BHI should be corrected for the differences in water intake. If, however, the aim was to estimate the effects of the different drinks on body water content, then the uncorrected values would be more appropriate. For clarity the data have been expressed both ways.

All other secondary outcome measures (net fluid balance, BHI corrected for water content, and cumulative urine electrolyte loss) were analyzed by paired t test.

All statistical analyses were completed with the use of a computerized statistical software package (GraphPad Prism version 6 for Windows). Statistical significance was accepted at P < 0.05. Data are presented as means ± SDs.

RESULTS

The study was conducted between February and August 2014. The study was completed when the target number of participants (n = 72) had finished the study, providing n = 17 observations on
each test drink in total across the 3 sites, with \( n = 72 \) observations on water. In total, \( n = 86 \) participants were recruited, preparticipation screening excluded \( n = 1 \) participant, and \( n = 85 \) were randomly assigned. Loss to follow-up occurred because of vomiting after ingestion of the tea (\( n = 6 \)) and ORS (\( n = 1 \)) or because of voluntary withdrawal from the study due to external factors (\( n = 6 \)).

**Institutional comparison of pretrial standardization and urine output response to a standard drink**

Before ingestion of drinks in the still-water trial, body mass, serum osmolality, and urine osmolality were not different, suggesting that participants’ preparation before trials was similar at each institution (Table 3). We also confirmed that cumulative urine mass after the still-water drink trial was similar at each institution, which further suggests that the participants in the 3 institutions had similar fluid regulation (Table 3). It was therefore deemed reasonable to combine the data from the 3 institutions for the main study.

**Predrink ingestion hydration status**

Serum osmolality (293 ± 6 mmol/kg, \( P = 0.88 \)) and urine osmolality (582 ± 265 mmol/kg, \( P = 0.56 \)) was similar immediately before drinks were ingested in each trial.

**Urine output and fluid balance**

Urine mass did not differ between trials immediately after the ingestion of the drinks (\( P > 0.19 \)). One hour after the ingestion of the drinks, cumulative urine mass was lower and net fluid balance was higher than for the still water drink after the ingestion of full-fat milk (\( P < 0.01 \)), skimmed milk (\( P < 0.01 \)), and ORS (\( P < 0.01 \)) (Figure 1). Two and three hours after drink ingestion, cumulative urine mass was lower and net fluid balance was higher than for the still water drink after the ingestion of full-fat milk (\( P < 0.01 \)), skimmed milk (\( P < 0.01 \)), ORS (\( P < 0.01 \)), and orange juice (\( P < 0.05 \)). Four hours after drinks were ingested, cumulative urine mass was lower and net fluid balance was higher for full-fat milk (\( P < 0.01 \)), skimmed milk (\( P < 0.01 \)), and ORS (\( P < 0.01 \)), but not orange juice (\( P = 0.06 \)). The effect sizes at 4 h for cumulative urine output compared with still water were 1.04 for full-fat milk, 0.85 for skimmed milk, and 1.09 for ORS (all large effects), with an effect size of 0.65 for orange juice (a medium effect). The mean differences in cumulative urine output were 294 g (95% CI: 154, 434) for full-fat milk, 339 g (95% CI: 190, 489) for skimmed milk, and 362 g (95% CI: 222, 505) for ORS.

**TABLE 3**

Institutional comparison of pretrial standardization and urine output response to a standard drink

<table>
<thead>
<tr>
<th></th>
<th>Bangor (n = 24)</th>
<th>Loughborough (n = 24)</th>
<th>Stirling (n = 24)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preingestion of still water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>76.1 ± 12.3</td>
<td>76.7 ± 7.3</td>
<td>78.2 ± 9.7</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum osmolality, mmol/kg</td>
<td>293 ± 8</td>
<td>291 ± 4</td>
<td>295 ± 3</td>
<td>0.14</td>
</tr>
<tr>
<td>Urine osmolality, mmol/kg</td>
<td>564 ± 243</td>
<td>607 ± 302</td>
<td>538 ± 176</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Postingestion of still water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine mass, g</td>
<td>1341 ± 360</td>
<td>1337 ± 352</td>
<td>1333 ± 288</td>
<td>0.99</td>
</tr>
</tbody>
</table>

1Values are means ± SDs. \( P \) values shown were obtained from a 1-factor repeated-measures ANOVA. No differences were observed between institutions for body mass, serum osmolality, or urine osmolality immediately before still-water ingestion or 4-h cumulative urine mass after 1 L still water ingestion, suggesting at each institution that participants’ preparation for trials was similar and that participants in the 3 institutions had similar fluid regulation.

**BHI**

After 2 h, full-fat milk, skimmed milk, ORS, and orange juice had a higher BHI than still water (all differences \( P < 0.05 \)) (Figure 2). The effect sizes at 2 h were 1.22 for full-fat milk, 1.37 for skimmed milk, 1.03 for ORS, and 0.87 for orange juice (all large to very large effects). The higher BHI between still water and full-fat milk, skimmed milk, ORS, and orange juice also exceeded twice the CV of the BHI measure. Mean
differences for 2 h BHI values were 0.50 (95% CI: 0.20, 0.80) for full-fat milk, 0.58 (95% CI: 0.28, 0.89) for skimmed milk, 0.54 (95% CI: 0.16, 0.93) for ORS, and 0.39 (95% CI: 0.05, 0.73) for orange juice. Additionally, full-fat milk, skimmed milk, ORS, and orange juice BHIs were greater than that for still water at 3 and 4 h after drink consumption ($P < 0.05$).

BHI corrected for water content

The water content of the drinks used in this study varied from 100% to 88% (Table 2), and consequently the amount of water ingested varied between drinks. It might be appropriate therefore to recalculate the BHI to take into account the different volumes of water ingested in the different trials. The BHI values presented in Figure 3 have been normalized by the drinks’ water content to reflect the effect of the drink itself on hydration status excluding the differences in water content. As was the case without the correction for drink water content, the corrected BHI for full-fat milk ($P = 0.02$), skimmed milk ($P < 0.01$), and ORS ($P = 0.01$) were higher than that for still water. The effect sizes for corrected BHI data at 2 h were 0.89 for full-fat milk, 1.14 for skimmed milk, and 0.98 for ORS (all large effects). The mean differences for corrected 2 h BHI were 0.32 (95% CI: 0.06, 0.58) for full-fat milk, 0.44 (95% CI: 0.16, 0.72) for skimmed milk, and 0.50 (95% CI: 0.13, 0.87) for ORS. The BHI for orange juice was, however, no longer different from still water ($P = 0.11$), with an effect size of 0.60 (a medium effect) and a mean difference of 0.24 (95% CI: −0.06, 0.54).

Urinary electrolyte excretion and balance

Several drinks had greater sodium or potassium balances than still water 2 h after drinks were consumed (Figure 4). Drinks with positive sodium or potassium balances were typically those with the highest BHI. That is, ORS had a positive sodium balance (Figure 4A), whereas orange juice and full-fat and skimmed milk had positive potassium balances (Figure 4B).

DISCUSSION

Adequate hydration status may be associated with a decreased risk of a range of adverse outcomes, including urologic, gastrointestinal, circulatory, and neurological disorders (14, 15). In addition, maintenance of euhydration is important for the preservation of physical and mental function (4, 5, 15, 16). Consequently, identification of beverages that promote long-term fluid retention and maintenance of fluid balance for prolonged periods would be of real clinical and practical benefit in situations in which free access to fluids is limited, or when frequent breaks for urination are not desirable (2–5). In this study we propose a novel tool to enable the objective assessment of a beverage’s effectiveness to maintain hydration status over a period of time after ingestion. The calculated BHI revealed that drinks containing the highest macronutrient and electrolyte contents were the most effective at maintaining fluid balance.

The differences noted in the urine volume and calculated BHI during the monitoring period might be attributed in part to differences in the water content of the different drinks. Stahl et al. (17) recognized that the amount of water present in a fixed volume of beverage varies because of the presence of other nutrients, meaning the amount of water available to influence hydration status can markedly differ, an observation these authors termed the “postabsorptive hydration index.” The water content of the test beverages in the present study ranged from 100% for
The ingestion of a bolus of still water (11, 18) has been shown to slow the emptying of the stomach more slowly than energy-free drinks and will thus prolong the presence of diuretic agents (primarily caffeine and alcohol). Ingested drinks with a high energy content, whether in the form of carbohydrate, fat, protein, or alcohol, will empty from the stomach at a slower rate than still water (24). In the present study, ORS and milk drinks contained relatively high concentrations of sodium and potassium, the orange juice contained a moderate amount of potassium, and the remaining drinks contained relatively trivial concentrations of these electrolytes. It is notable that the drinks with the highest electrolyte content tended to have the highest BHI.

The known diuretic effects of caffeine and alcohol, because of their action in inhibiting the release of arginine vasopressin (20, 21), would influence the response to ingested drinks that contain caffeine or alcohol. An acute dose of <250–300 mg caffeine is unlikely to have a measurable effect on urine output, although such an effect is likely to be seen when the dose exceeds ~300 mg (22). In line with these observations, we did not observe an impact from moderate caffeine intake (96–212 mg) on net fluid balance in the present study. Furthermore, the alcohol content of the lager did not increase diuresis over other drinks, but the alcohol may have counteracted the hypothesized positive influence of energy density on the BHI. Perhaps surprisingly, only one study has examined fluid balance responses to alcohol in a euhydrated state (23). That study reported a 12% greater diuresis after the ingestion of 1 L lager beer containing 4% alcohol compared with the ingestion of the same volume of a nonalcoholic control beer.

The BHI values presented here are based on the net fluid balance at 2 h after the end of the drink ingestion period. This time point was chosen for 4 reasons. First, this was the time at which drinks began to show differences. Second, the majority (82%) of urine output over the 4-h period had been passed by this point. Third, in a typical day, most people would expect not to have an interval longer than 2 h between drinks, and any subsequent food or fluid ingestion would override the effects of the initial drink. Fourth, for the drinks used in the present study, it made little difference to the calculated BHI whether this was based on the first 2 h or on the whole 4-h collection period.

Although the results of the present study relate only to the acute effects of a large bolus of fluid over the subsequent 4 h, there is evidence to support the suggestion that the results may be extrapolated to a longer time scale. Grandjean et al. (24) had subjects consume water or water plus varying combinations of beverages, including carbonated, caffeinated cola and coffee. They observed no significant differences in the effect of various combinations of beverages on 24-h hydration status. In addition, Tucker et al. (25) recently suggested that 24-h hydration status was not different when subjects drank only water or a variety of drinks, including water, cola, and fruit juice, provided that an adequate total volume was consumed.

In summary, the present study describes a novel tool to enable the objective assessment of the effectiveness of beverages to
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maintain hydration status. The BHI is reproducible and the pattern of response for a range of commonly consumed beverages is consistent with what is known about the effects of their constituents on water balance. An appreciation of the BHI has relevance for individuals for whom long-term maintenance of fluid balance is important, such as in professions in which fluid availability is limited (3–5), as well as in older (2) or incapacitated (15) patients. There is also a clear application to industry, where this tool could be employed to label products to indicate the hydration potential of beverages. Because of the complexity of the commercially available beverages used in this study, it was not possible to directly determine the relative influence of individual drink components on fluid balance (e.g., electrolyte content and energy density). Future studies should apply this model to further examine the significance of these nutrients in isolation, as well as to assign BHI values to a wider range of commercially available beverages.

The authors’ responsibilities were as follows—RJM: conceived of the project and had primary responsibility for the final content; RJM, PW, PAAC, NPW, SJO, NR-S, and SDRG: developed the overall research plan; PW, NPW, and SDRG: had study oversight; PAAC, AD, and NR-S: conducted the research and analyzed the samples; NPW and SJO: performed the statistical analysis; and RJM, PW, NPW, and SDRG: wrote the manuscript. PW has received funding in the last 3 y with PAAC, SJO, and NR-S. RJM is chair of the Scientific Advisory Board for the European Hydration Institute. PW has received funding in the last 3 y from the European Hydration Institute for other hydration-related research. None of the other authors reported a conflict of interest related to the study.

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