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Mild Dehydration by 24 h Fluid Restriction Increases Evening Fatigue and Sleep Duration

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Keywords: Fluid restriction, passive dehydration, sleep time, sleep quality.

Background: Dehydration negatively affects many key aspects of health and daily quality of life. Sleep is among the most fundamental influences on health that is known to be affected by dehydration. Given that investigations have demonstrated that some individuals live in a chronic state of mild dehydration, it is important to understand how dehydration affects basic determinants of health and well-being.

Objective: Our aim was to assess the effects of mild dehydration and subsequent rehydration on sleep time and sleep quality using subjective measures.

Methods: Study participants (n = 13 males, mean±SD; age, 23 ± 4 y; height, 177 ± 6 cm; weight, 81.5 ± 7.7 kg) were evaluated on 3 consecutive mornings (0700–0800 h): 1) Day 1 (Baseline measures): participants were instructed to arrive euhydrated and began a 24 h fluid restriction, 2) Day 2 (Dehydration measures): participants were evaluated, consumed fluid (30 min) to acute satiety, and then drank *ad libitum* for the remainder of the day, and 3) Day 3 (Rehydration measures): participants were evaluated to confirm rehydration. Hydration status was assessed using plasma osmolality (P_{OSM}), body weight changes, and urinary measures: 24 h urine osmolality (U_{OSM}), first morning sample urine specific gravity (U_{SG}), and urine color (U_{COL}). Perceived energy level was assessed every hour by a 0 (fatigued) to 100 (energized) Likert scale. The Karolinska Sleep Diary (KSD), a subjective sleep questionnaire validated by polysomnography to assess sleep time and quality, was measured at every visit. Repeated measures analysis of variance (Bonferroni *post hoc* comparisons) were performed to determine effects of fluid restriction and rehydration.

Results: Sleep, hydration, and perceptual results appear in Table 1. Percent body mass losses, first morning USG, and 24 h U_{OSM} significantly increased ($p \le 0.05$) with dehydration. Overall sleep time increased and corresponded to decreases in perceived energy levels during dehydration (vs. baseline); energy scores for 3 h before bedtime were lower on the dehydration day. Percent change in energy scores from Day 1 to Day 2 decreased in trend ($p = 0.061$), and significantly ($p \le 0.05$) decreased from Day 2 to Day 3.

Conclusions: Our results suggest that mild dehydration increased perceived fatigue during dehydration starting in the afternoon, and it is likely that an increased sense of fatigue prior to bedtime contributed to the increased duration of nighttime sleep during dehydration.

Table 1. Experimental design and morning values (for Abstract No. 1)

Study Design	24-hr Fluid Restriction	+	*Ad Libitum* Rehydration
	Day 1 AM	Day 2 AM	Day 3 AM
Body Mass Loss, Change From Day 1 (%)	0±0	1.8±0.5*	0.6±0.5*ψ
First Morning Sample U_{SG}	1.021±0.010	1.030±0.003	1.020±0.010ψ
First Morning Sample U_{COL}	4±1	6±1	4±2
24h Urine Osmolality (mOsm/kg)	554±276	927±131*	607±260ψ
Plasma Osmolality (mOsm/kg)	276±24	287±7	286±10
Bedtime Perceived Energy Level	39±13	28±14	45±12ψ
Perceived Energy Level, Change from Day 1 (%)	0±0	–24±32#	23±40ψ
Sleep Time (h)	7.2±0.7	8.0±1.2*	7.2±0.8
Sleep Quality	4±1	4±1	4±1

* Significantly different from Day 1, $p \le 0.05$.
ψ Significantly different from Day 2, $p \le 0.05$.
# Denotes a Day 1 versus Day 2 trend ($p > 0.05$, $p \le 0.10$).

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2

Initiating Endurance Exercise Hypohydrated attenuates the Positive Effect of Exercise on Cognition in Older Adults

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Keywords: Dehydration, urine color, urine specific gravity, executive function.

Background: Regular aerobic exercise mitigates the age-related cognitive decline in older adults [1]. This protective effect of exercise on aging brains can be partially attributed to the preservation or slight improvement in older adult's cerebrovascular homeostatic mechanisms [2]. However, older adults are predisposed to experiencing dehydration [3] which negatively impacts the cerebrovascular blood flow response to increased metabolic demands (e.g. exercise) [4]. Yet, it is unknown if dehydration coupled with aerobic exercise reduces the therapeutic impact of acute exercise on cognitive function.

Objectives: We sought to investigate the influence of pre-exercise hydration status on an attention and visual search cognitive task following prolonged endurance exercise resulting in ≥1% body mass loss.

Methods: This field study was conducted at a mass participation cycling event in Wichita Falls, Texas (ambient temperature, 26°C mean, 30°C maximum; relative humidity, 75% mean, 93% maximum). Thirty-two community dwelling older adults (mean ± standard deviation; 57 ± 5 y, range 51–70 y) were enrolled following informed consent and were retrospectively separated into 2 groups (euhydrated, EUH (n = 20); hypohydrated, HYP (n = 12) based on pre-exercise hydration status. Criteria for euhydration were ≥2 of the following hydration assessments: urine specific gravity (Usg) <1.020, urine color Ucol <5 arbitrary units, or plasma osmolality <295 mOsmol/kg [5]. All participants were screened for mild cognitive impairment via the validated Mini-Cog™ assessment (4 ± 1). At baseline, participants were familiarized with the visuospatial pencil-paper test (Trail Making Test A, TMT-A) and anthropometric measurements were recorded. Physical function was assessed by measuring habitual gait speed over 3 meters. Participants completed the TMT-A prior to and immediately following the 164-km exercise bout. Ratings of perceived exertion (RPE) and total exercise time were determined at the finish line. Pre- and post-TMT-A scores were analyzed via paired T-test and Cohen d effect size were recorded.

Results: Groups (EUH vs HYP) did not differ in age (57 ± 4 vs 58 ± 6 y), body fat (11.0 ± 4.3 vs 14.4 ± 4.8%), or habitual gait speed (1.11 ± 0.16 vs 1.08 ± 0.15 m/s). Significant differences were observed at baseline in Usg (1.015 ± 0.005 vs 1.022 ± 0.003) and Ucol (3 ± 1 vs 5 ± 1) (p < 0.0001) but not plasma osmolality (295 ± 4 vs 297 ± 4 mmol/kg). Post exercise RPE (16 ± 2 vs 17 ± 2) and total exercise time (351 ± 63 vs 359 ± 57 min) were similar for both groups but percent body mass loss was significantly different (2.5 ± 0.9 vs 1.9 ± 0.5%) (p = 0.04). Following the 164-km exercise bout, neither group significantly improved in the TMT-A (mean difference; 95% CI; p-value), HYP (4.2 sec; –0.01, 8.41; p = 0.05) vs EUH (3.8 sec; –3.68, 11.35; p = 0.29); however, the magnitude of the effect was greater in the EUH group (0.5 = moderate) than in the DEH group (0.3 = small).

Conclusion: Despite exhibiting significantly greater fluid deficits following aerobic exercise, older adults commencing exercise in a euhydrated state experienced a greater effect of exercise on a cognitive task when compared to hypohydrated adults. These findings suggest that maintenance of fluid balance prior to initiating aerobic exercise may enhance the potency of cognitive benefits for community dwelling older adults.

Disclosure Statement: B.A. Yates and L.E. Armstrong received travel expenses, accommodation, and registration fee from Danone Research to attend the 2018 Hydration for Health Scientific Conference.

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3

Urinary Acute Kidney Injury Biomarker Responses to Combined Dehydration, Muscle Damage, and Exertional Hyperthermia

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Keywords: Acute kidney injury, hyperthermia, dehydration.

Background: Dehydration combined with muscle damage, exercise, and heat stress is inherent in a variety of occupations [1–3]. Poor fluid intake may exacerbate renal injury during exposure to exertional hyperthermia [4]. Dehydration leads to significant reductions in creatinine clearance (i.e. glomerular impairment), however, the impact of dehydration on biomarkers of acute kidney injury (i.e. tubular damage) has received little investigation in humans [5].

Objective: We investigated the combined effects of dehydration, muscle damage, and exercise in the heat on urinary biomarkers of acute kidney injury.

Methods: Eighteen male participants (age 24 ± 5 y, mass 75.9 ± 10.0 kg, body fat 17.3 ± 6.2%, VO_2peak 51.0 ± 6.0 ml/kg/min) completed two trials, one euhydrated (EU; fluid replacement ≤2% body mass loss; actual body mass loss –1.2 ± 0.8%) and one hypohydrated (HY; fluid restriction 24-h prior to and throughout exercise; total body mass loss –4.4 ± 1.9%), separated by ≥28 days. Trials consisted of muscle damaging unilateral eccentric knee flexion, 60 minutes of treadmill running (~60% VO_2peak) and 30 minutes of passive recovery in the heat (33.0 ± 0.3°C, 54 ± 2% RH). Participants were provided a rehydration protocol to replace 100% of fluid losses after both trials and returned 24-h later for a follow-up visit. Biomarkers of acute kidney injury, including urine neutrophil gelatinous associated lipocalin (UNGAL) and kidney injury molecule-1 (UKIM-1), were analyzed using enzyme-linked immunosorbent assays.

Results: By design, urine osmolality was more concentrated during HY in the pre-trial single sample (EU 607 ± 232, HY 1012 ± 130 mOsm/kg, $P < 0.001$) and post-trial single sample (EU 503 ± 252, HY 977 ± 112 mOsm/kg, $P < 0.001$). There was no difference in urine osmolality between the 24-h follow-up urine single samples (EU 554 ± 295, HY 559 ± 392 mOsm/kg, $P = 0.96$). UNGAL was lower in the EU trial pre (EU 5.09 ± 1.77, HY 11.46 ± 6.23 ng/mL, $P < 0.001$) and post exercise (EU 6.56 ± 5.66, HY 11.99 ± 6.13 ng/mL, $P < 0.001$), but not at 24-h follow-up (EU 7.63 ± 9.33, HY 7.48 ± 8.94 ng/mL, $P = 0.91$). UKIM-1 was also elevated in the HY trial pre-exercise (EU 0.53 ± 0.55, HY 1.01 ± 0.95 ng/mL, $P < 0.001$) and post exercise (EU 0.67 ± 0.68, HY 1.49 ± 1.24 ng/mL, $P = 0.002$) but returned to EU levels by 24-h follow-up (EU 0.43 ± 0.41, HY 0.46 ± 0.46 ng/mL, $P = 0.58$). When corrected for urine concentration, however, there were no differences between trials for UNGAL (grand means; EU 11.2 ± 10.8, HY 11.3 ± 6.6 pg/mL/mOsm, $P = 0.94$) or UKIM-1 (grand means; EU 0.98 ± 0.74, HY 1.11 ± 0.80 pg/mL/mOsm, $P = 0.23$).

Conclusions: Exercise in the heat with muscle damage increased physiological and renal strain when HY, but our rapid rehydration protocol ameliorated differences by 24-h follow-up. These findings support the potential impact of proper fluid intake before and after exercise on mitigating renal biomarker elevations.

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4

Urine Specific Gravity as an Indicator of Fluid Balance and Hydration Status in Olympic Combat Athletes: A Systematic Review with Meta-Analysis of Controlled and Uncontrolled Studies

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Keywords: Dehydration, combat sports, blood sampling, water.

Background: Scientists and athletic trainers use different biochemical markers in order to screen fluid balance and hydration status, with urinary indicators being the most frequently reported in the literature [1, 2]. Urine specific gravity (U_{SG}) assessment represents a fast, non-invasive procedure in research and applied settings to detect hydration status in a variety of athletic populations. However, despite the popularity of its application in various athlete groups [3,4] and by the National Collegiate Athletic Association [5], there has been a growing debate regarding the diagnostic

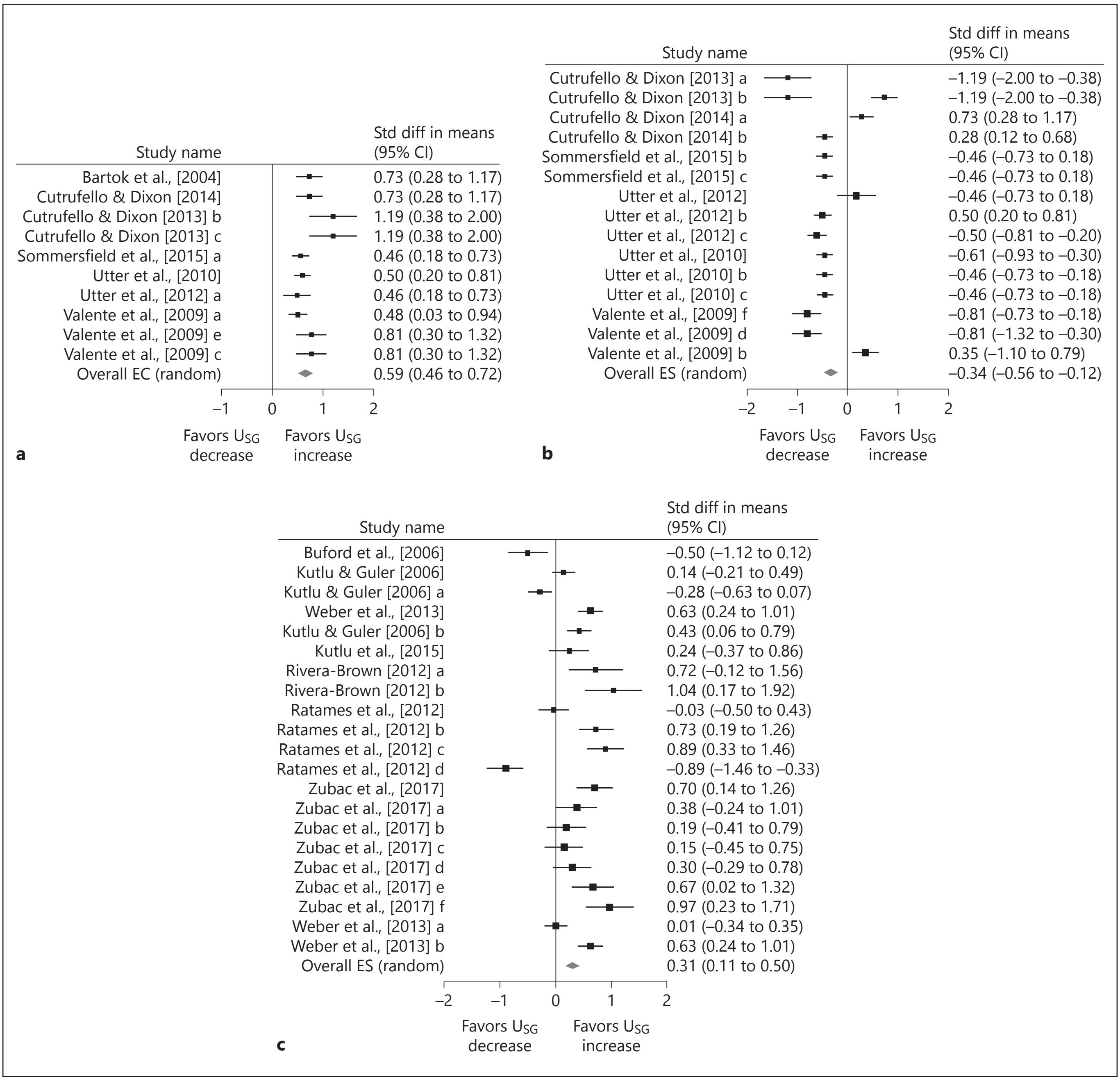

Fig. 1. Effects on diagnostic accuracy of urine specific gravity throughout different sampling protocols: **a**) dehydration; **b**) rehydration **c**) follow-up protocols. CI, Confidence interval; Std. diff. Standardized difference (for Abstract No. 4).

accuracy and precision of U_{SG} indices in detecting body fluid loss [4]. Indeed, several drawbacks to research designs and interpretations were discussed in the recent narrative review of Zubac et al. [4] regarding the on-going debate concerning both testing protocols and the interpretation of hydration status via urinary readings.

Objective: To resolve the ongoing debate, we performed a systematic review and meta-analysis of the applicability and diagnostic accuracy of U_{SG} indices in Olympic combat athletes.

Methods: Two independent reviewers performed the literature search, along with study identification, screening, quality assessment and data extraction. Three electronic databases were searched up to August 2017. Initially, 483 articles were identified, however, following evaluation 27 articles met the inclusion criteria for systematic review, while 15 experimental studies with U_{SG} pre–post measurements were included in the meta-analysis. U_{SG} was the main outcome variable. Meta-regression analyses were used to evaluate the interrelationship among body mass (B_M) oscillations, fluid intake and U_{SG}.

Results: Following three different urine sampling protocols i.e., dehydration (ES = 0.59; 95% CI 0.46–0.72; p = 0.001; $I^2 = 0\%$; p = 0.475), rehydration (ES = –0.34; 95% CI –0.56 to –0.12; p = 0.003; $I^2 = 67.8\%$; p = 0.001), and follow-up period (ES = 0.31; 95% CI 0.11–0.50; p = 0.002; $I^2 = 83.8\%$, p = 0.001, Figure 1), small but significant alterations of U_{SG} were observed. Findings from the meta-regression analysis revealed that only fluid intake significantly predicted the alterations in U_{SG} (p = 0.044) during rehydration protocols.

Conclusions: Urine specific gravity is a viable diagnostic tool to track whole-body fluid deficits and subsequent dehydration immediately after excessive fluid loss. During rehydration, U_{SG} should be assessed after ~2 hours have elapsed from the initial fluid intake. The applicability of U_{SG} in follow-up research designs remains unclear, primarily due to cross-sectional designs of studies in the currently available literature. According to the data presented, Olympic combat athletes usually underestimate daily fluid intake requirements and *ad libitum* fluid consumption is likely inadequate to match whole-body fluid loss. This warrants educational interventions focusing on optimal fluid intake practices and the awareness of health-related issues of suboptimal fluid intake. Therefore, establishment of evidence-based fluid consumption guidelines, specifically tailored for this athletic population, are clearly warranted.

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5

Cross-shift Body Mass Change and Associated Health Outcomes Related to Chronic Kidney Disease in Guatemalan Sugarcane Cutters

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Keywords: Dehydration, kidney function, glomerular filtration rate, whole blood creatinine.

Background: Sugarcane cutters are at an increased risk for having decreased kidney function [2, 3]. Repeated dehydration from heat stress and physical exertion is hypothesized to be a main contributing cause of this chronic kidney disease of an unknown origin (CKDu) [1].

Objectives: To evaluate if changes in kidney health during the sugarcane harvest were related to the frequency of cross-work shift dehydration (>1% body mass (BM) loss = dehydrated; BM loss of ≤1% = hydrated) in Guatemalan sugarcane cutters originating from the highlands (HC) or the local area (LC).

Methods: 290 male workers (HC n = 118, 28 ± 5 y, 160 ± 5 cm, 58.7 ± 6.0 kg, 0.87 ± 0.14 mg/dL whole blood creatinine (WBCr); LC n = 172, 31 ± 9 y, 161 ± 6 cm, 59.9 ± 8.5 kg, 0.91 ± 0.16 mg/dL WBCr) participated. The study included data collection at baseline and at three time-points during the sugarcane harvest. At each time point, pre- and post-shift BM and WBCr (to calculate estimated glomerular filtration rate, eGFR) were measured. Post-hoc, workers were divided into 3 groups based on the frequency of cross-work shift dehydration (pre- to post-shift BM loss >1% at 3 or 2 time points, at 1 time point, or at 0 time points). Percent body mass change was calculated as ((post-shift BM – pre-shift BM)·pre-shift BM^{-1})·100. One-way ANOVAs were used to evaluate the role of chronic hydration status on season changes in WBCr and eGFR.

Results: There was a significant difference in change of WBCr from pre-season to post-season between worker groups (HC –0.07 ± 0.20, LC 0.02 ± 0.25, P ≤ 0.01). Thirty (10.3%) sugarcane cutters developed mildly decreased kidney function, an eGFR <90 ml/min/1.73 m^2 and 11 (3.8%) developed an eGFR <60 ml/min/1.73 m^2, indicating possible kidney disease. Self-reported water intake during work was 17 ± 4 L/d for HC and 15 ± 2 L/d for LC. For all sugarcane cutters there was no difference in occurrence of developing eGFR ≤90 or ≤60 ml/min/1.73 m^2 based on times hydrated (*P* = 0.06, P = 0.55). However, there was a significant relationship between average %BM change and season change in WBCr and eGFR (Figure 1) (P = 0.04, $r^2 = 0.015$; P = 0.02, $r^2 = 0.018$).

Conclusions: Chronic hydration status based on frequency of cross-work shift BM >1% did not relate to workers' risk of developing kidney damage over the course of the sugarcane harvest. However, the HC maintained hydration better, drank more water, and had improved kidney function across the season. A possible explanation is the amount and distribution of water consumption during the day. In the present study 3.8% of workers developed an eGFR of ≤60 ml/min/1.73 m^2 while in an investigation of sugarcane cutters in El Salvador 14% developed an eGFR ≤60 ml/1.73 m^2; a possible explanation for the large difference in rates

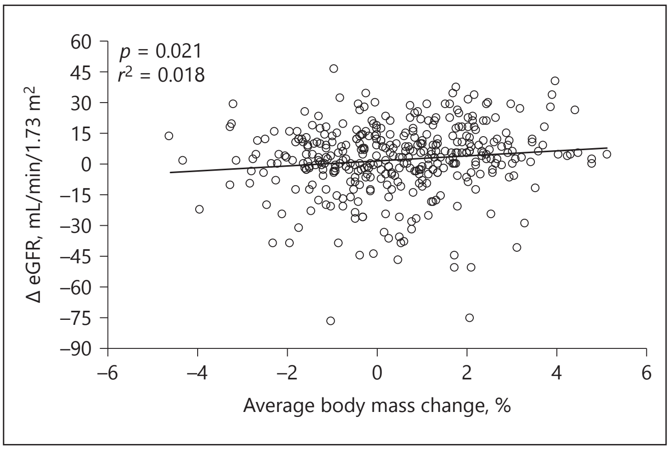

Fig. 1. Average body mass change and season change in estimated glomerular filtration rate (eGFR). Solid black line represents regression relationship (for Abstract No. 5).

of abnormal kidney function is water consumption during the work-shift, ≥15 L/d vs 3.8 L/d [4]. Although chronic dehydration may not be the only cause of decreased renal function resulting in the development of CKDu, increasing water intake appears to attenuate the risk of developing renal injury in sugarcane workers.

Acknowledgement: We thank the workers who participated in the study and the medical staff at Pantaleon, Santa Lucía Cotzumalguapa, Esquintla, Guatemala, for their support in the fieldwork.

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6

Effects of Water Supplementation on Cognitive Performance and Mood Among Male College Students in Cangzhou, China: A Randomized Controlled Trial

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Keywords: Water; hydration; cognitive performance.

Background: Water is an indispensable material for human survival and development. It has many physiological functions. Water accounts for about 75% of brain mass. There may be some associations between hydration states and cognitive performance. Current related studies provide inconsistent conclusions.

Objective: In this study, the effects of water supplementation on cognitive performance and mood was explored among male college students in Cangzhou, China.

Methods: A randomized controlled trial was designed and completed. A total of 68 male college students aged 18–25 years were recruited and participated in the study. They were randomly assigned into the water-supplementation group (WS group, n = 34) and no water-supplementation group (NW group, n = 34) after an overnight fast lasting 12 h. On the water supplementation day, the first morning urine was collected to determine urine osmolality (before water supplementation). Visual analogue scales for subjective sensation of thirst and POMS (profile of mood states) questionnaires were utilized. Questionnaires for cognitive performances (CP), including test of digit span forward and backward, digit symbol substitution, dose-work and Stroop effect were performed. Then, subjects in WS group were asked to drink 400 mL purified water within 5 minutes, while those in NW group did not drink any fluid. One hour after water supplementation, a urine sample was collected to determine urine osmolality again. Then, thirst, cognitive performance and mood were measured again after water supplementation. Mixed model repeated measures ANOVA were used to study the effects of water supplementation on hydration state, cognitive performances and mood with SAS 9.2 statistical software.

Results: There was TIME×GROUP interactions on hydration state ($Z = -2.63$, $P = 0.009$). The percentage of dehydration in NW group increased 5.8% after water supplementation ($\chi^2 = 0.302$, $P = 0.582$), whilst decreased 50% in WS group ($\chi^2 = 17.752$, $P = 0.000$). Significant interactions were found on urine osmolality and thirst between time and group, $F(1, 61) = -7.86$, $P < 0.001$, $F(1, 61) = -4.84$, $P < 0.001$. There were also significant interactions on fatigue, depression, vigor and TMD (total mood disturbance) be-

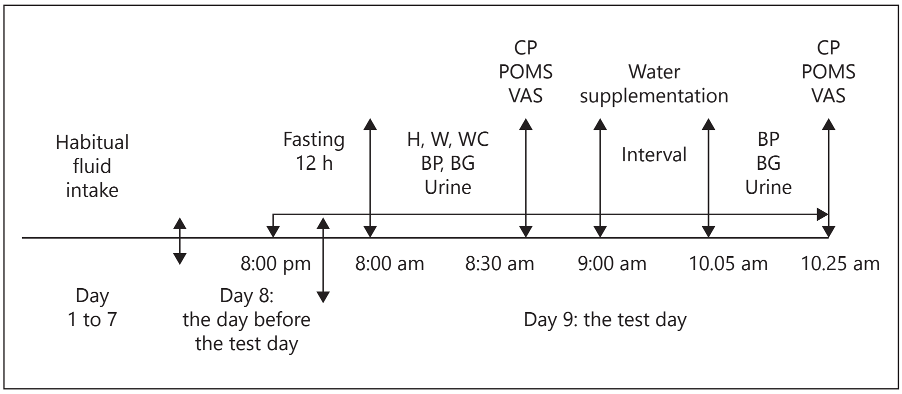

Fig. 1. Study procedure. H, Height; W, Weight; WC, Waist circumference; BP, Blood pressure; BP, Blood glucose; VAS, Visual analogue scales; CP, Cognitive performances; POMS, Profile of mood states (for Abstract no 6).

tween time and group, $F\ (1, 61) = –4.93$, $P < 0.0001$, $F\ (1, 61) = –2.06$, $P = 0.044$, $F\ (1, 61) = 5.56$, $P < 0.001$, $F\ (1, 61) = –2.16$, $P = 0.035$, respectively. In terms of cognitive performances, significant interactions effect on total score of digit span, digit span forward and backward were found between time and group, $F\ (1, 61) = 4.27$, $P < 0.001$, $F\ (1, 61) = 2.26$, $P = 0.028$; $F\ (1, 61) = 3.24$, $P = 0.002$, respectively. The total score of NW group decreased 0.03 without statistical significance after water supplementation, whilst increased 1.53 with statistical significance in WS group, $t\ (29) = –3.64$, $P = 0.001$.

Conclusions: Water supplementation had statistically significant effects on short-term memory, fatigue, depression, vigor and TMD among male college students.

Ethics Approval and Consent to Participate: The study protocol was reviewed and approved by the Ethical Review Committee of the Chinese Nutrition Society and was conducted according to the guidelines of the Declaration of Helsinki. Prior to the study, all subjects read and signed the informed consent form.

Disclosure Statement: All authors claim no conflict of interest. Na Zhang received travel expenses, accommodation, and registration fee from Danone Research to attend the 2018 Hydration for Health Scientific Conference.

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Editorial

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Tenth Annual Hydration for Health Scientific Conference Embodies Excellence and Research Exchange

A decade! The 10th anniversary of the Hydration for Health Scientific Conference was celebrated in Evian, France on June 26–27, 2018, with an opening day Hydration for Health Academy (first instituted in 2016), followed by a day-long scientific program that included research, clinical, and educational topics.

As one who has participated in the entire 10-year series, I can attest that this conference has greatly advanced our understanding of optimal human hydration and the effects of underhydration, within various demographic/socioeconomic groups and regions of the world. To illustrate, Table 1 presents selected topics that have been addressed since 2009. These topics were international in scope, as presented by professionals from the following countries and global regions: Australia, Brazil, Canada, China, Europe, France, Indonesia, Mexico, Poland, Sweden, Switzerland, United Kingdom, and United States. Thus, it is obvious to me that this annual conference has stimulated many new research ideas, produced peer-reviewed publications, developed a new generation of young hydration scientists, and encouraged collaborative efforts. The latter has been evident in the alliances formed with other scientific and clinical organizations. For example, the audiences at several conferences heard presentations by leaders of professional societies, including the European Federation of the Associations of Dietitians (EFAD), European Association for the Study of Obesity, International Society of Nephrology, Ensemble Prévenons l'Obésité Des Enfants (EPODE, Together Let's Prevent Childhood Obesity), and Drink Up! (Partnership for a Healthier America).

The 2018 Conference Program

In the pages which follow, brief articles describe the presentations that were delivered on June 27, 2018. Because this was the 10th Anniversary Conference, Dr. Erica Perrier, a physiologist affiliated with Danone Research in France, creatively designed her 30-minute talk around the theme of the "top 10" advances in hydration science. Her topics (i.e., including low volume drinkers, copeptin as a component of the neuroendocrine response to defend body water, and new statistical approaches that evaluate the role of vasopressin in chronic diseases) represent key advances during the past decade that originated at, or were encouraged by, this conference.

The next 3 manuscripts in this supplement of *Annals of Nutrition* and *Metabolism* focus on children. The first provides a review of water drinking habits and the barriers to

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School Programs in Austria: A Combined Behavioral and Environmental Intervention to Promote Healthy Hydration

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Keywords
School · Behavioral · Intervention · Nutrition · Hydration

Abstract
Founded in 2005, the Austrian Special Institute for Preventive Cardiology and Nutrition (SIPCAN) has established the goal of improving nutrition education, behavior, and environment (e.g., beverages offered at vending machines). Due to the existing infrastructure, school staff, facilities, policies, and environments, the school setting provides a logical choice as a context for implementing interventions to promote healthy hydration practices. Thus SIPCAN specializes in developing and implementing school programs focusing on the target group of 10–18-year-old pupils. The education is delivered by an on-staff teacher with whom the school children are familiar, and it is aimed to reach the school children's parents, to reinforce healthier hydration in the home environment. Therefore, no specially trained professionals are required. Additionally, such interventions require a minimum of money, effort, school time, and contain practical lessons regarding healthy nutrition and physical activity. Using achievable goals, the food and drink offered in school cafeterias and vending machines is changed, in a way that the target group is reached in the best possible way and the healthier choice clearly becomes the easier choice. Last year, every third school of the target group attended at least one of these programs. In the school year of 2017/18, SIPCAN influenced 153,000 students (21% of the target group) through various health promoting programs.

Introduction

A considerable increase in the prevalence of overweight and obesity has been observed. The WHO estimates that worldwide 340 million of the 5- to 19-year-olds are overweight or obese [1]. In Austria, 17% of the 7- to 14-year-old boys and 16% of the girls are overweight and 9% of the 7- to 14-year-old boys and 6% of the girls are obese [2]. In addition to numerous physical implications (i.e., high blood pressure, elevated triglycerides, reduced HDL) [3], childhood obesity is associated with an increased cardiovascular mortality in adulthood [4]. At the same time, the impairment of physical activity, quality of life, and mental health increase [5]. Recent evidence suggests that the intake of sugar-sweetened beverages has a strong impact on the development of overweight and

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Safe Water and Healthy Hydration

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Safe Water Community Project in Jalisco, Mexico

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Keywords
Acute kidney injury · Diarrhea · Chronic kidney disease

Abstract
Few studies have assessed kidney function in patients with gastrointestinal infections in low-resource settings. Although dehydration is a frequent complication of acute diarrhea, we do not know the frequency and severity of acute kidney injury (AKI) in this context. A high prevalence of chronic kidney disease (CKD) has been reported among the inhabitants of poor communities in Poncitlan, Mexico. Polluted drinking water has been implicated as a probable cause. These communities report a high mortality associated with gastrointestinal infection. It is possible that a high incidence of waterborne disease and consequent more episodes of AKI might contribute to the high prevalence of CKD in this population. In this study, we aim to determine the association between the use of unsafe water and the incidence of acute diarrhea and AKI, and to determine if the provision of clean water decreases these complications. The study will be conducted in 3 communities of the municipality of Poncitlan. Initially, we will determine the water, sanitation, and hygiene (WASH) characteristics in the population and evaluate the incidence of diarrheal disease. In the observation phase, outcomes will be assessed after families receive training in WASH techniques, but before they are provided with clean water. In the intervention phase, outcomes will be assessed after clean water is provided.

Introduction

The Global Burden of Disease study estimated that diarrhea was a leading cause of death among all ages: 1.31 million deaths, in 2015 [1]. Several studies have implicated diarrhea as a risk factor for malnutrition and impaired physical growth, and some have suggested that it might also impair cognitive development [2]. Approximately 88% of diarrhea-associated deaths are attributable to unsafe water, inadequate sanitation or insuffient hygiene, and approximately 2.4 billion people globally have no access to basic sanitation [3, 4]. Microbial contamination is widespread in lower- and middle-income countries and affects all water source types, including piped supplies. Guidelines for Drinking-Water Quality recommend that fecal indicator bacteria, preferably *E. coli* or alternatively thermotolerant coliforms, should not be detectable in any 100 mL drinking water sample (WHO 2011) [5]. Approximately 1.8 billion people globally use a source of drinking

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Table 1. Socioeconomic indicators of affected communities

	Marginality index	Population, *n*	Illiterate, %	Incomplete primary school, %	Households without sewage system, %	Households without running water, %	Households with dirt floor, %
Poncitlan	Medium	40,827	7.3	23.4	1.2	5.2	3.4
San Pedro ltzican	High	4,478	21.6	47.9	5.3	4.6	10.4
Mezcala	High	3,896	10.5	35.5	3.0	2.3	10.2
Agua Caliente	High	988	7.79	40.8	28.7	40.9	15.0

Data from references [11, 12].

water that suffers from fecal contamination; of these, 1.1 billion drink water that is of at least "moderate" risk (>10 *E. coli* or thermotolerant coliforms per 100 mL).

Acute kidney injury (AKI) is a frequent complication of acute diarrhea and gastrointestinal infections [6], but very few studies have assessed kidney function in patients with gastrointestinal infections in low-resource areas and rural communities with no or very limited access to health care [7, 8]. The impact of AKI development on the short- and long-term outcomes in patients with diarrheal disease is unknown.

In this project, we aim to determine the incidence of gastroenteritis, waterborne diseases, and AKI in 3 communities that have a high penetration of unsafe water and to evaluate the effect of safe water provision on these issues. We have selected 3 communities from the municipality of Poncitlan, Jalisco, Mexico, based on the high prevalence of gastroenteritis and waterborne disease and the knowledge of the water utilization source. We will partner with the Secretaria de Salud Jalisco (SSJ), in order to obtain information on the quality of water and baseline data on the epidemiology of gastroenteritis and waterborne disease.

The study will be conducted in the communities of San Pedro Itzican, Mezcala, and Agua Caliente located along the Lake Chapala lakeshore in the municipality of Poncitlan. In these communities, water quality has been an issue for many years. Lake Chapala is the ultimate receptor of a great variety of contaminants, including pesticides, industrial residues, and heavy metals such as chromium, lead, zinc, and mercury. Local sources of pollution are also visible [9]. The absence of an adequate sewer system causes Chapala lake water to be contaminated. Wells drilled to avoid the use of lake water did not resolve the issue, as water from wells is contaminated by water springs with a high content of arsenic and other harmful elements. Over the years, these communities have shown a high mortality rate, secondary to intestinal infection and malnutrition [10]. The socioeconomic indicators in these communities show an alarming high marginality index, a high illiteracy rate, and incomplete primary school rates; a large percentage of households lack both a sewage system and tap water, and a high percentage of homes have dirt floors [11, 12] (Table 1).

These communities have a high prevalence of chronic kidney disease (CKD) of unknown etiology. Popular opinion in the lay media has implicated polluted drinking water as a probable cause [13]. Since 2006, the Hospitales Civiles Foundation has used mobile units to assess the presence of CKD in the state of Jalisco. Trained personnel using mobile units travel to rural and urban areas to collect demographic and clinical data, in addition to blood and urine samples for serum chemistry and dipstick urinalysis [14]. This screening program has shown a high prevalence of CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2) and proteinuria in Poncitlan, two-fold and 3-fold higher, respectively, as compared to the adult population in other Jalisco municipalities [15]. In children, although the prevalence of CKD was similar to other Jalisco municipalities, the prevalence of proteinuria was 10 times higher [16]. Similarly, a recent cross-sectional study in children residing in these communities reported a prevalence of albuminuria and CKD of 45% and 33%, respectively; these rates of albuminuria are 3–5 times higher than reported in the state of Jalisco and the international literature [17]. Information from Jalisco's vital statistics shows a high prevalence of intestinal infection, associated with a high mortality rate among children under 5 years of age [10]. It is possible that a high incidence of waterborne disease, and consequently more frequent episodes of AKI, contribute to the high prevalence of proteinuria and CKD in this population. The role of heavy metals and other contaminants in the water may also be important determinants of this outcome [9].

The primary objectives of the study are to evaluate the association between safe water provision and gastroenteritis frequency, waterborne diseases, and kidney disease in

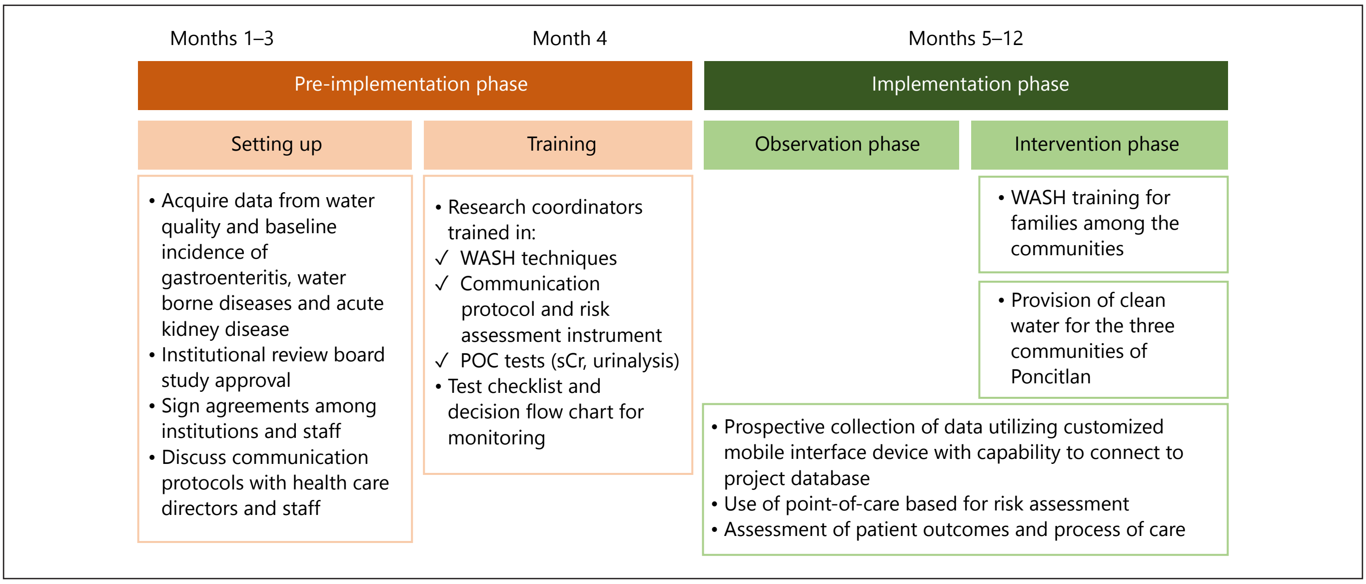

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Fig. 1. Study overview. WASH, water, sanitation and hygiene; POC, point of care; sCr, serum creatinine.

these communities. We have hypothesized that the use of unsafe water is associated with an increased incidence of gastroenteritis and waterborne diseases and leads to high prevalence of AKI. We aim to determine the frequency of AKI in patients with diarrheal disease based on serum creatinine (sCr) and biomarkers of kidney injury. Our secondary objectives are to determine the barriers for safe water use, to determine the association between water, sanitation, and hygiene (WASH) parameters and the prevalence of diarrheal illness. In addition, we will assess the effect of an educational strategy for WASH on diarrheal illness.

Materials and Methods

Preimplementation Phase

The study will be conducted in the communities of San Pedro Itzican, Mezcala, and Agua Caliente located along the Lake Chapala lakeshore in the municipality of Poncitlan, with a total population of approximately 10,000 individuals. Before study implementation, we will determine the WASH characteristics in the target population and evaluate the incidence of diarrheal disease in these communities. Following authorization from the SSJ and study approval from the Hospital Civil de Guadalajara Ethics and Research Committee, we will acquire data on water quality at different levels of distribution and utilization. Communication protocols among health-care facilities, families, and research coordinators will be established via the SSJ. We will train research coordinators in WASH techniques, in the validated risk assessment instrument, the performance of point of care (POC) tests, and for the collection and processing of serum and urine samples for storage for future biomarker assessment. All health providers and relevant staff will be trained in the protocol-based management of diarrheal disease and AKI that is appropriate to the setting in which they work. Providers will also be educated regarding the use of oral rehydration fluids for the treatment of dehydration, following the guidelines of Mexico's Ministry of Health [18]. The SSJ will help to coordinate these training sessions. All families will be taught WASH best practices (Fig. 1).

Implementation Phase

The implementation phase will consist of 2 parts. During the observation (first) phase, study outcomes will be assessed after families receive training in WASH techniques, but before they are provided with clean water. During the intervention (second) phase, study outcomes will be assessed after clean water is provided to the community.

Observation Phase

Patients with signs and symptoms of diarrheal disease will be encouraged to contact the local health-care center and/or study research coordinator. Patients with CKD stage 5 or in chronic dialysis and those with solid organ transplant will not be candidates for study participation. Patients meeting these criteria will be screened by the research coordinator and asked for consent. Patients (or surrogates) who sign informed consent will have a POC test for sCr and urinalysis by dipstick.

The results of the POC tests will be given to the health-care provider, who will be responsible for informing the patient of the results. The health-care provider will be given the accepted normal range of values for adults and children (adults: sCr 0.6–1.2 mg/dL; 53–105 μmol/L [19]; children 0–12 years old 0.0–0.7 mg/dL; 0–62 μmol/L, I) [20]. The health-care provider, however, will decide if the results are in the normal range according to the normative values and patient's comorbidities, age, and overall health characteristics. All health-care decisions will be made by the local health authorities.

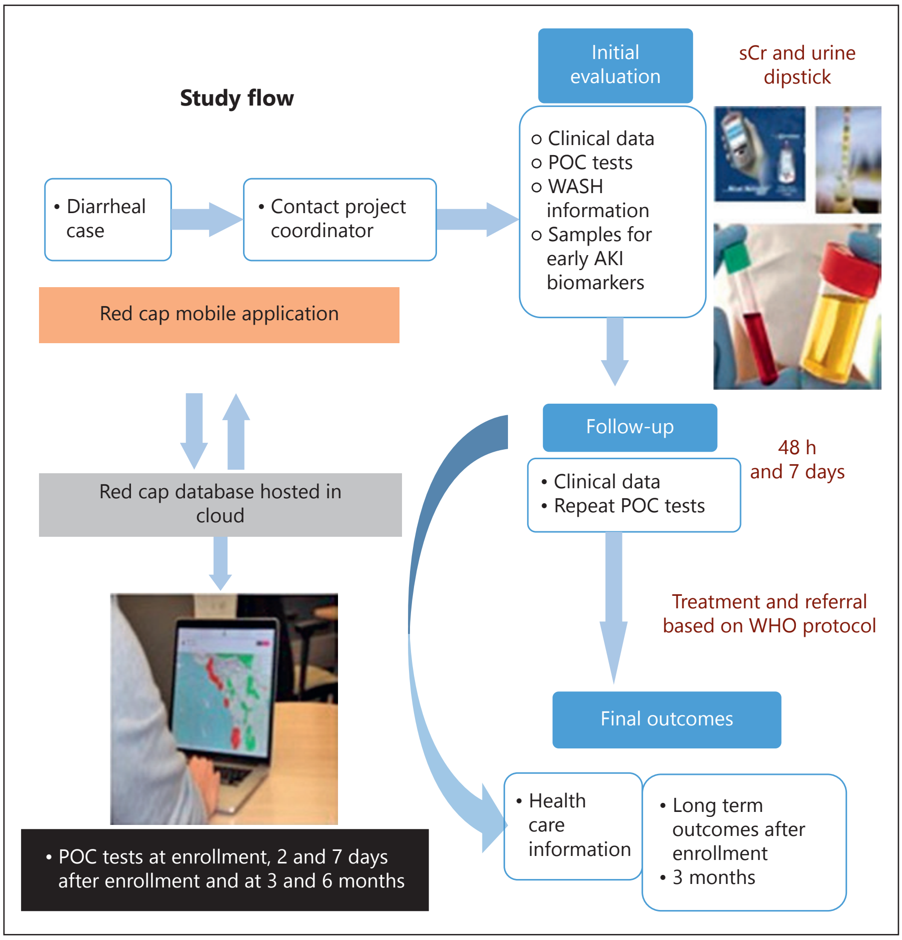

Fig. 2. Study flow during implementation phase. WASH, water, sanitation, and hygiene; POC, point of care; sCr, serum creatinine.

Blood and urine samples will be collected and stored for future biomarker analysis (Table 2). All enrolled patients will complete a clinical and WASH assessment and will be tracked throughout their clinical course by location (i.e., health-care center, hospital, and home). Outcomes will be recorded for 3 months following the initial health-care evaluation.

Patient level data will be tracked by the project research coordinator via communication with health-care facilities and families in the community. All relevant clinical data and the results of the POC test will be recorded in the electronic case report forms. Data will be recorded using the Red Cap Mobile Application. All captured information will be kept in a data repository site. The forms in Red Cap Mobile APP will be adapted for use in the community setting to capture data on the incidence, management and outcomes associated with diarrheal disease, dehydration, and AKI (Fig. 2).

Intervention Phase

In the second phase of the study, safe water will be distributed to the communities. We will repeat research coordinator and health provider training for the protocol-based management of diarrheal disease and AKI. The same study flow will be in place, and we will compare the incidence and severity of diarrheal diseases and patient outcomes. We will analyze the incidence of diarrheal disease and AKI based on whether or not patient and families are following WASH and also by water source.

Table 2. Study schedule and measurements for implementation phase

	Time point			
	enrollment	48 h	7 days	3 months
Medical history and physical assessment				
Physical exam	×	×	×	×
Blood pressure	×	×	×	×
Medication review	×	×	×	×
Renal functional assessment				
POC test sCr	×	×	×	×
Urinalysis	×	×	×	×
Urine and blood collection				
Biorepository for biomarkers	×	×	×	×
Other assessments				
Weight and height	×			×
WASH questionnaire	×			×

POC, point of care; sCr, serum creatinine; WASH, water, sanitation and hygiene.

Health-care providers will track patient clinical status and renal outcomes at 48 h, 7 days, and 3 months after enrollment. Urine and serum samples will be collected at all follow-up time points.

Analytical Plan

Observation Phase

We will capture data on the course of patients with signs and symptoms of diarrheal disease and gastrointestinal infections. During this phase, we will define the gaps in knowledge and local barriers for WASH techniques and use of clean water. We will determine the frequency of specific risk factors for acute and CKDs. We will describe the WASH characteristics of the families enrolled in the study and correlate them with patient characteristics and risk factors for kidney diseases. We expect to establish the baseline frequency of AKI development, progression to more severe stages of AKI, and development of CKDs. Based on preliminary data from the SSJ, we anticipate that we will need to enroll 200 patients during this phase in order to obtain an adequate data sample (Table 2).

Intervention Phase

Safe drinking water will be provided for the 3 communities. We will evaluate the penetration and the barriers to use of safe water. We will compare the frequency of diarrheal disease, AKI, and severity of renal dysfunction between the observation and intervention phases. We will perform an interim analysis after the enrollment of 200 patients and 400 patients during this phase. We will continue this phase in the second and third year, aiming to complete enrollment of 800 patients, if the interim analysis does not indicate a need for early cessation of the study.

After study completion, we will assess the serum and urine samples for biomarkers of glomerular and tubular function. We will assess a panel of tubular markers representing concentration, reabsorption, and secretion function, which correlate with AKI severity or CKD progression (Table 2). The sequential assessment of these biomarkers, at initiation and during the course of the disease process, will provide us with a unique opportunity to understand their pattern of change during gastrointestinal diseases with and without AKI. We will evaluate how these changes correlate with AKI development, severity, and recovery.

Conclusion

In summary, the study will provide an opportunity (a) to demonstrate that the use of unsafe water is associated with an increased incidence of gastroenteritis and waterborne diseases leading to episodes of AKI and (b) to determine if the provision of clean water to communities with high penetration of polluted water is associated with a decreased incidence of these complications.

Statement of Ethics

Subjects (or their parents or guardians) will give their written informed consent. The study has been submitted for approval to the Hospital Civil de Guadalajara Fray Antonio Alcalde Ethics and Research Committee.

Disclosure Statement

The authors have no conflicts of interest to declare. E.M., M.V.R., and G.G.-G. received travel expenses and registration fee from Danone Research to participate in the 2018 Hydration for Health Scientific Conference. All authors have contributed to the conception and design of the work and will equally contribute to the acquisition, analysis, and interpretation of data; drafting the work; approving the version to be published; and will be accountable for all aspects of the work.

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Safe Water and Healthy Hydration

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Abstract
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Introduction

The Global Burden of Disease study estimated that diarrhea was a leading cause of death among all ages: 1.31 million deaths, in 2015 [1]. Several studies have implicated diarrhea as a risk factor for malnutrition and impaired physical growth, and some have suggested that it might also impair cognitive development [2]. Approximately 88% of diarrhea-associated deaths are attributable to unsafe water, inadequate sanitation or insuffient hygiene, and approximately 2.4 billion people globally have no access to basic sanitation [3, 4]. Microbial contamination is widespread in lower- and middle-income countries and affects all water source types, including piped supplies. Guidelines for Drinking-Water Quality recommend that fecal indicator bacteria, preferably *E. coli* or alternatively thermotolerant coliforms, should not be detectable in any 100 mL drinking water sample (WHO 2011) [5]. Approximately 1.8 billion people globally use a source of drinking

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Table 1. Socioeconomic indicators of affected communities

	Marginality index	Population, *n*	Illiterate, %	Incomplete primary school, %	Households without sewage system, %	Households without running water, %	Households with dirt floor, %
Poncitlan	Medium	40,827	7.3	23.4	1.2	5.2	3.4
San Pedro ltzican	High	4,478	21.6	47.9	5.3	4.6	10.4
Mezcala	High	3,896	10.5	35.5	3.0	2.3	10.2
Agua Caliente	High	988	7.79	40.8	28.7	40.9	15.0

Data from references [11, 12].

water that suffers from fecal contamination; of these, 1.1 billion drink water that is of at least "moderate" risk (>10 *E. coli* or thermotolerant coliforms per 100 mL).

Acute kidney injury (AKI) is a frequent complication of acute diarrhea and gastrointestinal infections [6], but very few studies have assessed kidney function in patients with gastrointestinal infections in low-resource areas and rural communities with no or very limited access to health care [7, 8]. The impact of AKI development on the short- and long-term outcomes in patients with diarrheal disease is unknown.

In this project, we aim to determine the incidence of gastroenteritis, waterborne diseases, and AKI in 3 communities that have a high penetration of unsafe water and to evaluate the effect of safe water provision on these issues. We have selected 3 communities from the municipality of Poncitlan, Jalisco, Mexico, based on the high prevalence of gastroenteritis and waterborne disease and the knowledge of the water utilization source. We will partner with the Secretaria de Salud Jalisco (SSJ), in order to obtain information on the quality of water and baseline data on the epidemiology of gastroenteritis and waterborne disease.

The study will be conducted in the communities of San Pedro Itzican, Mezcala, and Agua Caliente located along the Lake Chapala lakeshore in the municipality of Poncitlan. In these communities, water quality has been an issue for many years. Lake Chapala is the ultimate receptor of a great variety of contaminants, including pesticides, industrial residues, and heavy metals such as chromium, lead, zinc, and mercury. Local sources of pollution are also visible [9]. The absence of an adequate sewer system causes Chapala lake water to be contaminated. Wells drilled to avoid the use of lake water did not resolve the issue, as water from wells is contaminated by water springs with a high content of arsenic and other harmful elements. Over the years, these communities have shown a high mortality rate, secondary to intestinal infection and malnutrition [10]. The socioeconomic indicators in these communities show an alarming high marginality index, a high illiteracy rate, and incomplete primary school rates; a large percentage of households lack both a sewage system and tap water, and a high percentage of homes have dirt floors [11, 12] (Table 1).

These communities have a high prevalence of chronic kidney disease (CKD) of unknown etiology. Popular opinion in the lay media has implicated polluted drinking water as a probable cause [13]. Since 2006, the Hospitales Civiles Foundation has used mobile units to assess the presence of CKD in the state of Jalisco. Trained personnel using mobile units travel to rural and urban areas to collect demographic and clinical data, in addition to blood and urine samples for serum chemistry and dipstick urinalysis [14]. This screening program has shown a high prevalence of CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2) and proteinuria in Poncitlan, twofold and 3-fold higher, respectively, as compared to the adult population in other Jalisco municipalities [15]. In children, although the prevalence of CKD was similar to other Jalisco municipalities, the prevalence of proteinuria was 10 times higher [16]. Similarly, a recent cross-sectional study in children residing in these communities reported a prevalence of albuminuria and CKD of 45% and 33%, respectively; these rates of albuminuria are 3–5 times higher than reported in the state of Jalisco and the international literature [17]. Information from Jalisco's vital statistics shows a high prevalence of intestinal infection, associated with a high mortality rate among children under 5 years of age [10]. It is possible that a high incidence of waterborne disease, and consequently more frequent episodes of AKI, contribute to the high prevalence of proteinuria and CKD in this population. The role of heavy metals and other contaminants in the water may also be important determinants of this outcome [9].

The primary objectives of the study are to evaluate the association between safe water provision and gastroenteritis frequency, waterborne diseases, and kidney disease in

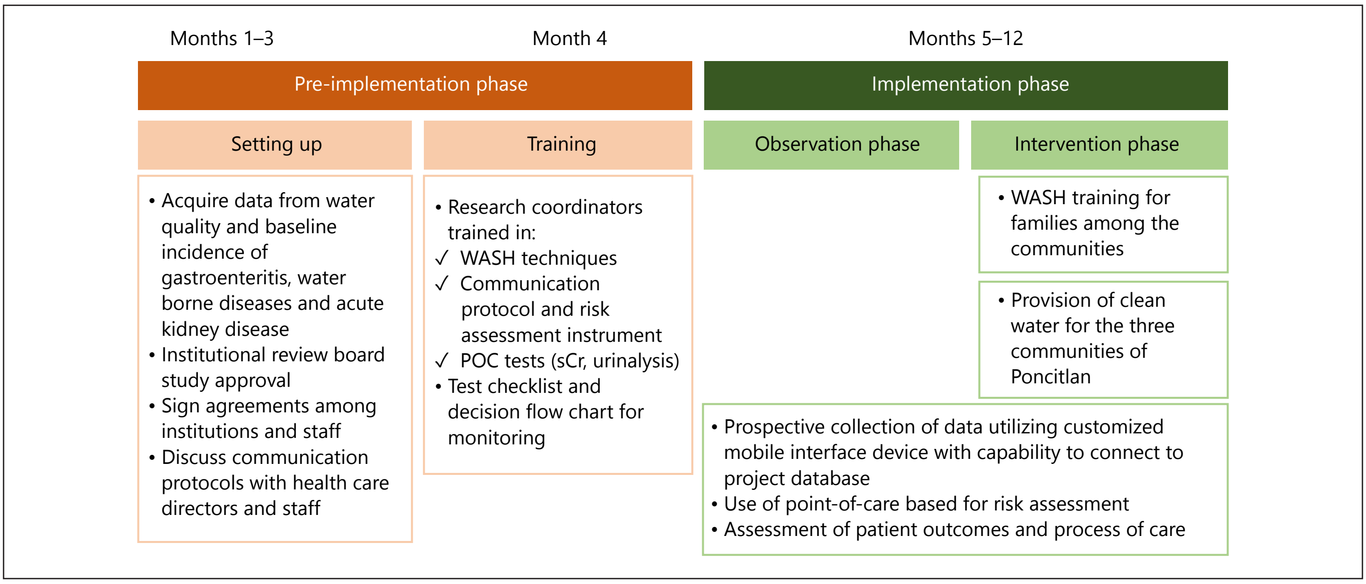

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Fig. 1. Study overview. WASH, water, sanitation and hygiene; POC, point of care; sCr, serum creatinine.

these communities. We have hypothesized that the use of unsafe water is associated with an increased incidence of gastroenteritis and waterborne diseases and leads to high prevalence of AKI. We aim to determine the frequency of AKI in patients with diarrheal disease based on serum creatinine (sCr) and biomarkers of kidney injury. Our secondary objectives are to determine the barriers for safe water use, to determine the association between water, sanitation, and hygiene (WASH) parameters and the prevalence of diarrheal illness. In addition, we will assess the effect of an educational strategy for WASH on diarrheal illness.

Materials and Methods

Preimplementation Phase

The study will be conducted in the communities of San Pedro Itzican, Mezcala, and Agua Caliente located along the Lake Chapala lakeshore in the municipality of Poncitlan, with a total population of approximately 10,000 individuals. Before study implementation, we will determine the WASH characteristics in the target population and evaluate the incidence of diarrheal disease in these communities. Following authorization from the SSJ and study approval from the Hospital Civil de Guadalajara Ethics and Research Committee, we will acquire data on water quality at different levels of distribution and utilization. Communication protocols among health-care facilities, families, and research coordinators will be established via the SSJ. We will train research coordinators in WASH techniques, in the validated risk assessment instrument, the performance of point of care (POC) tests, and for the collection and processing of serum and urine samples for storage for future biomarker assessment. All health providers and relevant staff will be trained in the protocol-based management of diarrheal disease and AKI that is appropriate to the setting in which they work. Providers will also be educated regarding the use of oral rehydration fluids for the treatment of dehydration, following the guidelines of Mexico's Ministry of Health [18]. The SSJ will help to coordinate these training sessions. All families will be taught WASH best practices (Fig. 1).

Implementation Phase

The implementation phase will consist of 2 parts. During the observation (first) phase, study outcomes will be assessed after families receive training in WASH techniques, but before they are provided with clean water. During the intervention (second) phase, study outcomes will be assessed after clean water is provided to the community.

Observation Phase

Patients with signs and symptoms of diarrheal disease will be encouraged to contact the local health-care center and/or study research coordinator. Patients with CKD stage 5 or in chronic dialysis and those with solid organ transplant will not be candidates for study participation. Patients meeting these criteria will be screened by the research coordinator and asked for consent. Patients (or surrogates) who sign informed consent will have a POC test for sCr and urinalysis by dipstick.

The results of the POC tests will be given to the health-care provider, who will be responsible for informing the patient of the results. The health-care provider will be given the accepted normal range of values for adults and children (adults: sCr 0.6–1.2 mg/dL; 53–105 μmol/L [19]; children 0–12 years old 0.0–0.7 mg/dL; 0–62 μmol/L, I) [20]. The health-care provider, however, will decide if the results are in the normal range according to the normative values and patient's comorbidities, age, and overall health characteristics. All health-care decisions will be made by the local health authorities.

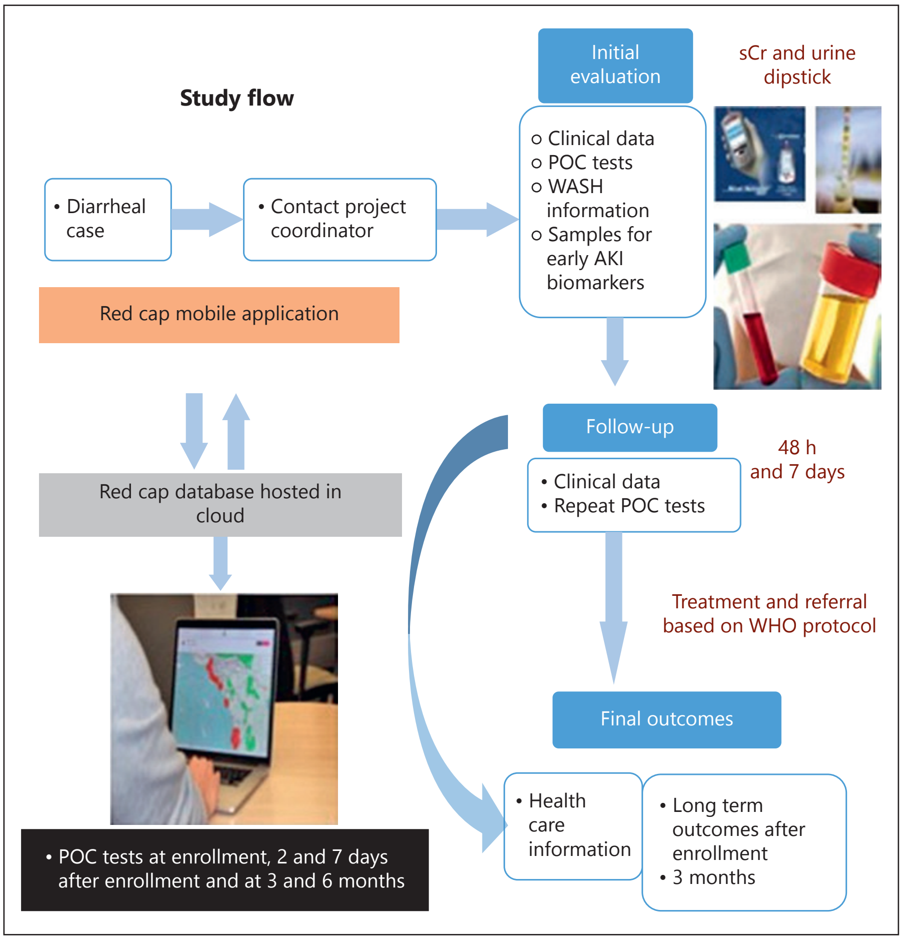

Fig. 2. Study flow during implementation phase. WASH, water, sanitation, and hygiene; POC, point of care; sCr, serum creatinine.

Blood and urine samples will be collected and stored for future biomarker analysis (Table 2). All enrolled patients will complete a clinical and WASH assessment and will be tracked throughout their clinical course by location (i.e., health-care center, hospital, and home). Outcomes will be recorded for 3 months following the initial health-care evaluation.

Patient level data will be tracked by the project research coordinator via communication with health-care facilities and families in the community. All relevant clinical data and the results of the POC test will be recorded in the electronic case report forms. Data will be recorded using the Red Cap Mobile Application. All captured information will be kept in a data repository site. The forms in Red Cap Mobile APP will be adapted for use in the community setting to capture data on the incidence, management and outcomes associated with diarrheal disease, dehydration, and AKI (Fig. 2).

Intervention Phase

In the second phase of the study, safe water will be distributed to the communities. We will repeat research coordinator and health provider training for the protocol-based management of diarrheal disease and AKI. The same study flow will be in place, and we will compare the incidence and severity of diarrheal diseases and patient outcomes. We will analyze the incidence of diarrheal disease and AKI based on whether or not patient and families are following WASH and also by water source.

Table 2. Study schedule and measurements for implementation phase

	Time point			
	enrollment	48 h	7 days	3 months
Medical history and physical assessment				
Physical exam	×	×	×	×
Blood pressure	×	×	×	×
Medication review	×	×	×	×
Renal functional assessment				
POC test sCr	×	×	×	×
Urinalysis	×	×	×	×
Urine and blood collection				
Biorepository for biomarkers	×	×	×	×
Other assessments				
Weight and height	×			×
WASH questionnaire	×			×

POC, point of care; sCr, serum creatinine; WASH, water, sanitation and hygiene.

Health-care providers will track patient clinical status and renal outcomes at 48 h, 7 days, and 3 months after enrollment. Urine and serum samples will be collected at all follow-up time points.

Analytical Plan

Observation Phase

We will capture data on the course of patients with signs and symptoms of diarrheal disease and gastrointestinal infections. During this phase, we will define the gaps in knowledge and local barriers for WASH techniques and use of clean water. We will determine the frequency of specific risk factors for acute and CKDs. We will describe the WASH characteristics of the families enrolled in the study and correlate them with patient characteristics and risk factors for kidney diseases. We expect to establish the baseline frequency of AKI development, progression to more severe stages of AKI, and development of CKDs. Based on preliminary data from the SSJ, we anticipate that we will need to enroll 200 patients during this phase in order to obtain an adequate data sample (Table 2).

Intervention Phase

Safe drinking water will be provided for the 3 communities. We will evaluate the penetration and the barriers to use of safe water. We will compare the frequency of diarrheal disease, AKI, and severity of renal dysfunction between the observation and intervention phases. We will perform an interim analysis after the enrollment of 200 patients and 400 patients during this phase. We will continue this phase in the second and third year, aiming to complete enrollment of 800 patients, if the interim analysis does not indicate a need for early cessation of the study.

After study completion, we will assess the serum and urine samples for biomarkers of glomerular and tubular function. We will assess a panel of tubular markers representing concentration, reabsorption, and secretion function, which correlate with AKI severity or CKD progression (Table 2). The sequential assessment of these biomarkers, at initiation and during the course of the disease process, will provide us with a unique opportunity to understand their pattern of change during gastrointestinal diseases with and without AKI. We will evaluate how these changes correlate with AKI development, severity, and recovery.

Conclusion

In summary, the study will provide an opportunity (a) to demonstrate that the use of unsafe water is associated with an increased incidence of gastroenteritis and waterborne diseases leading to episodes of AKI and (b) to determine if the provision of clean water to communities with high penetration of polluted water is associated with a decreased incidence of these complications.

Statement of Ethics

Subjects (or their parents or guardians) will give their written informed consent. The study has been submitted for approval to the Hospital Civil de Guadalajara Fray Antonio Alcalde Ethics and Research Committee.

Disclosure Statement

The authors have no conflicts of interest to declare. E.M., M.V.R., and G.G.-G. received travel expenses and registration fee from Danone Research to participate in the 2018 Hydration for Health Scientific Conference. All authors have contributed to the conception and design of the work and will equally contribute to the acquisition, analysis, and interpretation of data; drafting the work; approving the version to be published; and will be accountable for all aspects of the work.

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obesity in children and adults [6, 7]. However, fluid intake in schoolchildren is a cause for concern in many countries. Studies show that approximately 60% of children do not consume enough fluids for breakfast and consequently arrive at school with a hydration deficit [8–11]. This is especially concerning because an unpublished study by Special Institute for Preventive Cardiology And Nutrition (SIPCAN) showed that 16% of over 600 Austrian school children never drink anything at school [12].

The School as a Place for Implementing Measures

It has long been known that the promotion of healthy eating and drinking behavior in children has a positive effect on the development of noncommunicable chronic diseases in childhood and adulthood, such as obesity, diabetes mellitus, hypertension, cardiovascular diseases, as well as various types of cancer and caries [13, 14]. It is therefore obvious that health promotion should play an important role in childhood. In terms of infrastructure, staff, and many other factors, schools are a logical choice for the implementation of health promotion measures. However, schools differ in their structural conditions, the care structure, the school environment, and the availability of supermarkets and bakeries in the immediate school surroundings. On the other hand, each school exhibits individual internal dynamics resulting from the relationship between the school principal, parents, teachers, and children. It is postulated that lifestyle interventions can reduce the risk of obesity if they are incorporated into the curriculum [15]. In addition, the school environment has a significant influence on eating and drinking behavior, as schoolchildren spend a significant part of the day and eat a large proportion of daily food intake in the school setting [16, 17]. It has been shown several times that school-based prevention programs can be effective in reducing overweight and obesity in children [18, 19].

New Paths for Healthy Hydration at Schools

Conventional health promotion in the school setting usually involves external experts coming to the school to work with pupils. Workshops are held at schools, school representatives are invited to training courses, and parent lectures are offered. Often bans are imposed (e.g., sales bans at school cafeterias), and external experts decide what is suitable for the target group. School staff such as teachers and school counselors – the actual caregivers – often become extras. The problem with the use of external experts is that this is personnel- and cost-intensive and requires comprehensive appointment coordination. The sustainability of such interventions is often questionable.

In contrast, SIPCAN has been offering successful prevention programs beyond conventional health promotion with a focus on healthy hydration at school settings in Austria since 2005. The cooperation with over 1,000 schools throughout Austria has resulted in a wealth of experience, from which the following central points for implementable access to health promotion in schools can be derived.

Use of Internal Resources

As already mentioned, health promotion programs are often cost-intensive and linked to school-external experts. Our many years of experience in the school setting have shown that it is sensible to offer programs in which on-staff teachers are supported in such a way that health-promoting content is readily implemented by all target groups with measurable, long-term success. One example is the SIPCAN school program “Healthy Snack and Smart Hydration Specialist”. Developed in 2009, this pilot study founded by a national grant has been offered yearly since the school year of 2012–2013. This program is an innovative module set for the school subject “Biology and Environmental Sciences” in the 5th grade, in which nutritional knowledge is taught in an experience- and practice-oriented way, showing pupils the importance of a healthy diet and school snack. The contents of these curricula increase the direct benefit for the school and the teachers. For 5 weeks, teachers work through one module per week with the pupils. Parallel to the lessons, the pupils observe their nutritional behavior over a period of 4 weeks with the help of a snack diary. This encourages learning through self-awareness.

In addition, parents are informed weekly in order to ensure transfer of learned concepts into their home environment and to give parents the opportunity to support their children. The 5th module is followed by a theoretical and practical exam (in the form of a multiple-choice test and the last week of the 4-week self-observation phase with the snack diary). With a positive result, the pupils are presented with a Healthy Snack and Smart Hydration Specialist Award. Additionally, all modules contain exercise impulses for the pupils. Also included is an additional module for “Physical Education” in which the learned contents are linked to an activity game. The feedback of teachers shows that this concept is received very positively: 96% of teachers would recommend participation to colleagues and 92% would participate again themselves. It is also interesting to note that about 70% of parents and approximately 11% of all pupils in the 5th grade are currently participating.

Attainability of Objectives

Very often goals in health promotion are difficult to attain. For example, the WHO recommends an intake of free sugars of <10% of total energy intake [20]. Only 11% of women and 19% of men in Austria reach this recommendation [21]. This raises the question of how target groups can be reached in such a way that these recommendations can be perceived as achievable goals. SIPCAN developed – with regard to the sugar content of beverages – a unique practice-oriented method that has turned into a success story in recent years. Derived from the abovementioned WHO recommendation that <10% of the daily energy intake should be consumed from added sugars (e.g., sucrose, glucose, fructose, as well as sugar in honey and fruit juices), we developed a simple orientation criterion for beverages in coordination with a scientific expert committee in 2008. Considering the recommendations for children, this 10% of the 2,450 kcal daily energy intake (guideline for the average daily energy intake for 13- to 14-year-old boys and girls [22]) amounts to approximately 60 g of free sugars per day. Under the further stipulation that a half liter drink (usual container size) should not exceed half of this daily upper limit, this results in a value of 30 g of free sugars per 500 mland corresponds to a value of 6 g sugar per 100 mL. Taking into account the average sugar content in beverages at the time of the introduction of the orientation, this value of 6 g per 100 mL was deemed too low. Therefore, a tolerance range of 25% was added. Thus, a value of 7.4 g sugar per 100 mL was introduced as orientation criterion; this turned out to be a clearly achievable goal for both consumers and industry. In addition, another orientation criterion stated that no sweeteners may be added to a beverage. Adding sweeteners is controversial because consumers have no chance to accommodate to a less sweet taste [23], and the use of sweeteners is questionable for health reasons [24].

These orientation criteria were established in coordination with the Austrian Ministries of Health and Education as a guideline for the sale of beverages at schools. This applies to all areas of school catering including the school cafeteria [25] and vending machines [26].

Since 2010, SIPCAN has been collecting data on the sugar content in beverages annually as part of a nationwide research project and publishes the results in the so-called “SIPCAN Beverage List.” Thus, the sugar content of beverages can be compared, and the decision to consume a less sugary drink is promoted. Through the broad use of the beverage list as a basis for decision-making in the school sector, we are able to create an incentive for beverage producers to reduce their sugar content. As a result, Austrian industry began to gradually adjust the sugar content of beverages to the criteria. The average sugar content at the first monitoring in 2010 was 7.53 g (± 2.86) per 100 mL. In 2017, this value was 6.75 (± 2.79) g per 100 mL, corresponding to a reduction of 13% [24].

This sugar reduction in schools thus became a nationwide public health strategy. It was decided to further reduce the value of the sugar content from 7.4 to 6.7 g per 100 mL by September 2019. This was again coordinated with the Ministries of Health and Education and applied to all schools in Austria. Without the formulation of an attainable goal, this development would not have been possible and a change of this magnitude would very probably not have taken place.

Reaching Target Groups

With regard to the design of health-promoting catering conditions, schools represent a unique opportunity to reach and direct children and young people in a skillful and goal-oriented manner. A practical example of this is the design of beverage vending machines. According to a yet unpublished study by SIPCAN, 66% of all secondary schools in Austria have at least one vending machine. At the same time, there is direct competition from supermarkets and snack stands in the immediate vicinity of the school. In our experience, there is a very good chance that pupils will buy their beverages outside the school if they do not find appealing beverages at the school, whereas at school, the sugar content and the container size can be regulated. In response, SIPCAN developed the “Beverage Vending Machine Check” and implements it nationwide at >200 school locations. Instead of bans, an 80:20 rule is applied to vending machines. This means that at least 80% of the offering must correspond to the criteria for beverages (maximum of 7.4 g sugar/100 mL and no sweeteners). Water and sparkling fruit juice must be included in the range as ideal thirst quenchers. In this way, it is possible to reach all target groups and prevent the pupils from leaving the school building. On the part of the implementation, the beverage vending machine check is carried out as a teleproject with a school staff member providing the SIPCAN employee with all the necessary information about the vending machines. The teleproject approach represents an innovative approach in the field of health promotion. It is very well received and it enables us to support schools throughout Austria in a targeted and cost-efficient manner.

Making the Healthier Choice the Easier Choice

In addition to influencing behavior, the design of health-promoting catering plays a central role in schools. Without a change in the offerings at school cafeterias and vending machines, the pupils cannot implement the healthy eating knowledge they have learned, and in the worst case may be forced to eat an unhealthy diet. In addition to vending machines, school cafeterias offer a wide food assortment ranging from cold snacks to warm snacks and beverages. In 2007, SIPCAN began supervision of school cafeterias through the "School Cafeteria Check," a system in which each product group is classified and evaluated on the basis of 29 criteria. In addition to the design of the offerings, the presentation of goods also plays a decisive role. School cafeterias that meet 75% of all criteria receive an award. By this means, the healthier choice becomes the easier choice. SIPCAN currently supervises school cafeterias at 151 schools and reaches 100,000 pupils in that manner.

Conclusion

Health promotion programs should utilize internal school resources and provide as much support as possible to the targeted empowerment of teachers. It is important to formulate achievable goals that motivate all target groups. In this context, the school setting represents a unique opportunity because children spend most of the day in definable and controllable conditions. In order for measures to be implemented nationwide, the teleproject approach seems to be reasonable and successful. Complete module-sets and self-explaining materials represent a great added value for the teachers. Despite the great heterogeneity of the target group, it is also possible to reach the parents or guardians of children this way. As each school has its own dynamics, it makes the implementation of health promotion measures at schools particularly challenging and exciting. In order to achieve success in daily practice, however, it is necessary to adapt to each setting in the best possible way, to develop cost- and time-saving techniques, and employ a practical approach.

Disclosure Statement

M.S. received travel expenses and registration fee from Danone Research to attend the 2018 Hydration for Health Scientific Conference. J.S. and F.H. have no conflicts of interest to disclose.

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Perspective

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Hydration for Health: So What? Ten Advances in Recent Hydration History

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We have long understood that water is essential to life. From early experiments on water's importance for survival in extreme environments [1] to a thorough understanding of how hydration affects sports performance and safety [2–6], the importance of replacing body water losses is well-known and markers of water loss dehydration are well-understood. However, outside of sport and occupational health, water has remained to a large extent an essential but also an invisible nutrient [7–10]. The past decade marks a turning point in considering the importance of water and hydration for the general population, with significant advances in our understanding of water, hydration, and health. On this tenth anniversary of the Hydration for Health Scientific Conference, we offer the following "top ten list" describing key advances in the hydration and health sciences and present perspectives for the next decade.

The Concept of the *Low Drinker*

This concerns the physiological characterization of otherwise healthy adults who, despite free access to water and other beverages during their daily activities, routinely consume far less than the Adequate Intake for water as defined by European [11] or American [12] public health authorities. These *low drinkers* maintain a normal total body water volume and plasma osmolality and are thus not dehydrated. Yet, they remain in a state of near-

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constant water saving, as evidenced by consecutive days of low urine volume, high or approaching maximal urine concentration, with normal but elevated circulating arginine vasopressin (AVP) and cortisol [13–18], and, curiously, no evidence of increased thirst drive [17, 19] to stimulate increased drinking. This suggests that at least a segment of the general population is relatively insensitive to physiological cues to drink adequately, with possible implications to kidney or metabolic health (see below).

The First Acknowledgement of "Desirable" Urine Concentration in Setting a Dietary Reference Value for Water

The EFSA Scientific Opinion on Dietary Reference Values for water [11], published in 2010, considered for the first time that an adequate intake of water should provide a margin or buffer between "desirable" and maximal urine concentrating capacity. The committee concluded that it would be prudent to provide for a safe margin of "free water reserve" [8, 20]. The water requirement was thus targeted to achieve a urine osmolarity around 500 mosm/L, well below the maximum concentrating capacity of the kidneys.

A Heightened Interest in Accurately Recording Fluid Intake

A key aspect to understanding the relationships between water intake, hydration, and health begins with widespread and accurate recording of fluid intake in population surveys and clinical trials. As recently as 2014, a systematic review of fluid intake across age groups found that while most publications describing fluid intake in adults recorded water intake, more than half the publications involving teenagers or children did not record plain water consumption [21]. Recent work has highlighted that water and fluid intake are underestimated in combined food and beverage recording instruments [22, 23], suggesting the need for a fluid-specific tool. Recently a prospective, 7-day fluid-specific diary was validated against a gold-standard method of water turnover [24]. This validated tool, along with increasing publications describing fluid intake patterns worldwide [25–34], allows for a growing, global worldwide picture of what people drink, essential to understand the impact of fluid intake on health.

The Widespread Availability of an Ultrasensitive Copeptin Assay

AVP, or the antidiuretic hormone, is a key regulator of total body water. It acts via V2 receptors to modulate water reabsorption in renal collecting ducts and thus adjust urinary water losses to maintain body water homeostasis in response to changes in daily water intake. Beyond its role in body water homeostasis, AVP also has widespread central and peripheral effects that make it an interesting candidate in the study of many diseases [35]; however, its instability and rapid clearance have historically made reliable measurement difficult [36]. Copeptin, the C-terminal portion of the AVP prohormone, is released in equimolar concentration to AVP, and therefore would provide a quantitative measure of AVP release. The development and commercialization of an ultrasensitive sandwich immunoassay (B.R.A.H.A.M.S Copeptin pro-AVP, Thermo Scientific, Hennigsdorf, Germany) made possible an explosion of new research on AVP through its surrogate, copeptin. The research impact of this assay has already been profound: a full 3 quarters of scientific papers including copeptin have been published in just the past six years.[1] This includes explorations of the role AVP may play in the development of kidney and cardiometabolic disease (see below).

The Copeptin Explosion and the Rise of the Cohorts

The availability of the ultrasensitive copeptin assay has facilitated a surge of publications identifying copeptin, a surrogate marker of AVP, as an independent risk factor in kidney and cardiometabolic disease. More specifically, higher plasma copeptin (usually defined as the top quintile or quartile measured in population studies) has been independently associated with increased likelihood for incident impaired fasting glucose or type 2 diabetes mellitus (T2DM) as well as components of the metabolic syndrome including hypertension, high C-reactive protein, or abdominal obesity [37–40]. Moreover, in patients with existing T2DM, higher copeptin appears to be linked to higher risk for the onset of kidney pathology including a more rapid eGFR decline [41] or doubling of serum creatinine in addition to increasing risk for cardiovascular events [42]. This evidence, pooled with associations be-

[1] PubMed search on January 24, 2019 for "copeptin" in Title and/or Abstract. Of a total of 869 records returned in the search, 650 (75%) were published in 2013 or later.

tween low urine volume or low water intake and kidney or cardiometabolic disease [43–46], suggests that a combination of habitual low drinking, highly concentrated urine, and a higher circulating AVP may contribute to increased risk of metabolic disease in healthy individuals and may worsen comorbidities in those with existing T2DM.

New Statistical Approaches Help to Establish a Probable Causal Role of Vasopressin in Metabolic Disease

While large, prospective cohorts have documented associations between AVP and disease risk, these studies cannot establish whether higher circulating AVP plays a causal role in the development of metabolic dysfunction. A recent publication by Roussel et al. [39] attempts to shed light on the directionality of the relationship by exploring patterns of mendelian randomization. Briefly, the authors documented that participants (men and women) in the upper quartiles of copeptin had higher incidence of hyperglycemia and lower insulin sensitivity than those with lower plasma copeptin. They also found that specific variants of the AVP gene were also associated with increased risk for hyperglycemia, and that men expressing these variants also had higher plasma copeptin (no association was found in women, who, on average, tend to have lower plasma copeptin than men). This finding is consistent with previous preclinical evidence that AVP contributes to metabolic dysfunction via V1a and V1b receptors expressed in hepatocytes and pancreatic islets, respectively [47–50].

First Findings that Increasing Water Intake Lowers High AVP, a Risk Factor for Disease

If higher AVP (copeptin) is an independent risk factor for disease, might increasing daily water intake meaningfully lower circulating AVP? And would this reduction subsequently improve long-term health outcomes? Four recent, independent studies provide a convincing proof of concept that among low drinkers, and particularly in those with high baseline AVP, increasing water intake lowers AVP (or copeptin) over hours [51], days [17], or weeks [52, 53]. Promisingly, the copeptin-lowering effect appears to be most pronounced in individuals with higher baseline copeptin as well as other baseline signs of low drinking (such as low urine volume or high urine osmolality), suggesting a potential subpopulation of "water responders" for whom increased water intake may represent an attainable lifestyle intervention with real potential for health benefit. Important gaps still exist as to whether increasing water intake and subsequently lowering AVP would result in a reduction in disease incidence. A recent study by Enhörning et al. [53] found that in addition to reducing copeptin, 6 weeks of increased water intake resulted in a modest but significant lowering of fasting plasma glucose; furthermore, the reduction in glucose was predominantly driven by those with the highest baseline copeptin and the greatest reduction in response to the water intervention. Longer-term, larger-scale interventions are needed to verify whether increasing water intake to lower AVP reduces or slows the onset of disease.

Water Intake as a Potential Therapeutic Target for Renal Disease

Water intake has generated interest as a potential therapeutic agent for multiple kidney diseases including urolithiasis, chronic kidney disease (CKD), autosomal dominant polycystic kidney disease (ADPKD), and the mesoamerican nephropathy epidemic [54, 55]. In urolithiasis, low water intake and low urine volume are known risk factors for stone formation [56–60], and increasing water intake to promote the excretion of a large volume of dilute urine is recognized in secondary stone prevention [56, 61, 62]. Less is known about the potential therapeutic role of water intake and hydration in CKD and ADPKD. While a pilot study involving stage 3 CKD patients documented that increasing water intake increased urine volume and lowered plasma copeptin [63], a larger-scale randomized controlled trial failed to show that an increase in water intake slowed the progression of the disease [64]. However, the increase in urine volume was quite modest (+0.6 L.d) and the follow-up time relatively short. In ADPKD, the suppression of AVP by increased water intake may slow renal cyst growth; however, the limited human data available are conflicting. A large RCT is currently assessing the safety and efficacy of prescribed water intake to slow disease progression [65]. Finally, recurrent exposure to heat stress and dehydration has been identified as a key risk factor in the mesoamerican nephropathy [55], an epidemic of CKD of unknown etiology affecting young men working in Central American agricultural fields in the lower altitudes along the Pacific coast. Further investigation into these pathologies, the mechanisms by which water intake may alter the course of the disease, and the efficacy of water intake as a therapeutic agent, all represent exciting future research opportunities with the potential to impact public health.

The First RCT on Water Intake for the Prevention of Urinary Tract Infection

The recent publication of the first RCT on increased water intake to prevent urinary tract infection (UTI) recurrence demonstrated that water intake can play a powerful role in secondary prevention [66]. This 12-month study demonstrated that increasing water intake by 1.2 L/day cut UTI recurrence in half in women who suffered from recurrent UTI and who, at baseline, consumed <1.5 L of water and other beverages daily. This is especially relevant given the high prevalence of UTI (more than 60% of women worldwide); the widespread use of antibiotics to treat each recurrence or as prophylaxis; and the health-care costs associated with diagnosis and treatment. Moreover, this subject struck a chord with a decidedly nonscientific audience, generating mainstream media attention, a surge of activity on social media, in addition to becoming one of the most attended-to articles on the journal website,[2] suggesting widespread interest in the fact that something as simple as increasing water intake can measurably impact health.

Growing Academic Interest and Debate around What It Means to Be Well-Hydrated

The study of hydration is expanding, from its origins in dehydration, sports performance, and safety toward an increased understanding of how hydration plays a role in health. Until quite recently, however, the models, terminology, and biomarkers used to describe hydration remained rooted in the concept of body water gains and losses [67]. To be euhydrated was, for all intents and purposes, defined by the absence of dehydration (hypohydration) or measurable body water loss. Little attention was paid to the process by which euhydration was maintained, that is, by modulating urinary water losses as a function of water intake. Today, we see a growing interest and healthy debate over what it means to be well-hydrated that extends beyond simply replacing body water losses. Recent publications have weighed in on the distinction between the hydration state and the hydration process [18, 68–71]; have proposed cutoffs and criteria for defining underhydration, optimal hydration, and the question of daily water requirements [72–76]; have debated the validity of various hydration biomarkers in different circumstances [77–82]; and have introduced concepts for various beverage indices [83, 84]. Evidently, as in any academic field, there are differences of opinion, discrepancies that require clarification, conflicting evidence, and many subjects that have not been adequately addressed. However, the fact that the subject of hydration for health is now on the table and being vigorously debated is a positive development, which will encourage further scientific advances in the years to come.

Perspectives for the Next Ten Years

Today, we have a solid foundation upon which to build the next generation of hydration and health research. We have valid tools to measure fluid intake and easier access to measuring copeptin, a reliable surrogate for AVP and antidiuretic activity. We have a large body of epidemiological evidence that suggests that low water intake, low urine output, and high AVP are associated with kidney and metabolic disease risk. We have plausible mechanisms and supporting preclinical evidence for how low water intake or suboptimal hydration may contribute to disease. We have proof of concept studies which demonstrate that increasing water intake can lower high plasma copeptin, a key risk factor in disease, and a first large-scale randomized, controlled trial demonstrating that water is effective in secondary prevention of UTI. After ten years of developing the framework for research around hydration for health, where are the critical gaps? What still needs to be done? The following is a nonexhaustive list of opportunities to contribute to this growing field of research:

- Dig further into defining thresholds for copeptin that are predictive of disease risk and deepen our understanding of the apparent sex differences in the relationships between water intake, AVP, and disease.
- Need for large-scale, appropriate-length RCTs to determine under which conditions increased water intake may play a role in disease prevention or health maintenance.

[2] At the time of writing, the article has been viewed more than 42,000 times at the journal website, is ranked within the top 2% of all research reviewed by Altmetric for quality and quantity of online attention received, including news media, blogs, and social media.

- Support or improve thresholds or criteria for optimal hydration.
- Increase our knowledge of water intake, hydration, and health in underresearched populations, such as young children, pregnant and breastfeeding women, and the elderly.
- Understand the role water intake and hydration may play in modulating comorbidities (for instance, reducing the risk for diabetic nephropathy in T2DM).
- Dig deeper into water and fluid intake patterns of selected demographic groups and develop strategies to encourage healthier drinking habits.

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Hydration Status and Kidney Health of Factory Workers Exposed to Heat Stress: A Pilot Feasibility Study

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Keywords
Occupational heat stress · Dehydration · Feasibility study · Kidney

Abstract
Dehydration associated with heat stress increases the risk of workplace injury or illness, decreases productivity, and may contribute to the chronic kidney disease epidemic identified in outdoor workers from hot climates. There is limited research on the effects of chronic occupational heat stress among indoor workers. We aimed to test the feasibility of measuring markers of hydration and kidney function in foundry factory workers in Southern Brazil, exposed and not exposed to heat stress. Factory workers exposed to heat stress (wet bulb globe temperature ≥28.9) and not exposed to heat were identified by management and invited to participate. Clinical and biochemical markers of hydration and kidney function were evaluated before and after a single 8.5 h work shift (lunch time not included). Feasibility outcomes included rates of enrolment, % completion of study protocols, and time to complete data collection. This study was deemed feasible with 80% enrolment and 90% completion of the protocol. Among the preselected workers, the enrolment rate was 91%. All subjects completed the physiological measures and blood collection and 95% completed the urine studies. Mean time to complete data collection pre-shift was 19.1 ± 4.2 min and post-shift: 14.3 ± 4.0 min. Workers exposed to heat stress had a greater decline in estimated glomerular filtration rate compared to controls over the work shift (–13 ± 11 vs. –5 ± 7 mL/min; $p < 0.01$). We demonstrated the feasibility and challenges of conducting future hydration and kidney function research among indoor factory workers. Further study is needed to determine if exposure to indoor heat contributes to a decline in kidney function.

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Introduction

Occupational heat exposure affects millions of workers worldwide and although the effects of heat stress on hydration status and kidney health have been explored in those working in outdoor settings, there is limited research on indoor workers [1]. Occupational heat stress occurs in those working near furnaces, ovens, smelters, and boilers in kitchens; steel plants; foundries; automobile industries; and glass manufacturing units where high temperature is present and robust preventive measures are often not implemented [2].

In industrial settings, extreme temperatures are found even with mild outdoor temperatures [3]. The high temperatures contribute to increased prevalence of kidney stones [4] and signs of dehydration and symptoms of heat-related illness [5, 6]. Besides consequences in physical and psychological well-being, heat stress is also associated with worksite accidents and reduced productivity [7].

Concerns regarding the kidney health of workers exposed to heat stress were recently identified. Chronic kidney disease (CKD) has affected young agricultural workers without evidence of a recognized cause, in hot regions in Central America [8, 9] and Asia [10, 11] and has been recently named and categorized by the International Society of Nephrology as chronic kidney disease of unknown (CKDu) etiology [12].

Although a causal relationship has not been clearly defined, there is growing evidence that extreme occupational heat stress and repeated dehydration is likely one of the contributors to the epidemic of CKDu occurring in these regions [13, 14]. Other factors may also be contributing to CKDu, such as rhabdomyolysis due to extreme physical work, nonsteroidal anti-inflammatory drugs, illegal alcohol, renal-damaging infections, exposure to fructose-containing beverages, pesticides, other agrochemicals, heavy metals, and toxic pollutants [12, 15].

Studying the effect of heat stress among indoor workers has several advantages in the investigation of the relationship between heat stress and kidney health, including a controlled and measured environment, accurate documentation of fluid intake, reduction in confounding variables, and an environment conducive to assessing outcomes.

Our hypothesis is that it is feasible to conduct a study protocol on hydration and kidney health in factory workers. Our study describes the results of a pilot feasibility study that compared hydration and kidney health status in 2 cohorts of workers (a heat-exposed group and a control group not exposed to heat).

Our objectives were:

Primary: To determine the feasibility of factory worker participation in a single-center study examining the effects of work-related heat stress in 2 cohorts (workers exposed and not exposed to high temperatures), measured by rates of enrolment and completion of study protocols. This included measuring the time to complete data collection and impact on the work day.

Secondary: To determine the effect of heat exposure on the physiological, laboratory, and self-reported participant symptoms in workers exposed and not exposed to heat stress measured pre- and post-shifts.

Methods

Ethics

This protocol was approved by the Institutional Ethics Committee at Pontifícia Universidade Católica do Paraná, No. 2.310.225. Individuals participating in the study signed an informed consent form.

Study Design and Population

Participants were workers from the foundry division of one large metallurgical industry in Southern Brazil. The study group included male workers who perform their activities near furnaces (wet bulb globe temperature [WBGT] ≥28.9) while wearing heavy protective clothing (heat group); the control group was comprised of men that also perform manufacturing activities with similar physical effort, but not near furnaces. Only workers from the morning shift (05:30 h shift start) were invited to participate, and both groups had an 8.5 h/day work shift (lunch time not included), 5 days per week. A variety of jobs/tasks were performed by participants of both groups.

Inclusion criteria: male workers, 18–50 years old, working the same job during the preceding 2 months. Exclusion criteria: current use of diuretics or lithium. Eligible participants were selected and invited by their department manager to participate in the study. The manager of the heat group was instructed to invite all eligible participants. We expected the inclusion of approximately 20 workers from both groups.

Setting

Data collection was performed in the outpatient clinic of the metallurgical factory. Workers were instructed to visit the clinic before starting the working shift and just after finishing it. All measurements and data collection were performed at the clinic. Because most workers use preschedule public transportation, evaluations were performed during part of the working shift.

Protocol

Participants received a questionnaire to document demographics, life habits, general health information, working history, and cooling methods at home. They were instructed to complete this questionnaire and bring it on the study day. Answers were checked by the researcher (F.B.N.) to assure understanding, completeness, and quality.

Pre-shift, workers received a form to document the quality and quantity of beverages consumed during the shift, measured by standard plastic cup volumes. They were instructed to maintain their customary drinking habits. According to managers, workers were instructed to drink beverages according to their thirst. Fluids available for consumption near their worksite included plain water and fluid-replacement beverage. Coffee, tea, soft drinks and others were available during the meals. The fluid-replacement beverage was a recipe of water with a pharmaceutical electrolyte and glucose powder plus a dietetic artificial juice powder. Three samples of this fluid were collected on different days and chemically analyzed for electrolytes and carbohydrate content.

Heat-Related Illness Symptoms

Pre-shift, participants were questioned if they had any symptom of illness during the last week. The heat-related symptoms (headache, fever, excessive sweating, very small or no urine volume, dark urine, exhaustion, nausea, stomach ache, dizziness, heart racing, cramps, vomiting, fainting, and diarrhea) were assessed as described previously in an investigation with agricultural workers [16].

Thirst

Pre- and post-shift, participants were asked "How thirsty do you feel right now?" as calibrated on a visual analog scale. Workers were instructed to place a mark on a 10-cm horizontal line anchored by phrases "not at all" and "very thirsty" at the extremes.

In the post-shift survey, participants were asked the number of urine voids during the working day. The following open questions, as previously published in an occupational heat stress investigation, were used [17]: was today a typical workday for you? If not, why? Were the study visit times acceptable? Were you comfortable with the study? Which measurements did you find to be uncomfortable?

Physiological Measures

Body weight was measured using a certified and calibrated 150 kg electronic platform scale. Before weight measurement, participants were instructed to empty their bladder and remove extra coats and empty their pockets. They were advised to attend the clinic for post-shift evaluation wearing the same items. Height was assessed pre-shift.

Blood pressure (BP) and heart rate were measured in sitting position, after a minimum of 5-minute rest, with certified, calibrated digital equipment (Omron HBP, model 100, Kyoto, Japan). The mean of 3 measures was used as the BP.

Blood and urine specimens collected at the factory clinic pre- and post-shift were promptly delivered to a single laboratory for biochemical analysis. Blood was drawn and measured, complete blood count, plasma glucose, serum urea, uric acid, electrolytes, and creatinine were measured by enzymatic colorimetric test. Glomerular filtration rate was estimated using the formula from the CKD Epidemiology Collaboration [18]. Serum osmolarity (mOsm/L) was calculated using the following formula: (2 × Sodium) + (BUN/2.8) + (Glucose/18) [19]. Urine samples were used to evaluate electrolytes, urea, albumin/creatinine ratio, and urine specific gravity (USG). Urinary osmolarity (mOsm/L) was calculated by the formula: (sodium + potassium) × 2 + urea [20]. Euhydration cutoffs for USG (<1.020), serum osmolarity (< 290 mmol/L), and urinary osmolarity (<700 mmol/L) were obtained from the Position Stand of the American College of Sports Medicine [21]. Participants were asked if urine collection was the first, second, or another void of the day.

Heat Stress and Environment Assessment

The WBGT indices for each job of the study group participants were provided by the factory's safety engineering department following standards of assessment [22]. Although assessments were not performed in the same days of data collection for each participant, evaluations were performed in the same period of data collection, (November and December of 2017 – spring in Southern Hemisphere).

Outdoor temperature and relative humidity during the 13 data collection days were obtained from the public website http://ciram.epagri.sc.gov.br.

Statistical Analyses

Continuous variables are reported as the mean value and SDs when normally distributed, or as the median and interquartile range when not. A *t* test was used to compare groups where variables were normally distributed and the Mann-Whitney U test was used when not. Paired samples *t* test and Wilcoxon signed-rank test were used to compare changes in the same subjects pre- and post-shift, according to the distribution of variables. Chi-square or Fischer exact-test was performed to compare distribution, when appropriate.

Results

Characteristics of participants were similar between groups and are presented in Table 1. In general, they were young (range 19–50 years old), healthy, completed secondary level of education and were at the job <1 year (range 2–192 months). Only one participant did not have a cooling method at home and 64% reported having air-conditioning. Two participants from the control group reported frequent use of nonsteroidal anti-inflammatory drugs (2–3 times a week).

Feasibility

A total of 35 workers worked in a hot environment and 14 were preselected by management to be eligible to participate. All 14 workers consented to participate. The control group department had 70 workers and 17 agreed to participate out of the 20 invited. Two declined due to blood collection discomfort and one alleged religious reasons. The total enrolment rate was 91%. We finished data collection when the heat group manager said that he could not invite any other workers.

Blood collection and the physiological measures had 100% participation. One participant was not able to collect a urine sample pre- and post-shift and another, post-shift. Laboratory results of total blood count from one

Table 1. Descriptive characteristics of participants (n = 31)

	Heat (n = 14)	Control (n = 17)	p value
Age, years[a]	31 (26–39)	24 (20–34)	0.06
Ethnicity white, n (%)	9 (64)	11 (65)	0.88
Education, years[a]	11 (8–11)	11 (11–11)	0.49
Weight, kg[b]	86.1±13.1	82.5±15.8	0.50
BMI, kg/m^{2}, [b]	28.2±2.9	25.6±4.9	0.10
Active smoker, n (%)	3 (21)	2 (12)	0.63
Low alcohol intake, n (%)*	11 (79)	17 (100)	0.08
Hypertension, n (%)	1 (7)	1 (6)	0.71
Diabetes, n (%)	0 (0)	1 (6)	0.55
Nephrolithiasis, n (%)**	1 (7)	0 (0)	0.45
Months at the same job[a]	5 (3–30)	6 (3.5–9.5)	0.86
Cooling methods at home, n (%)	13 (93)	17 (100)	0.26

[a] Median (interquartile ranges).
[b] Mean ± SD.
* Never or less than once a week.
** If the episode was while working in a hot environment.
BMI, body mass index.

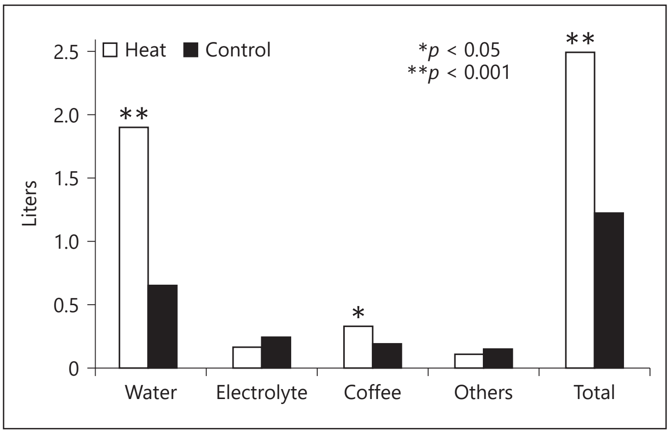

Fig. 1. Self-reported beverage intake during the shift (n = 31).

participant in the control group (pre-shift) were not obtained due to hemolysis. Six post-shift urine evaluations (2 from the heat group) of sodium, potassium, urea, and specific gravity were not measured due to technical problems in the laboratory. All participants completed the heat-related symptoms survey.

Mean time to complete data collection pre-shift was 19.1 ± 4.2 min (range 12–33 min), and the mean post-shift time was 14.3 ± 4.0 min (range 9–25 min). Participants worked 30–50 min less than on a regular day.

In the post-shift survey, 13% reported an atypical workday due to a lighter task than usual. Visit time was considered acceptable, in that 93% and 90% reported being comfortable during the study; 6% were not comfortable during blood collection, and 4% during BP measure. Thirst perception was equivalent at baseline 4.7 (2.4–5.5) in the heat group versus 3.5 (1.4–5.0) in controls and did not change over the shift 2.5 (1.3–4.9) versus 4.7 (2.2–5.5).

Self-reported total beverage intake was twice as high among heat group participants (2.3 [1.7–3.1] vs. 1.2 [0.9–1.4] L in the control group; $p < 0.001$) during the work shift. Plain water was the most consumed fluid, followed by coffee and a fluid-electrolyte replacement beverage (Fig. 1) composed of 34.5 mmol/L of sodium, 5.6 mmol/L of potassium, <7.1 mmol/L of chloride, and <0.8 g/L of carbohydrate. Heat-related symptoms of illness were reported by some participants. Only self-reported excessive sweating was significantly different between groups (29% in heat group and 0% in control group; $p = 0.03$).

Other Results

From 29 participants who collected a urine sample pre-shift, 38% reported it being the first urine of the day (50% of participants from the heat group 27% from the control group). Reported number of urine voids during the shift was not different 2 (2–4) times for the heat group and 2 (1–2) times for the control group ($p = 0.06$).

Table 2. Pre and post-shift comparisons intra and intergroup (n = 31; mean ± SD)

	Heat (n = 14)		Control (n = 17)	
	pre-shift	post-shift	pre-shift	post-shift
SBP, mm Hg	124.7±9.0	121.5±6.3	118.2±9.4	118.7±5.0
DBP, mm Hg	73.4±8.0	69.3±7.8**	67.3±8.4[a]	65.2±7.3
Heart rate, beats/min	63.7±6.1	69.9±8.5**	67.8±8.4	70.4±9.0
Weight, kg	86.1±13.1	85.9±12.9	83.1±15.3	83.0±15.7
Hematocrit, %	44.5±2.3	43.7±2.2	44.9±0.74	43.0±3.0**
Hemoglobin, g/dL	14.6±0.8	14.2±0.8	14.8±1.0	14.1±0.9**
Leucocytes, n/mm^3	7,726±1,745	7,960±1,459*	7,189±1,819	7,991±1,379**
Glucose, mg/dL	90.7±19.8	84.2±10.0	88.3±20.1	83.1±8.6
Serum creatinine, mg/dL	0.95±0.09	1.06±0.1**	0.85±0.13[a]	0.92±0.12**
eGFR, mL/min	106±13	93±11**	119±15[a]	114±16**
Serum uric acid, mg/dL	6.41±1.27	6.62±1.34*	5.13±0.68[b]	5.20±0.55
>7 mg/dL, %	29	43	0[a]	0[a]
Serum sodium, mmol/L	141.3±1.8	141.2±1.8	141.6±1.5	141.1±2.3
Serum potassium, mmol/L	4.52±0.31	4.69±0.42	4.43±0.26	4.57±0.80
Serum osmolarity, mmol/L	293.8±3.9	293.4±4.1	294.2±3.6	293.1±4.8
>290 mmol/L , %	93	100	88	88
Alb/creatinine, mg/g[c]	0.47 (0.34–0.63)	0.44 (0.41–0.65)	0.55 (0.46–0.77)	0.45 (0.4–0.75)
>30 mg/g, %	0	0	0	0
Urinary specific gravity	1.021±0.005	1.023±0.004	1.024±0.005	1.023±0.007
>1.020, %	71	67	73	58
Urinary osmolarity	817±197	940±182	967±181	1,138±310*
>700 mmol/L , %	79	92	82	83

* $p < 0.05$ vs. pre-shift.
** $p < 0.01$ vs. pre shift.
[a] $p < 0.05$ vs. heat group.
[b] $p < 0.001$ vs. heat group.
[c] Median (interquartile ranges).
SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate.

Evaluation of Hydration and Kidney Health Variables

Clinical and laboratory results pre- and post-shift in both groups are shown in Table 2. Diastolic BP and heart rate decreased in the heat group. Body weight did not vary in either group pre- and post-shift. In relation to lab results, serum sodium was maintained with some significant changes in the blood cell count being observed. Almost all participants had serum osmolarity above 290 mmol/L pre-shift (93% in heat group and 88% in control group) and post-shift (100% in heat group and 88% in control group). USG and osmolarity were also high in both moments and increased significantly in the control group.

The heat group had higher serum creatinine at the beginning of the working day (0.95 ± 0.09 vs. 0.85 ± 0.13; $p < 0.05$) and lower estimated glomerular filtration rate (eGFR) compared to the control group (106 ± 13 vs. 119 ± 15 mL/min; $p < 0.05$). Creatinine increased and eGFR decreased after a shift in both groups, but more significantly in the heat group, corresponding to a 12% decrease. No participant had a diagnosis of CKD (eGFR <60 mL/min and/or urinary albumin/creatinine ratio above 30 mg/g). Individual variations are shown in Figure 2.

Serum uric acid was also higher in heat group and increased only among those participants. At the end of the shift, 43% of patients had hyperuricemia (>7 mg/dL) compared to none in the control group.

Environmental Monitoring

Outdoor temperature and relative humidity during the 13 data collection days were mean minimum/maximum, 20.3 and 27.4ºC and mean minimum/maximum relative humidity, 67 and 98%.

WBGT evaluation for the job tasks performed by heat group participants varied from 28.9 in tasks that require a heavy work load to 31.8 in tasks that require a moderate work load.

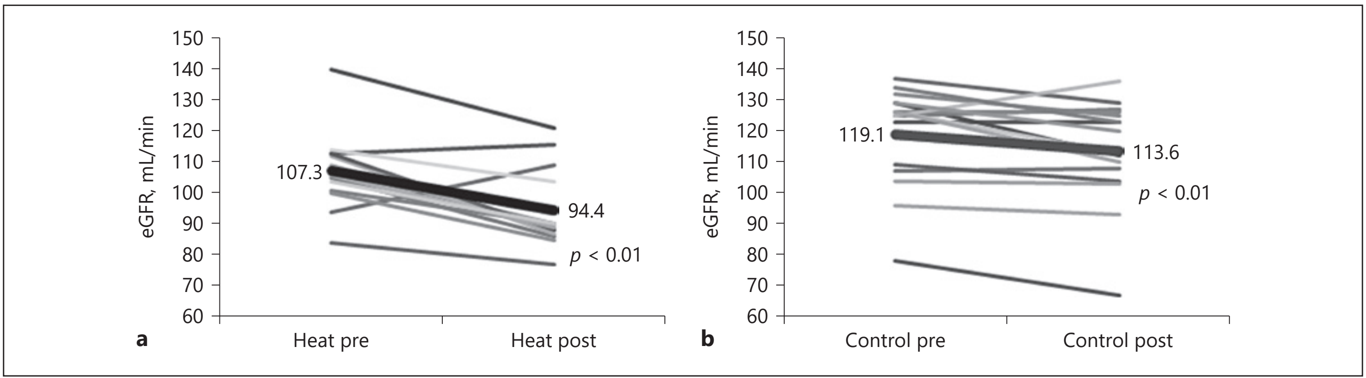

Fig. 2. eGFR pre- and post-shift in heat group (**a**) and control group (**b**). eGFR, estimated glomerular filtration rate.

Discussion

In this in-factory pilot feasibility study, we were unable to fully evaluate recruitment feasibility due to the restricted access to all eligible participants. However, among the workers invited to participate, enrolment rate met our enrolment target of 80%. In addition, we exceeded the target for protocol completion, and the time to complete measurements each day was acceptable to the workers and management.

Enrolling participants in a work environment has been challenging in previous studies for reasons such as high turnover, worksite changes, and constraints imposed by repeated testing within the work shift [23, 24]. Furthermore, the majority of participants answered the post-shift questions positively.

We evaluated hydration status by several techniques, with variable accuracy and applicability since no gold standard is available for such assessment [21, 25, 26]. Acute change in body mass has been postulated as an easy and efficient technique to detect hypohydrated subjects. Body mass loss >1% can compromise thermoregulation and >2% is followed by physical and psychological symptoms [21, 26]. In this investigation, mean body mass was assessed by body weight and did not change over the shift, with no worker having weight loss higher than 2%. However, the mass of liquids and of food consumed during the working day, as well as the mass of excreted solids and liquids affected this measurement, making interpretation difficult.

A very high prevalence of workers with serum and urine osmolarity above euhydration cutoff were observed in both groups, pre- and post-shift evaluation, showing that they began the workday in a hypohydrated status that was not recovered during the shift. A similar result was observed in Australian blast crew personal in surface mining, where 80% had a USG ≥1.020 upon commencing their shift and remained hypohydrated during and after work [27]. However, reference values for euhydration/hypohydration diagnosis are based on studies in athletes and military subjects to determine the effect of heat stress and its influence on performance [21]. It is currently unknown if it is applicable to the hydration assessment of workers exposed to heat stress on a continual basis, in which euhydration may be an incorrect assumption [28].

As expected, the heat group reported a higher intake of water and total beverages and both groups had a low consumption of fluid replacement beverage (median 0.2 L). According to the American National Institute for Occupational Safety and Health guidelines, during prolonged sweating lasting several hours, it is advisable to consume a beverage that contains balanced electrolytes and carbohydrate to replace losses [7]. It has been shown that a beverage with 10–30 mmol/L of sodium and 4–8% of carbohydrate may induce a greater voluntary intake, aid rehydration, improve work performance, and delay the onset of fatigue [29]. Taking it as a reference, in our investigation, sodium content was adequate but carbohydrate was almost absent.

The frequency of self-reported heat-related symptoms in the previous week was lower compared to investigations with sugarcane workers in Mesoamerica [16, 30]. This might reflect the significant differences in general health, socioeconomic profile, and work conditions between these 2 populations. Furthermore, heat acclimation might have contributed to this finding.

Regarding kidney function, our results indicate that indoor working conditions were associated with a decrease in eGFR more pronounced in the heat group. This

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change is in accordance with findings in other study populations exposed to heat stress such as sugarcane workers [31, 32] and athletes in endurance competitions [33], but not under sedentary conditions [34]. Authors considered as potential mechanisms for the kidney function decrease observed in these investigations dehydration, volume depletion, rhabdomyolysis, systemic inflammation, and oxidative stress triggered by environmental heat and the extreme physical activity. It has been postulated that these repeated episodes of injury or illness eventually result in abnormal repair mechanisms and subsequent CKD [14, 35]. In our small sample, the connection between acute episodes and CKD was not possible to explore due to the short follow-up.

A striking difference between groups was in the serum levels of uric acid. In fact, marked hyperuricemia and uricosuria with crystal formation with a rise in both serum and urine uric acid during the workday have been documented in sugarcane workers [32, 36]. Together, these findings contribute to the hypothesis that uric acid associated with high vasopressin expression may be important etiologic factors of CKDu [31].

WBGT threshold limit values indicated that workers should be on work/rest cycles of 50% work + 50% rest or 25% work + 75% rest each hour depending on the task, to reduce the risk of heat illness or injury. In our setting, although there are air-conditioned rooms for cooling near work sites, workers were not on regular work/rest cycles.

Our investigation has some limitations. First, management selected the workers who could be approached for the study due to the factory's personnel department concerns of misinterpretation. This influenced the number of participants and possibly the enrolment rate. Second, serum and urinary osmolarity were calculated rather than measured directly. Third, hydration status is better evaluated by first-morning urine, but its values can provide misleading information if obtained during rehydration periods [21], and plasma osmolality does not accurately detect whole-body hydration, especially when total body water, fluid intake, and fluid loss are fluctuating [25]. Fourth, lack of control for body gains and losses affects interpretation of body mass change. Finally, usual beverage intake and urine habits could be influenced by data collection awareness. Our study had favorable management involvement and support and appropriate infrastructure for data collection. These data may not be generalized to other settings due to the favorable environment we observed as the high department manager's involvement and an appropriate infrastructure in the factory setting for data collection. The present results encourage further investigations of hydration status and kidney health in factories and other settings with similar conditions.

Conclusion

Research in factory workers is challenging and requires buy-in from management. We were able to demonstrate feasibility for enrolment and protocol completion for a preselected group of workers. We demonstrated the negative physiological acute effects on kidney function of indoor heat stress. Further research is needed to study the effects of indoor heat on kidney function both in the short and long term in larger studies.

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Safe Water and Healthy Hydration

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Safe Water Community Project in Jalisco, Mexico

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Keywords
Acute kidney injury · Diarrhea · Chronic kidney disease

Abstract
Few studies have assessed kidney function in patients with gastrointestinal infections in low-resource settings. Although dehydration is a frequent complication of acute diarrhea, we do not know the frequency and severity of acute kidney injury (AKI) in this context. A high prevalence of chronic kidney disease (CKD) has been reported among the inhabitants of poor communities in Poncitlan, Mexico. Polluted drinking water has been implicated as a probable cause. These communities report a high mortality associated with gastrointestinal infection. It is possible that a high incidence of waterborne disease and consequent more episodes of AKI might contribute to the high prevalence of CKD in this population. In this study, we aim to determine the association between the use of unsafe water and the incidence of acute diarrhea and AKI, and to determine if the provision of clean water decreases these complications. The study will be conducted in 3 communities of the municipality of Poncitlan. Initially, we will determine the water, sanitation, and hygiene (WASH) characteristics in the population and evaluate the incidence of diarrheal disease. In the observation phase, outcomes will be assessed after families receive training in WASH techniques, but before they are provided with clean water. In the intervention phase, outcomes will be assessed after clean water is provided.

Introduction

The Global Burden of Disease study estimated that diarrhea was a leading cause of death among all ages: 1.31 million deaths, in 2015 [1]. Several studies have implicated diarrhea as a risk factor for malnutrition and impaired physical growth, and some have suggested that it might also impair cognitive development [2]. Approximately 88% of diarrhea-associated deaths are attributable to unsafe water, inadequate sanitation or insuffient hygiene, and approximately 2.4 billion people globally have no access to basic sanitation [3, 4]. Microbial contamination is widespread in lower- and middle-income countries and affects all water source types, including piped supplies. Guidelines for Drinking-Water Quality recommend that fecal indicator bacteria, preferably *E. coli* or alternatively thermotolerant coliforms, should not be detectable in any 100 mL drinking water sample (WHO 2011) [5]. Approximately 1.8 billion people globally use a source of drinking

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Table 1. Socioeconomic indicators of affected communities

	Marginality index	Population, *n*	Illiterate, %	Incomplete primary school, %	Households without sewage system, %	Households without running water, %	Households with dirt floor, %
Poncitlan	Medium	40,827	7.3	23.4	1.2	5.2	3.4
San Pedro ltzican	High	4,478	21.6	47.9	5.3	4.6	10.4
Mezcala	High	3,896	10.5	35.5	3.0	2.3	10.2
Agua Caliente	High	988	7.79	40.8	28.7	40.9	15.0

Data from references [11, 12].

water that suffers from fecal contamination; of these, 1.1 billion drink water that is of at least "moderate" risk (>10 *E. coli* or thermotolerant coliforms per 100 mL).

Acute kidney injury (AKI) is a frequent complication of acute diarrhea and gastrointestinal infections [6], but very few studies have assessed kidney function in patients with gastrointestinal infections in low-resource areas and rural communities with no or very limited access to health care [7, 8]. The impact of AKI development on the short- and long-term outcomes in patients with diarrheal disease is unknown.

In this project, we aim to determine the incidence of gastroenteritis, waterborne diseases, and AKI in 3 communities that have a high penetration of unsafe water and to evaluate the effect of safe water provision on these issues. We have selected 3 communities from the municipality of Poncitlan, Jalisco, Mexico, based on the high prevalence of gastroenteritis and waterborne disease and the knowledge of the water utilization source. We will partner with the Secretaria de Salud Jalisco (SSJ), in order to obtain information on the quality of water and baseline data on the epidemiology of gastroenteritis and waterborne disease.

The study will be conducted in the communities of San Pedro Itzican, Mezcala, and Agua Caliente located along the Lake Chapala lakeshore in the municipality of Poncitlan. In these communities, water quality has been an issue for many years. Lake Chapala is the ultimate receptor of a great variety of contaminants, including pesticides, industrial residues, and heavy metals such as chromium, lead, zinc, and mercury. Local sources of pollution are also visible [9]. The absence of an adequate sewer system causes Chapala lake water to be contaminated. Wells drilled to avoid the use of lake water did not resolve the issue, as water from wells is contaminated by water springs with a high content of arsenic and other harmful elements. Over the years, these communities have shown a high mortality rate, secondary to intestinal infection and malnutrition [10]. The socioeconomic indicators in these communities show an alarming high marginality index, a high illiteracy rate, and incomplete primary school rates; a large percentage of households lack both a sewage system and tap water, and a high percentage of homes have dirt floors [11, 12] (Table 1).

These communities have a high prevalence of chronic kidney disease (CKD) of unknown etiology. Popular opinion in the lay media has implicated polluted drinking water as a probable cause [13]. Since 2006, the Hospitales Civiles Foundation has used mobile units to assess the presence of CKD in the state of Jalisco. Trained personnel using mobile units travel to rural and urban areas to collect demographic and clinical data, in addition to blood and urine samples for serum chemistry and dipstick urinalysis [14]. This screening program has shown a high prevalence of CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2) and proteinuria in Poncitlan, two-fold and 3-fold higher, respectively, as compared to the adult population in other Jalisco municipalities [15]. In children, although the prevalence of CKD was similar to other Jalisco municipalities, the prevalence of proteinuria was 10 times higher [16]. Similarly, a recent cross-sectional study in children residing in these communities reported a prevalence of albuminuria and CKD of 45% and 33%, respectively; these rates of albuminuria are 3–5 times higher than reported in the state of Jalisco and the international literature [17]. Information from Jalisco's vital statistics shows a high prevalence of intestinal infection, associated with a high mortality rate among children under 5 years of age [10]. It is possible that a high incidence of waterborne disease, and consequently more frequent episodes of AKI, contribute to the high prevalence of proteinuria and CKD in this population. The role of heavy metals and other contaminants in the water may also be important determinants of this outcome [9].

The primary objectives of the study are to evaluate the association between safe water provision and gastroenteritis frequency, waterborne diseases, and kidney disease in

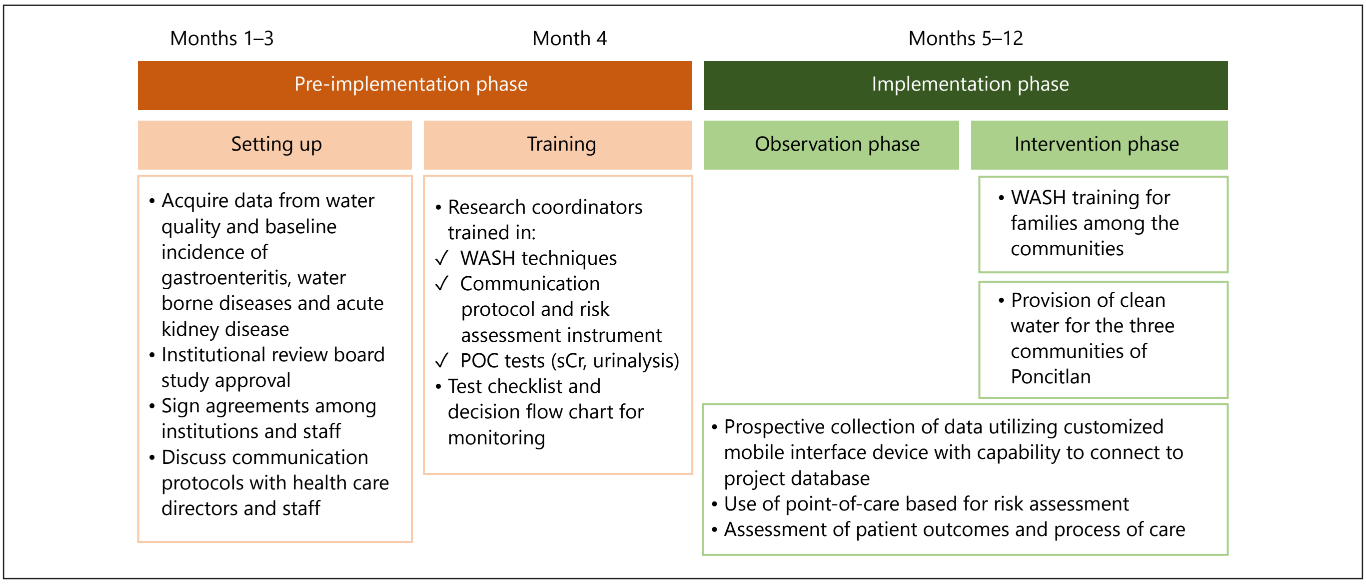

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Fig. 1. Study overview. WASH, water, sanitation and hygiene; POC, point of care; sCr, serum creatinine.

these communities. We have hypothesized that the use of unsafe water is associated with an increased incidence of gastroenteritis and waterborne diseases and leads to high prevalence of AKI. We aim to determine the frequency of AKI in patients with diarrheal disease based on serum creatinine (sCr) and biomarkers of kidney injury. Our secondary objectives are to determine the barriers for safe water use, to determine the association between water, sanitation, and hygiene (WASH) parameters and the prevalence of diarrheal illness. In addition, we will assess the effect of an educational strategy for WASH on diarrheal illness.

Materials and Methods

Preimplementation Phase

The study will be conducted in the communities of San Pedro Itzican, Mezcala, and Agua Caliente located along the Lake Chapala lakeshore in the municipality of Poncitlan, with a total population of approximately 10,000 individuals. Before study implementation, we will determine the WASH characteristics in the target population and evaluate the incidence of diarrheal disease in these communities. Following authorization from the SSJ and study approval from the Hospital Civil de Guadalajara Ethics and Research Committee, we will acquire data on water quality at different levels of distribution and utilization. Communication protocols among health-care facilities, families, and research coordinators will be established via the SSJ. We will train research coordinators in WASH techniques, in the validated risk assessment instrument, the performance of point of care (POC) tests, and for the collection and processing of serum and urine samples for storage for future biomarker assessment. All health providers and relevant staff will be trained in the protocol-based management of diarrheal disease and AKI that is appropriate to the setting in which they work. Providers will also be educated regarding the use of oral rehydration fluids for the treatment of dehydration, following the guidelines of Mexico's Ministry of Health [18]. The SSJ will help to coordinate these training sessions. All families will be taught WASH best practices (Fig. 1).

Implementation Phase

The implementation phase will consist of 2 parts. During the observation (first) phase, study outcomes will be assessed after families receive training in WASH techniques, but before they are provided with clean water. During the intervention (second) phase, study outcomes will be assessed after clean water is provided to the community.

Observation Phase

Patients with signs and symptoms of diarrheal disease will be encouraged to contact the local health-care center and/or study research coordinator. Patients with CKD stage 5 or in chronic dialysis and those with solid organ transplant will not be candidates for study participation. Patients meeting these criteria will be screened by the research coordinator and asked for consent. Patients (or surrogates) who sign informed consent will have a POC test for sCr and urinalysis by dipstick.

The results of the POC tests will be given to the health-care provider, who will be responsible for informing the patient of the results. The health-care provider will be given the accepted normal range of values for adults and children (adults: sCr 0.6–1.2 mg/dL; 53–105 μmol/L [19]; children 0–12 years old 0.0–0.7 mg/dL; 0–62 μmol/L, I) [20]. The health-care provider, however, will decide if the results are in the normal range according to the normative values and patient's comorbidities, age, and overall health characteristics. All health-care decisions will be made by the local health authorities.

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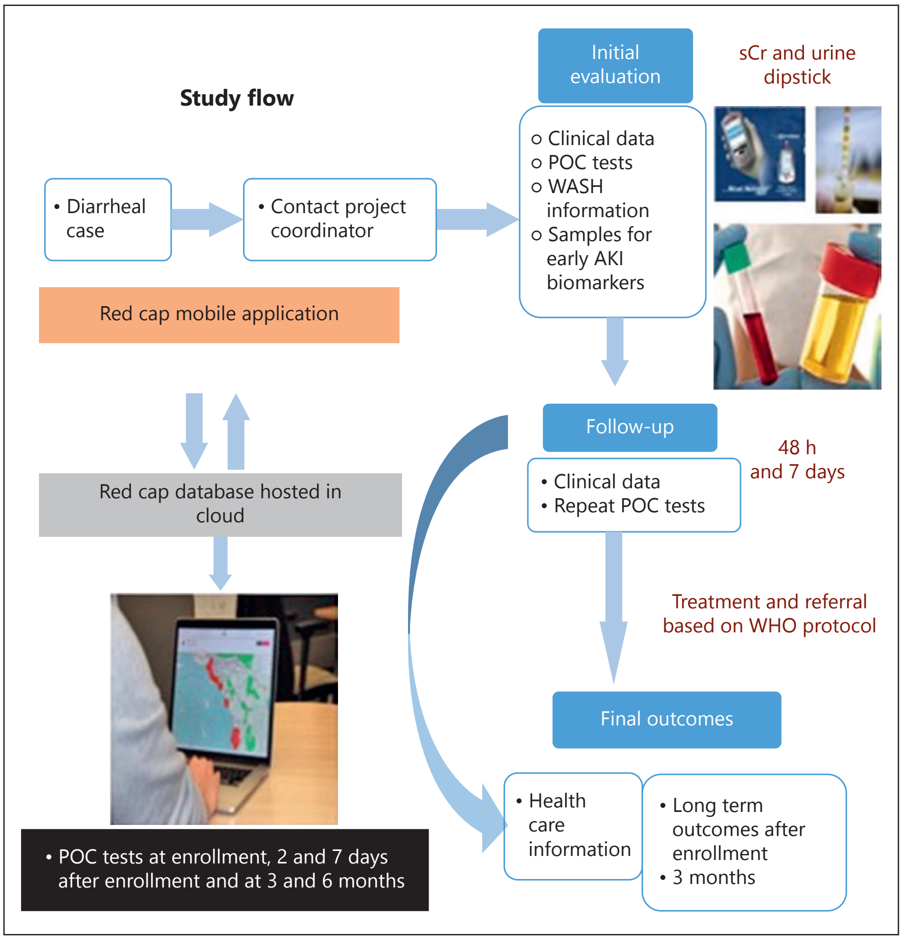

Fig. 2. Study flow during implementation phase. WASH, water, sanitation, and hygiene; POC, point of care; sCr, serum creatinine.

Blood and urine samples will be collected and stored for future biomarker analysis (Table 2). All enrolled patients will complete a clinical and WASH assessment and will be tracked throughout their clinical course by location (i.e., health-care center, hospital, and home). Outcomes will be recorded for 3 months following the initial health-care evaluation.

Patient level data will be tracked by the project research coordinator via communication with health-care facilities and families in the community. All relevant clinical data and the results of the POC test will be recorded in the electronic case report forms. Data will be recorded using the Red Cap Mobile Application. All captured information will be kept in a data repository site. The forms in Red Cap Mobile APP will be adapted for use in the community setting to capture data on the incidence, management and outcomes associated with diarrheal disease, dehydration, and AKI (Fig. 2).

Intervention Phase

In the second phase of the study, safe water will be distributed to the communities. We will repeat research coordinator and health provider training for the protocol-based management of diarrheal disease and AKI. The same study flow will be in place, and we will compare the incidence and severity of diarrheal diseases and patient outcomes. We will analyze the incidence of diarrheal disease and AKI based on whether or not patient and families are following WASH and also by water source.

Table 2. Study schedule and measurements for implementation phase

	Time point			
	enrollment	48 h	7 days	3 months
Medical history and physical assessment				
Physical exam	×	×	×	×
Blood pressure	×	×	×	×
Medication review	×	×	×	×
Renal functional assessment				
POC test sCr	×	×	×	×
Urinalysis	×	×	×	×
Urine and blood collection				
Biorepository for biomarkers	×	×	×	×
Other assessments				
Weight and height	×			×
WASH questionnaire	×			×

POC, point of care; sCr, serum creatinine; WASH, water, sanitation and hygiene.

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Health-care providers will track patient clinical status and renal outcomes at 48 h, 7 days, and 3 months after enrollment. Urine and serum samples will be collected at all follow-up time points.

Analytical Plan

Observation Phase

We will capture data on the course of patients with signs and symptoms of diarrheal disease and gastrointestinal infections. During this phase, we will define the gaps in knowledge and local barriers for WASH techniques and use of clean water. We will determine the frequency of specific risk factors for acute and CKDs. We will describe the WASH characteristics of the families enrolled in the study and correlate them with patient characteristics and risk factors for kidney diseases. We expect to establish the baseline frequency of AKI development, progression to more severe stages of AKI, and development of CKDs. Based on preliminary data from the SSJ, we anticipate that we will need to enroll 200 patients during this phase in order to obtain an adequate data sample (Table 2).

Intervention Phase

Safe drinking water will be provided for the 3 communities. We will evaluate the penetration and the barriers to use of safe water. We will compare the frequency of diarrheal disease, AKI, and severity of renal dysfunction between the observation and intervention phases. We will perform an interim analysis after the enrollment of 200 patients and 400 patients during this phase. We will continue this phase in the second and third year, aiming to complete enrollment of 800 patients, if the interim analysis does not indicate a need for early cessation of the study.

After study completion, we will assess the serum and urine samples for biomarkers of glomerular and tubular function. We will assess a panel of tubular markers representing concentration, reabsorption, and secretion function, which correlate with AKI severity or CKD progression (Table 2). The sequential assessment of these biomarkers, at initiation and during the course of the disease process, will provide us with a unique opportunity to understand their pattern of change during gastrointestinal diseases with and without AKI. We will evaluate how these changes correlate with AKI development, severity, and recovery.

Conclusion

In summary, the study will provide an opportunity (a) to demonstrate that the use of unsafe water is associated with an increased incidence of gastroenteritis and waterborne diseases leading to episodes of AKI and (b) to determine if the provision of clean water to communities with high penetration of polluted water is associated with a decreased incidence of these complications.

Statement of Ethics

Subjects (or their parents or guardians) will give their written informed consent. The study has been submitted for approval to the Hospital Civil de Guadalajara Fray Antonio Alcalde Ethics and Research Committee.

Disclosure Statement

The authors have no conflicts of interest to declare. E.M., M.V.R., and G.G.-G. received travel expenses and registration fee from Danone Research to participate in the 2018 Hydration for Health Scientific Conference. All authors have contributed to the conception and design of the work and will equally contribute to the acquisition, analysis, and interpretation of data; drafting the work; approving the version to be published; and will be accountable for all aspects of the work.

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Hydration in Children

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Cognitive Assessments in Hydration Research Involving Children: Methods and Considerations

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Keywords

Water · Adolescents · Neuropsychological assessment · Executive function · Neuroimaging · Academic achievement

Abstract

The effects of optimal and insufficient hydration on human health have received increasing investigation in recent years. Specifically, water is an essential nutrient for human health, and the importance of hydration on cognition has continued to attract research interest over the last decade. Despite this focus, children remain a relatively understudied population relative to the effects of hydration on cognition. Of those studies investigating children, findings have been inconsistent, resulting from utilizing a wide variety of cognitive domains and cognitive assessments, as well as varied hydration protocols. Here, our aim is to create a primer for assessing cognition during hydration research in children. Specifically, we review the definition of cognition and the domains of which it is composed, how cognition has been measured in both field- and laboratory-based assessments, results from neuroimaging methods, and the relationship between hydration and academic achievement in children. Lastly, future research considerations are discussed.

Introduction

The study of hydration and nutrition influences on human brain and cognition is a developing field of study. Much of the current literature has focused either on the effects of dehydration on health outcomes [1] or the detriments of dehydration on cognition. Few studies have sought to investigate the benefits of improved hydration on cognition, and even fewer have focused on children [see 2, 3 for reviews]. Within this limited literature, methods for assessing or modulating hydration have varied across child populations, with the majority focusing either on associations of urinary biomarkers, such as osmolality [4], or acute manipulations whereby hydration is manipulated via water intake and compared to addition-

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al intake conditions or control groups [5–12]. However, it is important to note that not all studies provide measures of urinary biomarkers. Where possible these measures will be described. To date, only one study has focused on the manipulation of dehydration by inducing reductions in body mass through thermal exercise, and this study was conducted with adolescent children [13]. Additional methods have included measuring dietary water intake via survey [14] and a mouth rinsing/drying protocol [15]. While methods of manipulation have differed, all studies have endeavored to explore how varied areas of cognition are affected by changes of body water. Accordingly, the focus of this article is not to provide an extensive review of the literature, which is provided elsewhere [16], but rather to serve as a primer for assessing cognition of children in studies aimed at understanding how optimal and insufficient hydration may affect cognitive and brain health.

Cognition

Cognition is a vast, umbrella term, which is generally thought of as how people think, learn, perceive, and remember information [17]. Many domains exist within cognition including sensation, perception, consciousness, attention, memory, language, problem-solving, creativity, decision-making, reasoning [see 17 for review], and executive function or cognitive control [18]. Additionally, executive function is typically thought to be composed of inhibitory control, working memory, and cognitive flexibility [18], but more broadly reflects higher-order cognitive operations underlying the intentional component of environmental interactions. As such, the paradigms used to study the field of cognition are equally as vast as the term itself.

Unsurprisingly, within the extant literature of hydration and cognition in children, there appears to be differential effects of drinking water, urinary markers, or mouth rinsing on different aspects of cognition. That is, simply being better hydrated does not necessarily improve cognition in the broad sense, and any improvements might depend on how hydration is manipulated, measured, and what aspects of cognition are measured. Broadly speaking, areas of cognition that have illustrated the benefits of improved hydration and acute water intake include attention [7, 9–12], short-term memory [4, 5, 7, 9], delayed memory [6], visual search [9, 10, 12, 15], and executive function [14]. However, not all studies have supported a relationship between various hydration measures and cognition, with some reporting null or negative findings for short-term memory [9, 11, 12, 15]. Of the studies referenced above, only 3 have collected urinary markers of hydration. A cross-sectional study conducted by Bar-David et al. [4] found that insufficient hydration, as indicated by urine osmolality >800 mOsmol/kg, was associated with poorer short-term memory. Similarly, Fadda et al. [5] conducted an intervention study where one group of children received supplemental water and the control group did not receive any additional water. Their findings indicated that improved urinary markers of hydration were associated with improved short-term memory. However, it is worth noting that better performance in verbal analogies was associated with insufficient hydration [5]. In another intervention, Perry et al. [9] compared children who received water to those who did not, while controlling for baseline measures of urine concentration. They found that children who received water and showed small changes in urine concentration performed better on measures of attention, short-term memory, and visual search. However, children that received water and showed large changes in urine concentration did not show improvements, and in the case of memory showed a decrease in performance [9].

To unpack the broad relationship observed for hydration and cognition in the recent literature, the following sections will discuss the different methods by which cognition has been measured, including neuropsychological tests, academic achievement, laboratory-based cognitive tests, and neuroimaging tools.

Neuropsychological Tests

Many paradigms with which to study cognition exist in the literature. Table 1 provides a brief overview of the different domains of cognition along with common neuropsychological and cognitive tests that have been used to assess them. However, the table is limited to a brief list of assessment tools, as more extensive reviews are available elsewhere in the literature [e.g., 19]. Neuropsychological tests have traditionally been delivered via paper-and-pencil assessments and many times are part of larger standardized batteries. Many of these tests were initially designed as part of larger neuropsychological assessments administered by a trained neuropsychologist. However, in recent years, multiple tests have been used in laboratory- and field-based research to measure different aspects of cognition. One significant advantage of these tasks for field-based research is that the paper-and-pencil

Table 1. Neuropsychological, cognitive, and academic tests

Example tasks	Subdomain	Test type	Example in hydration literature	Result
Executive functions				
Eriksen flanker task	Inhibitory control	Cognitive test	Khan et al. [14], 2015	Greater water intake, greater performance
Making groups		Neuropsychological test	Bar-David et al. [4], 2005	No effect
Attention				
Spot the difference, direct	Visual attention	Neuropsychological test	Trinies et al. [11], 2016	Water consumption group improved performance
			Edmonds and Burford [7], 2009	Water consumption group improved performance
			Edmonds and Jeffes [8], 2009	Improved performance after water consumption
Deux de Barrage	Selective attention	Neuropsychological test	Fadda et al. [5], 2012	No effect
Shakow	Sustained attention	Neuropsychological test	Benton and Burgess [6], 2009	No effect
Ravin Rabbids	Visual attention/ Visuomotor performance	Video game	Booth et al. [10], 2012	Water consumption group improved performance
Memory				
Spot the difference, indirect	Short-term memory	Neuropsychological test	Trinies et al. [11], 2016	No effect
			Edmonds and Burford [7], 2009	Water consumption group improved performance
			Edmonds and Jeffes [8], 2009	No effect
Auditory number span	Short-term memory	Neuropsychological test	Fadda et al. [5], 2012	Water consumption group improved performance
			Bar-David et al. [4], 2005	Hydrated students had better performance
Recall of objects (British Ability Scale)	Delayed memory	Neuropsychological test	Benton and Burgess [6], 2009	Improved performance after water consumption
Story memory	Delayed memory	Neuropsychological test	Edmonds and Burford [7], 2009	No effect
Delayed match to sample	Short-term memory	Neuropsychological test	Perry et al. [9], 2015	No effect
Digit span, forwards and backwards	Attention/Working memory	Neuropsychological test	Perry et al. [9], 2015	Improved performance after water consumption in low change group
Forward digit span	Short-term memory	Neuropsychological test	Trinies et al. [11], 2016	No effect
			Edmonds et al. [12], 2017	No effect
			Edmonds et al. [15], 2018	No effect
Backward digit span	Short-term memory/ Working memory	Neuropsychological test	Trinies et al. [11], 2016	No effect
Visual perception				
Mentally manipulate 2 dimensional figures	Visual spatial ability	Neuropsychological test	Fadda et al. [5], 2012	No effect
Letter cancellation	Visual search	Neuropsychological test	Edmonds and Burford [7], 2009	Water consumption group improved performance
			Booth et al. [10], 2012	Water consumption group improved performance
			Edmonds et al. [12], 2017	Water consumption group improved performance
			Edmonds et al. [15], 2018	Mouth rinsing group improved performance
Pair cancellation	Visual search	Neuropsychological test	Perry et al. [9], 2015	Improved performance after water consumption in low change group
Motor function				
Line tracing	Visuomotor performance	Neuropsychological test	Edmonds and Burford [7], 2009	No effect
			Edmonds and Jeffes [8], 2009	No effect
			Trinies et al. [11], 2016	No effect
Ball catching task	Visuomotor performance	Physical test	Booth et al. [10], 2012	No effect
Step ups	Gross motor skills	Physical test	Booth et al. [10], 2012	No effect

delivery is relatively easy to administer to larger groups of children; this affords an opportunity to collect larger amounts of data over shorter periods of time. Another advantage is that these tests go through extensive validity and reliability testing and provide referenced norms and percentile values, allowing for easier comparison across studies. However, it is important to consider that (a) many of these neuropsychological batteries were designed to detect neuropathology [20], as opposed to smaller (health- or lifestyle-based) differences within a population and (b) many neuropsychological test manuals indicate that the examiner should have appropriate training in neuropsychology when used for neuropsychological assessment.

Cognitive Tests

Laboratory-based cognitive tests are typically more complicated to use in school settings because they generally require the use of a computer or tablet to present stimuli on a screen; also, behavioral responses based on task instructions to the participant are necessary to provide a quantifiable set of performance outcomes. Such experiments typically occur between one participant and one experimenter, requiring considerable time for data collection and analyses. However, these laboratory-based tests afford substantially more control over the environment and allow for the opportunity to manipulate presentation parameters of the task to best suit the particular population that is being sampled (i.e., as opposed to a "one size fits all" approach that may be a limitation of some neuropsychological tests). In addition, many computer-based cognitive tasks require a large number of trials during test administration in order to gain the requisite number of samples to assess specific aspects of behavior or task performance (e.g., response speed, variability, and accuracy). As such, the benefits of this type of cognitive testing affords a more nuanced analysis of cognitive processes, allowing for a more precise ability to detect differences in cognition as a function of changes in hydration. An additional benefit is that these types of tests pair well with neuroimaging measures for simultaneous collection, which will be discussed below.

The NIH Toolbox® (http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox) is a relatively easy platform through which to administer different cognitive tasks and a large variety of surveys. Conveniently, this toolbox uses an iPad®, which affords easier administration in field settings such as schools. Executive function is one domain of cognition that has been frequently studied using laboratory-based cognitive tests. Unfortunately, there is a lack of research investigating hydration effects on executive function among children. In the only published study, Khan et al. [14] performed a median split of participants based on their reported total water intake, as measured via a 3-day diet record, and found that the higher consumption group exhibited shorter reaction times on a flanker task that manipulated inhibitory control, one aspect of executive function. In a similar vein, no studies to date have used laboratory-based measures of memory. Yet, measures of executive function and memory are affected by other health behaviors such as fitness [21], weight status [22], diet [23], and are integrally associated with development [24, 25]. Table 1 provides a list of executive function measures, but also see [26] for a list of other measurements that have been used.

Neuroimaging

Neuroimaging tools provide an additional avenue of research for delivering insight into the effects of hydration on brain health. Although not directly a measure of cognition, neuroimaging tools allow us to better understand brain outcomes (i.e., neural architecture, function, and network connectivity) that subserve cognitive operations. Much like the study of cognition, study of the human brain includes a variety of imaging approaches, including magnetic resonance imaging (MRI), functional MRI, electroencephalography and event-related brain potentials, magnetoencephalography, and functional near infrared spectroscopy. Previous MRI work has demonstrated that brain regions that support executive function [21, 24, 25] and memory [21] undergo protracted development throughout childhood and appear sensitive to other health behaviors such as fitness [21].

However, only one study has endeavored to use neuroimaging techniques to better understand brain mechanisms underlying hydration-induced changes in cognition. Kempton et al. [13] utilized an acute thermal-exercise dehydration protocol designed to decrease body mass by 1–2% in 90 min. Dehydration was associated with lateral ventricular volume increase and greater functional activation during the tower of London task (a measure of planning), with no differences in behavioral performance. From the adult literature, Streitbürger et al. [27] also found that not only did dehydration cause ventricular volume increase but also hyperhydration caused ventricular volume decrease compared to normal hydration. Dehydration is accompanied by reduced blood volume and increased serum osmolality, which results in reduced brain volume and cell shrinkage, leading to increased ventricular volume [13, 27]. Thus, dehydration is associated with gross measures of brain structures (ventricular volume) and may relate to changes in executive functioning, such as planning [13].

Academic Achievement and other Externally Valid Tasks

Academic achievement assessments share many of the same benefits as neuropsychological tests, in that they are valid and reliable, and can be easily administered via paper-and-pencil format to larger groups of children. Despite these benefits, there has been a surprising lack of investigation into hydration and academic measures, to date. Yet, examination of the extant literature indicates that measures of academic performance are affected by other health outcomes and behaviors such as physical activity, fitness [28], diet [29], and excess adiposity [30]. The varieties of academic tests include subject-based grades or school grade-point average, standardized achievement tests, released state standardized test marks, and others. For standardized tests of academic performance, the Wide Range Achievement Test – 4th edition [31], Kaufman Test of Educational Achievement – 3rd edition [32], and the Woodcock-Johnson – 4th edition [33] are examples of age-normed, paper-and-pencil batteries that measure reading, spelling, and math skills; these have been used to assess academic achievement using similar research paradigms.

One additional investigation of hydration effects on real-world cognitive outcomes in adults examined university students who brought water bottles with them to exams. Having a water bottle was associated with achieving higher scores on exams, even after adjusting for baseline academic ability, as measured by previously assigned grades [34].

Many of the tasks mentioned above are designed to focus on specific cognitive abilities, thus their measurement as well as the way they are administered may limit ecological (external) validity. That is, no prior research has endeavored (a) to use ecologically valid tests designed for use in environments (e.g., school) that children typically frequent or (b) how hydration or dehydration may influence ability to perform cognitive tasks within these environments. Examples of ecologically valid tasks could include paying attention in the classroom, academic test taking, completing homework, learning class material, navigating attentionally demanding environments, and even street crossing. In the case of street crossing, prior research had children with higher and lower fitness levels cross a virtual street while either undistracted, listening to music, or conversing on a hands-free cellphone. Higher fit children were better able to safely cross the street across the three conditions compared to lower fit children, who performed more poorly under the two distraction conditions [35]. Although promising, additional research is needed to better understand the depth of associations between hydration and dehydration with cognition across a variety of real-world settings.

Conclusion

The extant literature regarding how hydration affects cognition in children continues to emerge. However, there is still much to explore to better understand the importance of this nutrient for cognition and brain health. The current literature is largely comprised of a variety of neuropsychological paper-and-pencil tasks with few examples of supplemental neuroimaging techniques and laboratory-based cognitive assessments. As such, future studies should expand the type of measurements to other neuropsychological and cognitive tests. This research area is ripe for the use of neuroimaging methods to better inform the nature of the effects of optimal and insufficient hydration on brain health (e.g., brain structure and function). Surprisingly, to date, a lack of research investigating the effects of hydration on academic performance also exists. Additionally, in studies where hydration is modulated, there is a lack of consistency in the manipulation protocols, whether by water provision or dehydration. These varied methods may confound the current results and make interpretation and comparison across studies difficult. Not all studies have included assessments of hydration and instead assume that hydration modulates with water intake. Including hydration assessment allows for better understanding of the effectiveness of the water intake protocol, as well as individual differences in hydration modulation and their effects on cognition. Future research would benefit from different measures of hydration, including dehydration, optimal hydration, and hydration process. In particular, hydration process has been found to be important for many different health outcomes in adults, but its importance for cognition in children remains largely unexplored [36]. In summary, the current state of the literature is sparse and would benefit from a more programmatic approach to assessing the effects of optimal and insufficient hydration on cognition and brain functions using a variety of laboratory and field techniques, ranging from brain imaging to academic behaviors.

Disclosure Statement

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Climate Change, Labor, and Kidney Health

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Climate Change and the Kidney

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Keywords
Global warming · Heatstroke · Heat waves · Mesoamerican nephropathy · Kidney stones

Abstract
The worldwide increase in temperature has resulted in a marked increase in heat waves (heat extremes) that carries a markedly increased risk for morbidity and mortality. The kidney has a unique role not only in protecting the host from heat and dehydration but also is an important site of heat-associated disease. Here we review the potential impact of global warming and heat extremes on kidney diseases. High temperatures can result in increased core temperatures, dehydration, and blood hyperosmolality. Heatstroke (both clinical and subclinical whole-body hyperthermia) may have a major role in causing both acute kidney disease, leading to increased risk of acute kidney injury from rhabdomyolysis, or heat-induced inflammatory injury to the kidney. Recurrent heat and dehydration can result in chronic kidney disease (CKD) in animals and theoretically plays a role in epidemics of CKD developing in hot regions of the world where workers are exposed to extreme heat. Heat stress and dehydration also has a role in kidney stone formation, and poor hydration habits may increase the risk for recurrent urinary tract infections. The resultant social and economic consequences include disability and loss of productivity and employment. Given the rise in world temperatures, there is a major need to better understand how heat stress can induce kidney disease, how best to provide adequate hydration, and ways to reduce the negative effects of chronic heat exposure.

Introduction

Increasing worldwide temperatures are now well documented, and the mean temperature increase in the last 50 years approximates 0.8 °Centigrade. While the absolute rise in temperature may not seem large, it is already having major effects on human health [1]. One of the more striking consequences is a marked increase in extreme heat events, termed heat waves [2–4]. Heat waves are the

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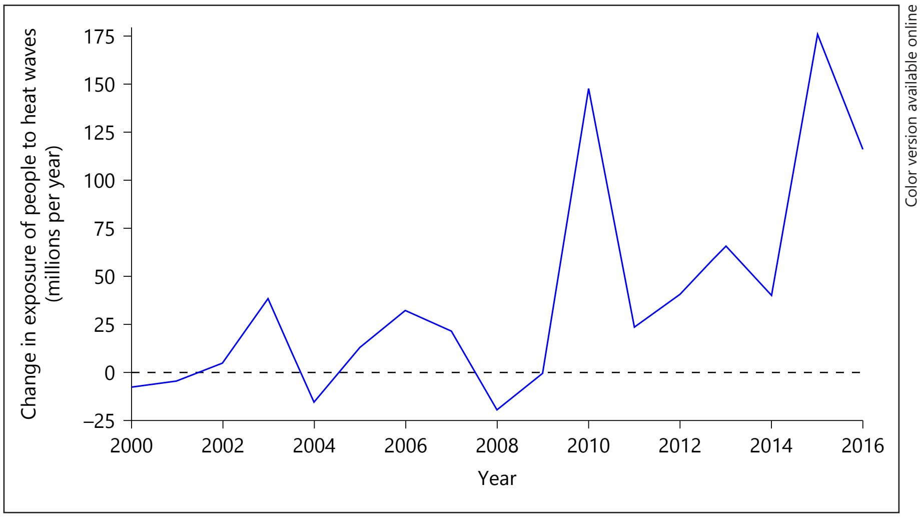

Fig. 1. Change in heat wave exposure (in individuals >65 years old) relative to the 1986–2008 average. Here heat waves are defined as a period of 3 days or more in which the minimal temperature exceeds the 99th percentile of the average temperature between 1986 and 2008, and the population was limited to individuals 65 years or older. Reused with permission from the Lancet [7].

most common cause of mortality of all weather-related events in the United States (including tornados, hurricanes, and lightning strikes) [5]. Heat waves are also among the top 10 worldwide causes of death by natural disasters between 1980 and 2017 (Table 1). Different definitions have been used to classify heat waves, but one of the more common definitions is a temperature that is 5 °C greater than the mean high temperature for a given day, and one that persists for at least 5 days [6]. Numerous studies have reported a dramatic increase in heat waves worldwide [7] (Fig. 1). For example, one estimate suggests that in 2015 alone there were 175 million more people exposed to heat waves as a consequence of climate change [7]. Heat waves are dangerous not only because of the risk of overheating the human body but also due to increased mortality of individuals with cardiovascular and respiratory disorders [6]. One of the worse heat waves was the one that struck Europe in August 2003, resulting in 73,000 deaths [8]. However, heat waves have caused significant mortality throughout the world, including Chicago in 1995 [9], Andhra Pradesh in 2014 and 2015 [10, 11], and Karachi, Pakistan in 2015 [12]. Heat waves and extreme heat also affect labor performance and efficiency [13] and may affect crop performance [14]. Some heat waves have been associated with such extreme temperatures that even wildlife are endangered, and there are predictions that in the future some parts of the world could become so hot that they will become uninhabitable [15–17]. Thus, regulating body temperature is a key to survival. Maintaining a well-hydrated state is critical to this process, but it is of additional concern that the availability of safe water supplies is dwindling worldwide. Indeed, there is now evidence that as much as 10% of the world population faces a serious shortage of water availability [18, 19]. In addition, studies suggest that many individuals, including children and adolescents, who do have access to potable water are considered to be underhydrated [20].

Table 1. The most fatal natural disasters between 1980 and 2017

Event (location, date)	Deaths
Tsunami/Earthquake (Thailand, 2004)	220,000
Earthquake (Haiti, 2010)	159,000
Cyclone, storm surge (Myanmar, 2008)	140,000
Cyclone, storm Surge (Bangladesh, 1991)	139,000
Earthquake (Pakistan, 2005)	88,000
Earthquake (China, 2008)	84,000
Heat wave, Drought (Europe, 2003)	**70,000**
Heat wave (Russia, 2010)	**56,000**
Earthquake (Iran, 1990)	40,000
Earthquake (Iran, 2003)	26,000

Adapted from data published by Münchener Rückversicherungs-Gesellschaft. Heat waves accounted for the 7th and 8th most fatal natural disasters during this period. From: https://www.munichre.com/site/corporate/get/params_E1716525033_Dattachment/1707976/munichre-natural-catastrophes-in-2018.pdf.

In this review, we discuss the effect of climate change on diseases of the kidney. The kidneys have a supreme function in maintaining blood volume to support blood pressure as well as extracellular and intracellular osmolality ("the internal milieu") that allows for normal metabolism. One of their more important functions is urinary concentration, in which it minimizes fluid loss while assuring the excretion of nitrogenous wastes. Unfortunately, the high metabolic work, as well as the concentrated excretion of wastes, makes the kidney very susceptible to injury from climate change. Indeed, studies have reported that increasing temperatures translate into increased admissions through the emergency room of a wide range of renal disorders, including acute kidney injury, chronic kidney disease (CKD), kidney stones, and urinary tract infections (UTIs) [21, 22]. Occupational exposure to heat stress has also been linked with higher incidence rates of kidney disease [23] and to a loss in productivity of workers when their kidney function becomes compromised [13]. Here we discuss some of these associations as well as potential links with the epidemics of CKD of unknown origin in hot regions throughout the world.

Heatstroke and Acute Kidney Injury

One of the major health consequences of extreme heat is heatstroke, which results when one cannot adequately control body temperature, resulting in hyperthermia (typically defined as a temperature >40.6 °C, >105°F) that can lead to delirium, coma, seizures, and multiorgan failure [5]. Heatstroke can occur during heat waves (termed epidemic or classic heatstroke) and also in association with exercise or labor in the heat (termed exertional heatstroke) [24].

Exertional heatstroke is especially common among military personnel, marathon runners [25–28], as well as workers in mines or agricultural fields (especially sugarcane) [29]. It is especially common among new workers who are not acclimatized and those that are overweight [29]. Epidemic heatstroke most commonly occurs in association with heat waves and affects those vulnerable to illness, such as the elderly, those with obesity or diabetes, those who are malnourished, individuals who have no air conditioning, and those with underlying cardiovascular or respiratory diseases.

Both classical and exertional heatstroke can be severe, in which case they are characterized by confusion or delirium, often coupled with acute liver and kidney failure. Indeed, acute kidney injury is a common manifestation in individuals presenting with epidemic heatstroke. For example, in the 1995 heat wave in Chicago, over 50% of those presenting with heatstroke had acute kidney injury [9]. While acute kidney injury may accompany severe manifestations with coma and liver failure, milder forms of heatstroke may be only associated with fevers and acute kidney injury.

There appear to be 2 types of acute kidney injury [24]. One form appears to be classical rhabdomyolysis (typically with creatine phosphokinase levels >1,000 μ/L), often associated with hyperuricemia and signs of dehydration. This form may be more common with exertional heatstroke. The other form is associated with normal or only mildly elevated creatine phosphokinase levels and is more common in epidemic heatstroke [24]. Indeed, unlike rhabdomyolysis, in which the injury appears more like an acute tubular injury, the second form of acute kidney injury clinically manifests more as an acute interstitial nephritis, with urinary leukocytosis and hematuria, and with a renal biopsy showing acute tubulointerstitial nephritis. It is thought that this condition results from ischemia, temperature-induced oxidative stress, and decreasing intracellular energy stores [30, 31].

Heatstroke is also commonly associated with electrolyte abnormalities [24, 32]. One study of 66 subjects with exertional heatstroke reported acute kidney injury in 91%, hyponatremia in 53%, hypokalemia in 71%, hypophosphatemia in 59%, hypocalcemia in 51%, and hypomagnesemia in 35% [32]. In particular, the low serum potassium, phosphate, and magnesium were all associated with increased urinary excretion of these electrolytes, suggesting a tubular defect. Other potential causes include loss of sodium and potassium through the sweat. Some subjects also present with respiratory alkalosis, which is known to reduce serum phosphate, although metabolic acidosis appears to be more common.

Some individuals (10–30%) with heatstroke-associated acute kidney injury require dialysis [32]. If the patient survives the acute illness, kidney function usually returns to normal [32]. However, some cases of heatstroke may progress to CKD months later with the presence of chronic tubulointerstitial nephritis on biopsy [33, 34].

Heat Stress Nephropathy as a Cause of CKD

In recent years, epidemics of CKD have been identified in various hot regions of the world where it preferentially affects workers who labor manually under extremely hot conditions [35]. One of the major sites of this disease is along the Pacific Coast of Central America, developing among sugarcane workers and others working in agricultural communities [36]. There is evidence that this epidemic has been progressively increasing since the 1970s [37]. The observation that the disease tends to occur in the hotter regions of Central America, coupled with evidence that the workers are placed under a great deal of heat stress [38, 39], has led to the hypothesis that the disease may be driven by global warming [40]. Indeed, a recent study suggests that working in the sugarcane fields is associated with higher humidity due to the presence of the cane and that heat waves are driven not only by increasing mean temperatures but also by El Niňo events [41].

There is increasing evidence that the development of CKD may result from repeated acute kidney injury driven by subclinical or clinical heatstroke [42]. Specifically, repeated acute kidney injury has been recently reported across work-shifts in sugarcane workers from this region [43–46]. While most cases are asymptomatic, some subjects present with fever, leukocytosis, leukocyturia, and acute kidney injury that may require admission to the local hospital [47–49]. These latter cases resemble heatstroke, as they may present with similar electrolyte abnormalities and also with acute interstitial nephritis on biopsy [47–49]. There is also evidence that some develop CKD over time [48], similar to that which occurs with exertional heatstroke [34].

Experimental studies support this association. Indeed recurrent heat stress and dehydration can induce chronic inflammation and tubular injury in mice and rats [50–52]. The mechanism of the kidney injury is likely related to increased internal body temperatures, the effects of hyperosmolarity to activate the polyol-fructokinase pathway, and the chronic effects of vasopressin to induce tubular and glomerular injury [50–52]. In addition, clinical studies suggest that the effects of heat and dehydration induce a concentrated and acidic urine, which can also lead to urinary urate crystallization with tubular damage [53]. Indeed, some experimental data suggest that lowering uric acid might provide protection [54, 55].

Acute kidney injury is now being reported throughout the world in hot agricultural communities including India (Andhra Pradesh), Sri Lanka (north central province), Mexico (Vera Cruz), central Florida, and the Central Valley of California [56–58]. In many of these areas, epidemics of CKD are also being reported [59–61]. A major concern is that these epidemics may be driven by increasing temperatures and heat waves, and that they may presage epidemics to come.

Other Effects of Heat Stress on the Kidney: Stones and Infections

Kidney stones (nephrolithiasis) are increasing in prevalence [62] and have also been proposed to result from increasing temperatures associated with climate change [63]. Heat stress and dehydration predispose to urinary concentration and low urine volumes that increase the risk for stones [64]. In the United States, for example, the "stone belt" that characterizes the hotter regions in the southern United States is projected to move northward as climate warming continues [63]. Experimental studies show that the primary kidney stone substance associated with heat stress is uric acid, due to its increased generation following exercise-induced muscle damage and the urinary acidification that occurs during the concentrating process [64].

UTIs may also be related to underhydration and potentially affected by climate change. Indeed, a recent study found that increased daily water consumption could increase urine output and reduce the risk for UTIs [65].

Effect of Soft Drinks in Heat Stress-Associated Kidney Damage

Soft drinks contain fructose, a sugar that results in local tubular injury, inflammation, and oxidative stress when metabolized by the kidney [66]. Recent studies suggest that soft drinks may increase the risk for acute and chronic kidney injury [67]. Indeed, experimental studies have shown that rehydration with soft drinks could enhance kidney damage in dehydrated rats [51, 68]. In addition to the injury associated with fructose metabolism, fructose may be able to stimulate vasopressin that can then augment the renal injury [51, 69]. Indeed, a recent clinical study also reported that rehydration with soft drinks could induce markers of kidney damage in healthy subjects following exercise in high temperatures [70], although epidemiologic studies conducted in hot field settings to date have found no association.

Additive Effects of Toxins and Toxicants

A prevailing theory suggests that in the context of heat and dehydration, naturally occurring toxins and man-made toxicants may concentrate in the kidney during periods of recurrent acute kidney injury. Candidates under investigation include potentially nephrotoxic agrochemicals, heavy metals, use of nonsteroidal anti-inflammatory drugs, tobacco, and silica. Further research is ongoing, including environmental risk assessments that include meteorological conditions.

Summary

In summary, while the kidney has a major role in protecting the host from the effects of heat stress, it is also a target for heat stress associated injury. The effects of heat can lead to both acute and CKD, electrolyte abnormalities, and kidney stones and UTIs. As global warming continues, major efforts are required to assure adequate hydration and prevent overheating in vulnerable populations who are at risk for heatstroke. Heat warning systems, changes in occupational practices, and public health initiatives also are needed [71, 72]. Most importantly, scientific investigations should be directed at identifying how to slow, stop, and reverse global warming.

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International Society of Nephrology 0 by 25 Project: Lessons Learned

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Keywords

Acute kidney injury · Dehydration · Mortality · Epidemiology

Abstract

Acute kidney injury (AKI) is a common disorder with a high risk of mortality and development of chronic kidney disease. With the validation of the recent classification systems, RIFLE in 2004 and KDIGO, in use today, our understanding of AKI has evolved. We now know that community-acquired AKI is also associated with an increased risk of worse outcomes. In addition, several epidemiological studies, including cohorts from low-income and low-middle income countries, have confirmed common risk factors for community-acquired AKI. In 2013, the International Society of Nephrology launched the 0 by 25 campaign with the goal that no patient should die from preventable or untreated AKI in low-resource areas by 2025 [Mehta et al.: Lancet 2015; 385:2616–43]. The initial effort of the initiative was a meta-analysis of AKI epidemiology around the world. The second project of the 0 by 25 initiative, the Global AKI Snapshot (GSN) study, provided insights into the recognition, treatment, and outcomes of AKI worldwide [Mehta et al.: Lancet 2016;387:2017–25]. Following the GSN, a Pilot Project was designed to test whether education and a simple protocol-based approach can improve outcomes in patients at risk of community-acquired AKI in low-resource settings [Macedo: J Am Soc Nephrol 2017]. In this review, we will comment on the main findings and lessons learned from the 0 by 25 initiative.

Introduction of 0 by 25 Projects

The worldwide application of the RIFLE/AKIN (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease/Acute Kidney Injury Network) and KDIGO (Kidney Disease: Improving Global Outcomes) classification systems has confirmed the increasing incidence of AKI in different settings [5–9]. The efforts of nephrology and critical care societies to create a unified classification system have enabled comparisons of AKI incidence and outcomes across diverse populations. The resultant epidemiological studies have shown increasing severity of AKI cases and a higher risk of death associated with AKI, in both hospital and community settings [10–12]. In addition, AKI is now a recognized important risk factor for new-onset chronic kidney disease (CKD), determining acceleration in the progression to end-stage renal disease [13–15].

The International Society of Nephrology (ISN) 0 by 25 initiative aims to eliminate or at least reduce avoidable AKI-related deaths around the world by 2025 [1]. Two key

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points were essential for the initiative: defining preventable death from AKI and promoting local recommendations for AKI care considering the health-care infrastructure and socioeconomic conditions [1, 16–19]. Based on previous studies, preventable deaths from AKI are known to occur as a result of 3 different situations [1]: (1) secondary to public health problems such as unclean water, diarrhea, and endemic infections; (2) delayed or lack of recognition, lack of access to laboratory studies, inadequate response, or iatrogenic factors resulting in additional insults to a failing kidney; and (3) lack of dialysis support to treat life-threatening hyperkalemia, fluid overload, and acidosis [1].

Although knowledge of the epidemiology of AKI has improved immensely since the use of a standardized AKI classification system, few studies have focused on community-acquired AKI in low-resource settings. In the meta-analysis by the 0 by 25 initiative, the main issues regarding the epidemiology of AKI were raised [1]. Information was presented regarding the increasing associated mortality of even mild AKI, the effects of an AKI episode on long-term outcomes, and early detection and treatment of AKI in outpatient and low-resource settings. However, to reduce AKI-related mortality and morbidity, knowledge of the factors that affect AKI outcomes is a key step in implementing initiatives. The strategies to reduce the burden of AKI need to be based on the identification of patients at risk, implementation of preventive actions, application of diagnostic methods, and timely referral for specialist care [20, 21]. Development of educational and training tools for raising awareness and standardizing care of AKI cases is also essential.

As most studies on AKI are derived from developed countries and mainly focus on ICU populations, the 0 by 25 initiative developed 2 projects to assess how AKI contributes to the global burden of health loss: the Global AKI Snapshot (GSN) study, and the Pilot Study. The GSN study was a prospective multinational cross-sectional project that included all patients with AKI who presented to the participating physicians on a given index day in 2014 [2]. The study included 4,018 patients with AKI across 6 continents and 72 countries. The Pilot Study is a prospective cohort of patients with high risk for community-acquired AKI in 3 different countries [3, 4]. The following paragraphs will comment on the main findings from the 0 by 25 initiative so far.

AKI Meta-Analysis

A systematic search of the literature was performed, including papers from January 2012 to August 2014. Four hundred and ninety-nine papers that included all AKI definitions, plus 266 papers based on KDIGO or equivalent AKI definitions, were analyzed [1]. The pooled incidence rate by KDIGO stage in 266 studies (4,502,158 subjects) showed an overall rate of 20.9% of hospital admissions and affected 3,000–5,000 patients per 1 million population per year. Recent studies have described an incidence as high as 15,000 per 1 million population per year. The data from these studies showed that the mortality rates continue to be high in all regions and that there was a continued association of nonrenal recovery following AKI.

Nevertheless, AKI incidence in low-middle income countries (LMICs) is still uncertain as some studies have shown lower levels than in high-income countries (HICs). It is likely that underreporting is the most common reason for the discrepancy when comparing HICs and combined low-incomes plus LMIC. In addition, epidemiological data from LMICs are difficult to interpret as there are nonuniform cohorts and involve heterogeneous methods of reporting as well as wide variations in ability to diagnose and treat AKI [1].

Another factor to consider is the high incidence of AKI in the hospital settings of areas with more resources, in contrast to community hospitals and rural areas, where AKI is often not detected [8, 19, 22–26]. Nonetheless, AKI in this population is often preventable and reversible, affecting young, previously healthy individuals and might be secondary to tropical infectious diseases, animal venoms, the use of herbal medicine, complications of pregnancy including septic abortion, and infectious diarrhea (Table 1).

GBD Study

The Global Burden of Disease (GBD) Study is an effort of the World Health Organization to quantify leading causes of health loss secondary to illness or injury throughout the world [27]. The GBD Study categorizes causes of health loss by age, sex, and geography for a specific time point. This time-based measure combines years of life lost due to premature mortality (YLL) and years of life lost due to time lived in states of less than full health (DALY). The DALY metric was developed in the original GBD 1990 study to assess the burden of disease consistently across diseases, risk factors, and regions.

As a part of the 0 by 25 initiative, the ISN has collaborated with the Institute of Health Metrics and Evaluation that coordinates the GBD study to include AKI in future GBD reports. Incorporating AKI into the GBD will involve determining the relationship between AKI as an intermediate event associated with disability or death. It

Table 1. Main risk factors for developing AKI

Patient		Exposures	
nonmodifiable	modifiable	environmental	infrastructure
Comorbid medical conditions Chronic kidney disease Diabetes mellitus Cancer Chronic heart disease Chronic lung disease Chronic gastrointestinal disease Demographic factors Gender Older age	Dehydration Intravascular volume depletion Hypotension Anemia Hypoxia Use of nephrotoxic agents (antibiotics, iodinated contrast, nonsteroidal anti-inflammatory drugs, anticancer drugs, antiretroviral, calcineurin blockers)	Diarrhea Obstetric complications (including septic absorption) Infectious diseases (malaria, leptospirosis, dengue, cholera, yellow fever, tetanus, Hantavirus) Animal venoms (snakes, bees and wasps, Loxosceles spiders, Lonomia caterpillars) Natural medicines Natural dyes Prolonged physically overwhelming work in an unhealthy environment	Inadequate sanitation Limited clean water availability Inadequate control of parasites Inadequate control of infection-carrying vectors Poor transportation Inadequate health budget Insufficient health care human resources Insufficient health services and hospitals

Modified from [1].
AKI, acute kidney injury.

will be possible to follow the leading causes of AKI and the segments of the population most susceptible to AKI-related health loss. The main goal is to add strength to the concept that a high proportion of cases of AKI in the community setting of low resource areas are preventable; it also attempts to demonstrate that investment toward early recognition can be translated into reduce mortality and improve outcomes.

In order to enable the inclusion of AKI in GBD, the ISN 0 by 25 initiative helped to generate AKI epidemiological data at the population level. The 0 by 25 initiative enabled the AKI Global Snapshot, a prospective observational cohort study, to compare risk factors, etiologies, diagnoses, management, and outcomes of AKI. The study was conducted from September 29, 2014, to December 7, 2014, with over 600 participating centers in over 93 countries [2]. Patients were classified as having community-acquired AKI if they presented with AKI and hospital-acquired AKI if they developed it in the hospital setting. Patients were considered as de novo AKI, AKI on CKD, or AKI with unknown prior kidney history if a baseline creatinine was not known. Countries were classified into HICs, upper-middle-income countries (UMICs), and LMICs according to their 2014 gross national income per person, using thresholds defined by the World Bank Atlas method [28].

Overall, community-acquired AKI was more frequent than hospital-acquired AKI, and the difference was greater in LMIC, where 79% of AKI cases occurred in the community. Most patients (46%) were at the ward or step-down unit when AKI diagnosis occurred, with similar rates across all country categories. Eighty percent of the cases were considered de novo AKI.

Hypotension/shock and dehydration were the more frequent risk factors associated with AKI development. In HIC and UMIC, hypotension/shock was the most prevalent cause, whereas dehydration was the most frequent contributory factor for the development of AKI in LMIC. Most dehydration episodes were associated with inadequate oral intake (60%), followed by vomiting (44%).

Patients with stage 3 AKI were higher in LMICs than in HICs and UMICs (58 vs. 47 and 41%, respectively). However, more patients in LMICs experienced recovery from AKI than did patients from HICs and UMICs. The large proportion of patients presenting with stage 3 AKI has important implications.

In a separate analysis of children, the main factors associated with AKI in HIC were hypotension (30%), post-surgical complications (27%), and dehydration (26%). In contrast, dehydration was the most common etiologic factor in LMIC (43.5%) and UMIC (30.6%) [9].

Mortality rate varied from 11.45% in patients from LMIC to 13.6% in patients from UMIC. In pediatric patients, the mortality rate was significantly different (19.6%) in LMIC compared to 1.2% in HIC [9]. Mortality in community-acquired AKI was higher in LMIC (11%)

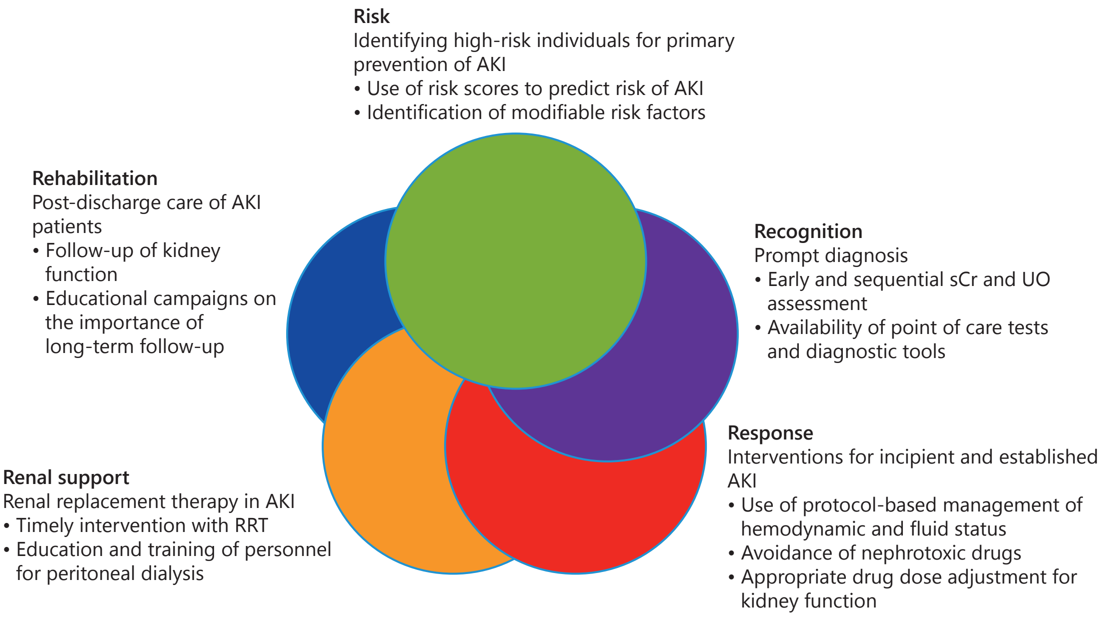

Fig. 1. ISN AKI 0 by 25 key elements for a sustainable infrastructure to support AKI care. sCr, serum creatinine; RRT, renal replacement therapy; UO, urine output; AKI, acute kidney injury. Modified from [1].

vs. 9% in HIC. In the pediatric population, this difference was even more pronounced, 3% in HIC and 20% in LMIC. In LMIC, mortality was higher among ICU patients (21%) in comparison to HIC (13%). AKI recovery was more often complete in LMIC (39%) than in HIC (33%) or UMIC (28%). Recovery rates from community vs. acquired AKI were very similar in HIC and UMIC. In LMIC, the recovery occurred in 79% of patients with community-acquired AKI and in only 20% of patients with hospital-acquired AKI.

The results of the GSN underline the need to raise awareness of AKI to increase the detection of patients who present with earlier stages of AKI. It also indicates that the main causes of AKI in LMICs are dehydration, infection, and sepsis.

Pilot Study

In the GSN study [2], we were able to demonstrate that there are significant similarities in the risk factors and causes of AKI worldwide; however, there was an underrepresentation of community-acquired AKI, particularly in rural settings. The primary aim of the 0 by 25 AKI Pilot Feasibility Project was to assess the feasibility of implementing an education and training program to optimize care of AKI, based on a protocol-driven approach in rural areas. The Pilot feasibility study was conducted at 3 sites located in Asia (Dharan, Nepal), Africa (Blantyre, Malawi), and Latin America (Cochabamba, Bolivia). Each site comprised a health-care cluster (including 3–4 community health centers, 1 district hospital, 1 regional referral hospital) that provided services to the population around the site area. The study was approved by the Institutional Review Board and the Ethics Committee of University of California San Diego and by the 3 local sites. Patients were screened for signs or symptoms a priori associated with high/moderate risk of developing AKI. AKI was confirmed within 7 days by a serum creatinine concentration increase or decrease of 0.3 mg/dL, or 1.5 times from the reference value.

The results of the pilot study, soon to be published, will provide an assessment of the current approach to diagnosis and management of AKI in community health centers and will identify barriers to optimize care of these patients. It will demonstrate the effect of simple interventions, including education and provision of point-of-care tests, on the course and outcomes of patients with a high risk of developing AKI. As a part of the project, we devel-

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oped partnerships with the governments of the participating countries to establish the best approaches to decrease preventable deaths from AKI.

Next Steps

AKI has been associated with high mortality rates; however, it is likely that a significant number of deaths associated with AKI could be avoided. In addition, AKI is now a recognized important risk factor for new-onset CKD, determining acceleration in progression to end-stage renal disease, leading to poor quality of life, disability, and long-term costs [29]. The Global Snapshot was the first large, epidemiologic study to map and scale the outcomes associated with AKI around the world, including data from ICU and non-ICU patients. It provided a solid basis to direct efforts for the ambitious goal of zero deaths from AKI by 2025.

The ISN 0 by 25 initiative offers a critical opportunity to help improve education, training, care delivery, and the implementation of diagnostic and intervention studies in AKI. A comprehensive approach for education and training of health-care personnel is fundamental to achieve increased awareness and better care delivery in AKI. Additional key elements include improvement in health care and diagnostic tool availability and provision of acute renal replacement therapy for those in need. The worldwide heterogeneity in the cause, setting, and course of AKI demands an integrative approach. The 0 by 25 initiative proposed the utilization of the 5R framework: Risk assessment, Recognition, Response, Renal support, and Rehabilitation (Fig. 1) [1, 30].

Furthermore, this initiative is enabling the development of sustainable infrastructure to improve education, training, care delivery, and implementation of diagnostic and intervention studies. It provided evidence suggesting that the majority of AKI cases would be treatable and often reversible, with early identification in high-risk patients and implementation of basic treatment.

Disclosure Statement

E.M., G.G.-G., and M.R. received travel expenses and registration fee from Danone Research to participate in the 2018 Hydration for Health Scientific Conference. R.L.M. has nothing to disclose.

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Safe Water Community Project in Jalisco, Mexico

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Keywords

Acute kidney injury · Diarrhea · Chronic kidney disease

Abstract

Few studies have assessed kidney function in patients with gastrointestinal infections in low-resource settings. Although dehydration is a frequent complication of acute diarrhea, we do not know the frequency and severity of acute kidney injury (AKI) in this context. A high prevalence of chronic kidney disease (CKD) has been reported among the inhabitants of poor communities in Poncitlan, Mexico. Polluted drinking water has been implicated as a probable cause. These communities report a high mortality associated with gastrointestinal infection. It is possible that a high incidence of waterborne disease and consequent more episodes of AKI might contribute to the high prevalence of CKD in this population. In this study, we aim to determine the association between the use of unsafe water and the incidence of acute diarrhea and AKI, and to determine if the provision of clean water decreases these complications. The study will be conducted in 3 communities of the municipality of Poncitlan. Initially, we will determine the water, sanitation, and hygiene (WASH) characteristics in the population and evaluate the incidence of diarrheal disease. In the observation phase, outcomes will be assessed after families receive training in WASH techniques, but before they are provided with clean water. In the intervention phase, outcomes will be assessed after clean water is provided.

Introduction

The Global Burden of Disease study estimated that diarrhea was a leading cause of death among all ages: 1.31 million deaths, in 2015 [1]. Several studies have implicated diarrhea as a risk factor for malnutrition and impaired physical growth, and some have suggested that it might also impair cognitive development [2]. Approximately 88% of diarrhea-associated deaths are attributable to unsafe water, inadequate sanitation or insuffient hygiene, and approximately 2.4 billion people globally have no access to basic sanitation [3, 4]. Microbial contamination is widespread in lower- and middle-income countries and affects all water source types, including piped supplies. Guidelines for Drinking-Water Quality recommend that fecal indicator bacteria, preferably *E. coli* or alternatively thermotolerant coliforms, should not be detectable in any 100 mL drinking water sample (WHO 2011) [5]. Approximately 1.8 billion people globally use a source of drinking

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Table 1. Socioeconomic indicators of affected communities

	Marginality index	Population, *n*	Illiterate, %	Incomplete primary school, %	Households without sewage system, %	Households without running water, %	Households with dirt floor, %
Poncitlan	Medium	40,827	7.3	23.4	1.2	5.2	3.4
San Pedro ltzican	High	4,478	21.6	47.9	5.3	4.6	10.4
Mezcala	High	3,896	10.5	35.5	3.0	2.3	10.2
Agua Caliente	High	988	7.79	40.8	28.7	40.9	15.0

Data from references [11, 12].

water that suffers from fecal contamination; of these, 1.1 billion drink water that is of at least "moderate" risk (>10 *E. coli* or thermotolerant coliforms per 100 mL).

Acute kidney injury (AKI) is a frequent complication of acute diarrhea and gastrointestinal infections [6], but very few studies have assessed kidney function in patients with gastrointestinal infections in low-resource areas and rural communities with no or very limited access to health care [7, 8]. The impact of AKI development on the short- and long-term outcomes in patients with diarrheal disease is unknown.

In this project, we aim to determine the incidence of gastroenteritis, waterborne diseases, and AKI in 3 communities that have a high penetration of unsafe water and to evaluate the effect of safe water provision on these issues. We have selected 3 communities from the municipality of Poncitlan, Jalisco, Mexico, based on the high prevalence of gastroenteritis and waterborne disease and the knowledge of the water utilization source. We will partner with the Secretaria de Salud Jalisco (SSJ), in order to obtain information on the quality of water and baseline data on the epidemiology of gastroenteritis and waterborne disease.

The study will be conducted in the communities of San Pedro Itzican, Mezcala, and Agua Caliente located along the Lake Chapala lakeshore in the municipality of Poncitlan. In these communities, water quality has been an issue for many years. Lake Chapala is the ultimate receptor of a great variety of contaminants, including pesticides, industrial residues, and heavy metals such as chromium, lead, zinc, and mercury. Local sources of pollution are also visible [9]. The absence of an adequate sewer system causes Chapala lake water to be contaminated. Wells drilled to avoid the use of lake water did not resolve the issue, as water from wells is contaminated by water springs with a high content of arsenic and other harmful elements. Over the years, these communities have shown a high mortality rate, secondary to intestinal infection and malnutrition [10]. The socioeconomic indicators in these communities show an alarming high marginality index, a high illiteracy rate, and incomplete primary school rates; a large percentage of households lack both a sewage system and tap water, and a high percentage of homes have dirt floors [11, 12] (Table 1).

These communities have a high prevalence of chronic kidney disease (CKD) of unknown etiology. Popular opinion in the lay media has implicated polluted drinking water as a probable cause [13]. Since 2006, the Hospitales Civiles Foundation has used mobile units to assess the presence of CKD in the state of Jalisco. Trained personnel using mobile units travel to rural and urban areas to collect demographic and clinical data, in addition to blood and urine samples for serum chemistry and dipstick urinalysis [14]. This screening program has shown a high prevalence of CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2) and proteinuria in Poncitlan, two-fold and 3-fold higher, respectively, as compared to the adult population in other Jalisco municipalities [15]. In children, although the prevalence of CKD was similar to other Jalisco municipalities, the prevalence of proteinuria was 10 times higher [16]. Similarly, a recent cross-sectional study in children residing in these communities reported a prevalence of albuminuria and CKD of 45% and 33%, respectively; these rates of albuminuria are 3–5 times higher than reported in the state of Jalisco and the international literature [17]. Information from Jalisco's vital statistics shows a high prevalence of intestinal infection, associated with a high mortality rate among children under 5 years of age [10]. It is possible that a high incidence of waterborne disease, and consequently more frequent episodes of AKI, contribute to the high prevalence of proteinuria and CKD in this population. The role of heavy metals and other contaminants in the water may also be important determinants of this outcome [9].

The primary objectives of the study are to evaluate the association between safe water provision and gastroenteritis frequency, waterborne diseases, and kidney disease in

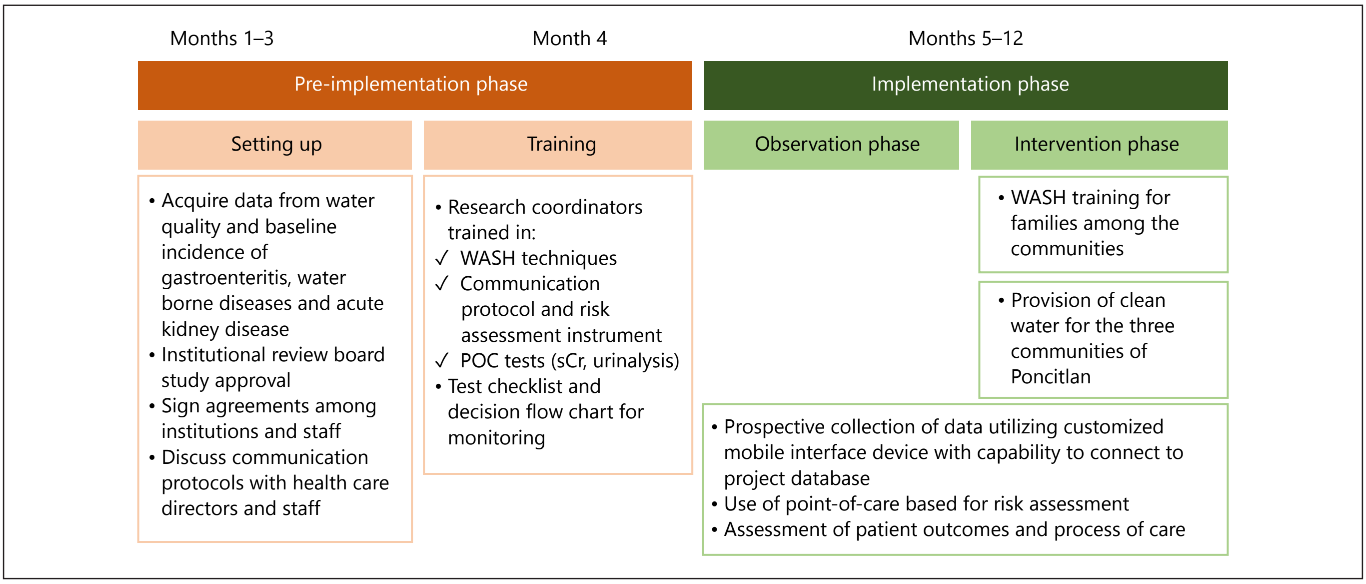

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Fig. 1. Study overview. WASH, water, sanitation and hygiene; POC, point of care; sCr, serum creatinine.

these communities. We have hypothesized that the use of unsafe water is associated with an increased incidence of gastroenteritis and waterborne diseases and leads to high prevalence of AKI. We aim to determine the frequency of AKI in patients with diarrheal disease based on serum creatinine (sCr) and biomarkers of kidney injury. Our secondary objectives are to determine the barriers for safe water use, to determine the association between water, sanitation, and hygiene (WASH) parameters and the prevalence of diarrheal illness. In addition, we will assess the effect of an educational strategy for WASH on diarrheal illness.

Materials and Methods

Preimplementation Phase

The study will be conducted in the communities of San Pedro Itzican, Mezcala, and Agua Caliente located along the Lake Chapala lakeshore in the municipality of Poncitlan, with a total population of approximately 10,000 individuals. Before study implementation, we will determine the WASH characteristics in the target population and evaluate the incidence of diarrheal disease in these communities. Following authorization from the SSJ and study approval from the Hospital Civil de Guadalajara Ethics and Research Committee, we will acquire data on water quality at different levels of distribution and utilization. Communication protocols among health-care facilities, families, and research coordinators will be established via the SSJ. We will train research coordinators in WASH techniques, in the validated risk assessment instrument, the performance of point of care (POC) tests, and for the collection and processing of serum and urine samples for storage for future biomarker assessment. All health providers and relevant staff will be trained in the protocol-based management of diarrheal disease and AKI that is appropriate to the setting in which they work. Providers will also be educated regarding the use of oral rehydration fluids for the treatment of dehydration, following the guidelines of Mexico's Ministry of Health [18]. The SSJ will help to coordinate these training sessions. All families will be taught WASH best practices (Fig. 1).

Implementation Phase

The implementation phase will consist of 2 parts. During the observation (first) phase, study outcomes will be assessed after families receive training in WASH techniques, but before they are provided with clean water. During the intervention (second) phase, study outcomes will be assessed after clean water is provided to the community.

Observation Phase

Patients with signs and symptoms of diarrheal disease will be encouraged to contact the local health-care center and/or study research coordinator. Patients with CKD stage 5 or in chronic dialysis and those with solid organ transplant will not be candidates for study participation. Patients meeting these criteria will be screened by the research coordinator and asked for consent. Patients (or surrogates) who sign informed consent will have a POC test for sCr and urinalysis by dipstick.

The results of the POC tests will be given to the health-care provider, who will be responsible for informing the patient of the results. The health-care provider will be given the accepted normal range of values for adults and children (adults: sCr 0.6–1.2 mg/dL; 53–105 μmol/L [19]; children 0–12 years old 0.0–0.7 mg/dL; 0–62 μmol/L, I) [20]. The health-care provider, however, will decide if the results are in the normal range according to the normative values and patient's comorbidities, age, and overall health characteristics. All health-care decisions will be made by the local health authorities.

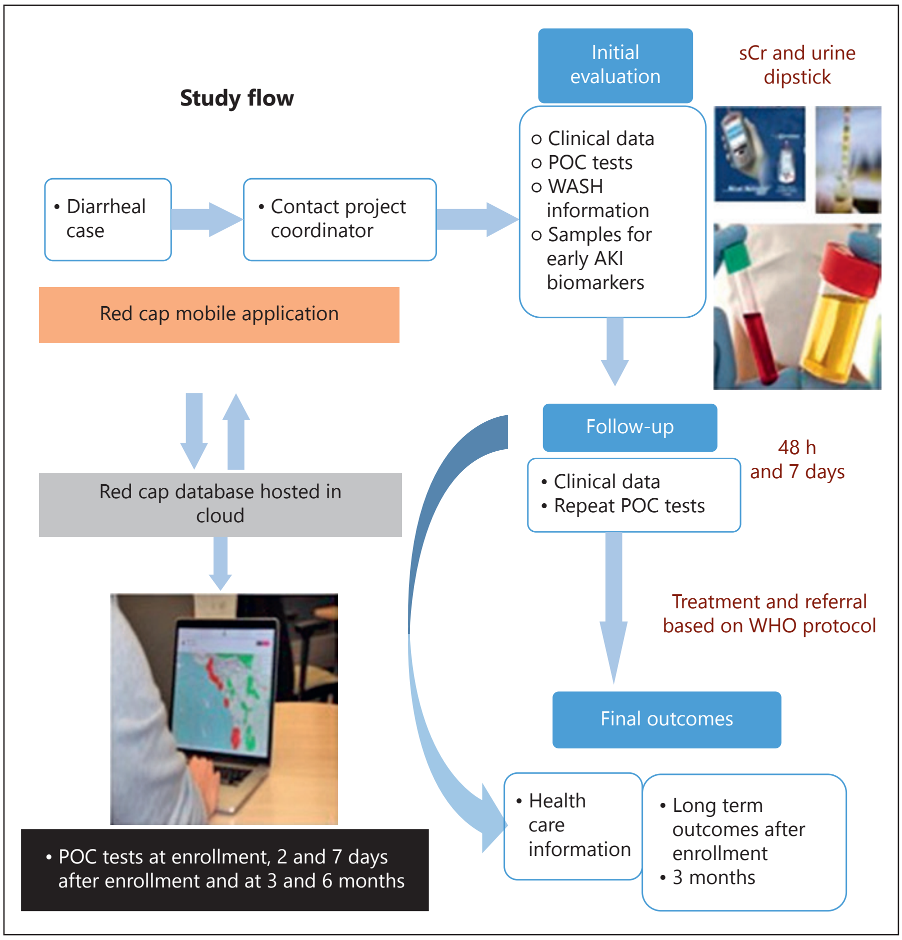

Fig. 2. Study flow during implementation phase. WASH, water, sanitation, and hygiene; POC, point of care; sCr, serum creatinine.

Blood and urine samples will be collected and stored for future biomarker analysis (Table 2). All enrolled patients will complete a clinical and WASH assessment and will be tracked throughout their clinical course by location (i.e., health-care center, hospital, and home). Outcomes will be recorded for 3 months following the initial health-care evaluation.

Patient level data will be tracked by the project research coordinator via communication with health-care facilities and families in the community. All relevant clinical data and the results of the POC test will be recorded in the electronic case report forms. Data will be recorded using the Red Cap Mobile Application. All captured information will be kept in a data repository site. The forms in Red Cap Mobile APP will be adapted for use in the community setting to capture data on the incidence, management and outcomes associated with diarrheal disease, dehydration, and AKI (Fig. 2).

Intervention Phase

In the second phase of the study, safe water will be distributed to the communities. We will repeat research coordinator and health provider training for the protocol-based management of diarrheal disease and AKI. The same study flow will be in place, and we will compare the incidence and severity of diarrheal diseases and patient outcomes. We will analyze the incidence of diarrheal disease and AKI based on whether or not patient and families are following WASH and also by water source.

Table 2. Study schedule and measurements for implementation phase

	Time point			
	enrollment	48 h	7 days	3 months
Medical history and physical assessment				
Physical exam	×	×	×	×
Blood pressure	×	×	×	×
Medication review	×	×	×	×
Renal functional assessment				
POC test sCr	×	×	×	×
Urinalysis	×	×	×	×
Urine and blood collection				
Biorepository for biomarkers	×	×	×	×
Other assessments				
Weight and height	×			×
WASH questionnaire	×			×

POC, point of care; sCr, serum creatinine; WASH, water, sanitation and hygiene.

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Health-care providers will track patient clinical status and renal outcomes at 48 h, 7 days, and 3 months after enrollment. Urine and serum samples will be collected at all follow-up time points.

Analytical Plan

Observation Phase

We will capture data on the course of patients with signs and symptoms of diarrheal disease and gastrointestinal infections. During this phase, we will define the gaps in knowledge and local barriers for WASH techniques and use of clean water. We will determine the frequency of specific risk factors for acute and CKDs. We will describe the WASH characteristics of the families enrolled in the study and correlate them with patient characteristics and risk factors for kidney diseases. We expect to establish the baseline frequency of AKI development, progression to more severe stages of AKI, and development of CKDs. Based on preliminary data from the SSJ, we anticipate that we will need to enroll 200 patients during this phase in order to obtain an adequate data sample (Table 2).

Intervention Phase

Safe drinking water will be provided for the 3 communities. We will evaluate the penetration and the barriers to use of safe water. We will compare the frequency of diarrheal disease, AKI, and severity of renal dysfunction between the observation and intervention phases. We will perform an interim analysis after the enrollment of 200 patients and 400 patients during this phase. We will continue this phase in the second and third year, aiming to complete enrollment of 800 patients, if the interim analysis does not indicate a need for early cessation of the study.

After study completion, we will assess the serum and urine samples for biomarkers of glomerular and tubular function. We will assess a panel of tubular markers representing concentration, reabsorption, and secretion function, which correlate with AKI severity or CKD progression (Table 2). The sequential assessment of these biomarkers, at initiation and during the course of the disease process, will provide us with a unique opportunity to understand their pattern of change during gastrointestinal diseases with and without AKI. We will evaluate how these changes correlate with AKI development, severity, and recovery.

Conclusion

In summary, the study will provide an opportunity (a) to demonstrate that the use of unsafe water is associated with an increased incidence of gastroenteritis and waterborne diseases leading to episodes of AKI and (b) to determine if the provision of clean water to communities with high penetration of polluted water is associated with a decreased incidence of these complications.

Statement of Ethics

Subjects (or their parents or guardians) will give their written informed consent. The study has been submitted for approval to the Hospital Civil de Guadalajara Fray Antonio Alcalde Ethics and Research Committee.

Disclosure Statement

The authors have no conflicts of interest to declare. E.M., M.V.R., and G.G.-G. received travel expenses and registration fee from Danone Research to participate in the 2018 Hydration for Health Scientific Conference. All authors have contributed to the conception and design of the work and will equally contribute to the acquisition, analysis, and interpretation of data; drafting the work; approving the version to be published; and will be accountable for all aspects of the work.

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Safe Water and Healthy Hydration

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European Healthy Hydration Awareness Campaign for Dietitians

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Abstract
Up to 50% of the adult population fail to meet the recommended total water intake despite the adverse health outcomes associated with chronic low fluid intake. Total fluid intake plays an important role in the energy and nutrient intake of individuals. Dietitians' role is to advise and guide the population toward a healthier diet. However, based on existing evidence, dietitians' current knowledge and practices regarding healthy hydration is an area for improvement. The European Healthy Hydration Awareness Campaign (EuHHAC) is an initiative between the European Federation of the Associations of Dietitians (EFAD) and the Hydration and Health Department of Danone Research, which aims to increase knowledge and awareness of healthy hydration and provide dietitians with evidence-based resources to use in practice. Since 2016, a series of tasks were undertaken by the EuHHAC group targeting dietitians across Europe. These tasks included an online survey addressing gaps in hydration knowledge, a webinar providing information on the terminology and impact of hydration on health, an interactive session addressing facilitators and barriers to healthy hydration, and a tutorial summarizing key hydration information and take-home messages. Dietitians were actively engaged in each aspect. Based on the feedback received, awareness of hydration was increased among dietitians. To further enhance understanding, an online Hydration Resource Center, including the resources of EuHHAC, will be created and uploaded on the EFAD website. Once completed an evaluation study will be undertaken to assess the usefulness of the resources in practice. The deliverables will be cascaded across Europe and worldwide via social media, conferences, and publications.

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Introduction

Water is a core component of the human body, it represents on average 60% of the body weight of adult men and 50–55% of adult women [1, 2]. Maintaining fluid balance is therefore critical for optimal functioning of the human body. The European Food Safety Authority (EFSA) recommends a daily total water intake (TWI) for adult males of 2.5 L and for adult females 2.0 L, with specific recommendations for children, adolescents, pregnant, and lactating women [2]. Evidence from large cross-sectional surveys conducted across Europe, Asia, and South America found that only 39% of children, 25% of adolescents, and 51% of adults met the EFSA guidelines for adequate intake of water from fluids [3]. Chronic low fluid intake has been associated with an increased incidence of diseases of the urinary system, including urolithiasis, urinary tract infection, chronic kidney disease (CKD), bladder cancer [4], and kidney stones [5]. In healthy adults, it has been shown that individuals habitually consuming low fluid volumes had an increased urine osmolality, urine specific gravity, and solute concentrations [6]. There are many methods to assess hydration status in individuals (e.g., body mass change, urine osmolality, salivary osmolality) with their validity depending on variables such as individual lifestyle characteristics (e.g., exercise level) or whether the measurement is taken under controlled environmental factors (e.g., laboratory) or in the field [7]. Twenty-four hour urine osmolality was found to be strongly correlated with total fluid intake (TFI) among healthy sedentary adults in free-living conditions [6]. Water homeostasis is maintained by the action of the arginine vasopressin hormone on the kidney. High levels of copeptin, a surrogate marker of arginine vasopressin, have been associated with an increased risk of type 2 diabetes [8], metabolic syndrome [9], CKD, and cardiovascular risk in both people with diabetes and the general population [10, 11]. High levels of copeptin are also associated with the development of CKD and CKD progression in the general population [12]. Recently, it has been shown that increasing water intake in low-volume drinkers reduces copeptin levels in healthy adults [13, 14] and decreases by 48% the recurrence of urinary tract infections [15]. Also, increasing water intake seems to benefit individuals of all stages of CKD or at risk of CKD [16].

The term TWI has been used in studies to include the sum of water from fluids and food [17]. Fluids included all kind of beverages (milk, juices, coffee, tea, soft drinks) and plain water [17]. Fluids and foods both contribute to TWI of individuals. Liquid foods (soups, broths), yogurt, and some vegetables contain 80–99% water, while even solid or dried foods such as butter and raisins contain some amount (10–19%) of water [1]. Data from nutrition surveys in the United Kingdom and France found that water from fluids contributed 59 to 76% of TWI, and water from food contributed 24.7 to 41% of TWI in the different age-groups of the populations [18]. Fluids and food are also an integral part of diet due to their nutrient and energy content. In particular, data from large population surveys in Spain, Mexico, and the United States revealed that mean energy intakes from foods and beverages ranged from 1,816 to 2,437 kcal with fluids contributing 12% (in Spain) to 21.7% (in Mexico) of total energy intake [19]. Dietitians are particularly concerned about the increased intakes of sugar-sweetened beverages (SSB) due to their detrimental consequences on oral health and body weight in children [20] and adults [21]. The World Health Organization suggests that intake of added sugars should not exceed 10% of daily total caloric intake, with additional benefits occurring if intakes are limited to 5% [22]. Evidence from large cross-sectional surveys across Europe found that juices and SSB contributed 35–45% of TFI in children and adolescents and 15–20% in adults [3]. In the United States, data from the national survey showed that SSB intake contributed 6% of total caloric intake [19]. Drinking water instead of SSB is recommended by health organizations, as water is free of calories [1], while an increased water intake has been associated with higher diet quality [23]. Moreover, SSB consumption has been shown to be positively associated with and has an impact on body weight measured in children [24]. Water-based interventions in children have been associated with weight loss, mainly due to the substitution of caloric beverages with water intake, particularly in children who were overweight or obese at baseline [25].

Assessing TFI is challenging, with evidence showing that the most common methods used in research are single or multiple 24-h recalls, food diaries, or food frequency questionnaires validated against specific nutrients or energy intake [17]. Dietitians sometimes underestimate drinking behavior (alcohol, plain water) outside of meal times as they are mainly interested in assessing nutrient and energy intake from food and fluids [26]. Seven-day records were found to be more reliable in capturing fluid intake when compared with 24-h recalls in an adult population [27]; for example, a 2017 study by Johnson et al. [28] validated a 7-day fluid record against body water turnover in healthy adults. However, the use of fluid records might be less appropriate for assessing TFI in other

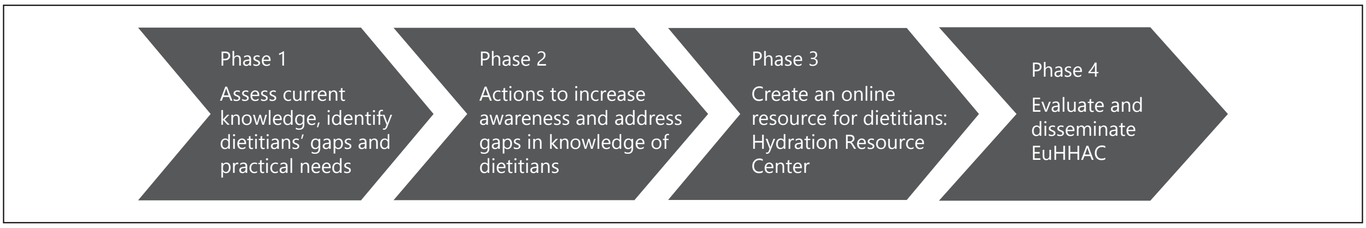

Fig. 1. EuHHAC project phases and key components (the roadmap). EuHHAC, European Healthy Hydration Awareness Campaign.

age-groups such as children and adolescents or older people. According to the review by Warren et al. [29], the use of repeated 24-h recall is a very suitable method for assessing TFI in adolescents, but less appropriate for children aged 5–8 years. Similarly, Jimoh et al. [30] found that the use of a self-reported Drinks Diary in older people with cognitive capacity to complete it, assessed more accurately their daily TFI when compared to the intake recorded on fluid charts by staff (direct observation of TFI was used as the reference method in this study). When assessing TFI, it is also important to consider factors that might lead to poor documentation, such as lack of staff or time in a busy ward [31] or the use of online instead of paper tools, which have been found to facilitate recording [32]. As a result, using the most appropriate method to assess TFI depends on the targeted population, whether TFI is assessed as part of dietary intake or it is the primary objective, and the availability of time and resources to undertake the assessment.

Individuals should aim to reduce the intake of added sugars from foods and fluids, drink water instead of sugary and alcoholic drinks, and reach the recommended fluid intake for their age and gender [2]. To achieve that, dietitians should have a sound knowledge of the role of water in human body, the different types of fluids and their impact on health, the recommended fluid intakes for each group of people, and use valid tools to assess TFI and hydration status of individuals. Findings from a cross-sectional study among dietitians in the United Kingdom suggest that half or less of respondents were aware of the dietary reference values of fluid and water for adults as well as the water content of foods and drinks [33]. In addition, although most dietitians considered themselves as responsible for managing hydration in patients, during a practical session, 24% of them did not mention anything about hydration and 33% spent <10 min talking about hydration with patients [33]. Only 18% of dietitians answered that they "always" assess patients' hydration status and the majority perceived as "very important" that dietitians should receive education on hydration. These findings highlight the importance of increasing awareness on healthy hydration among dietitians, clarify any misconceptions, and provide evidence-based tools to use in practice.

In an effort to address the above objectives, the European Federation of the Associations of Dietitians (EFAD) in collaboration with experts on healthy hydration from Danone Research developed the European Healthy Hydration Awareness Campaign (EuHHAC). This joint initiative aims to promote healthy hydration in the current food "climate" expressed in the World Health Organization European Food and Nutrition Action Plan 2015–2020 [34] and complemented in the EFAD European Dietetic Action Plan [35]. Primary objectives of the current project are to address gaps in the current knowledge of dietitians regarding healthy hydration, to undertake actions to increase awareness of healthy hydration, and to provide evidence-based resources for dietitians to use in their daily practice. Secondary EuHHAC objectives include evaluation of the project and communication of its outputs internationally, to encourage hydration science research and engage policy makers to adjust/apply fluid intake recommendations in their country. The EuHHAC project plan, showing the key components of each phase, is outlined in Figure 1. The project was launched in 2017 and will be completed in 2019. The following paragraphs describe in chronological order the actions that have been taken and the lessons learned from each experience (Table 1).

Actions Taken to Date

Identifying Gaps in Hydration Knowledge

Initially, a questionnaire based on the knowledge, attitude, and practice model [36] was developed by the working group of EuHHAC, to assess gaps in the hydration knowledge among dietitians in Europe. The questionnaire was disseminated through 10 European Spe-

Table 1. Actions taken as part of the EuHHAC project

Actions	Year	Duration	Participants	Aim	Brief description of content	Main outcomes
Online survey	2016	3 months	102 dietitians	To assess gaps in hydration knowledge	A questionnaire based on the KAP model (*n* = number of questions): – Water balance/EFSA recommendations for age-groups/total water intake (*n* = 6) – Country-based recommendations of fluid intake (*n* = 4) – Definition/sugar content of beverages (*n* = 2) – Definition/signs of dehydration (*n* = 3) – Practical hydration advice (*n* = 4)	Inadequate knowledge was found for recommended intakes of fluid and water, terminology of fluids, regulatory mechanisms of water and sugar content of fizzy drinks
Webinar	2017	1 h	98 dietitians attended online (514 views to date)	To increase awareness and provide evidence about healthy hydration and prevention of chronic diseases	The webinar was developed on the basis of online survey results. Content included: – Functions of water in body – Factors affecting hydration requirements – Recommended water intake – Epidemiological data of fluid intake – Hydration and health (kidney diseases, obesity) – Use of copeptin as a predictor for disease risk	90% of attendees rated themselves as satisfied or very satisfied with the webinar. FAQs were posed about water intake and kidney diseases, country-based recommendations, and water content in foods. FAQs were answered, and responses were sent to attendees together with resources
Interactive session	2018	1 h	~100 dietetic or nutrition students	To increase awareness and provide practical tools and tips about hydration and fluid intake	The lecture included: – Terminology of fluids – Recommended fluid intakes – Methods for assessing hydration status – Tips about water and fluid intake – Use of intravenous fluids in dehydrated older people. Interactive activities included (dietitians were asked to): – Estimate their total fluid intake and energy content of fluids via 24-h recall – Guess the volume (mL) of water contained in different shapes of glasses – Record perceived barriers and facilitators of fluid intake in older people living in care homes	Dietitians were efficient in using a 24-h recall to assess fluid intake but found it difficult to guess the amount of water contained in glasses of different shapes. Attendees also addressed potential barriers and facilitators of fluid intake in older people living in care homes and methods to increase water intake in community settings (Table 2)
Tutorial on Hydration	2018	2 days	Delegates of the 40th EFAD conference	To summarize key messages about hydration and communicate the launch of EuHHAC	A short (4 min) video tutorial presenting: – Water balance and losses in the body – An overview of the current EFSA recommendations – Definitions and classifications of fluids – Demonstration of country-based fluid recommendations for adults – Definition and symptoms of dehydration – Take-home messages. The video was displayed on monitors near a booth located in the conference exhibition area	Many delegates stopped to watch the video and take notes. A quiz was given to challenge their knowledge. Hydration experts were available to inform delegates about the scope and progress of the EuHHAC project and discuss any queries. Educational materials (e.g., EFSA recommendations leaflets, urine color chart) were provided to delegates

EuHHAC, European Healthy Hydration Awareness Campaign; EFSA, European Food Safety Authority; KAP, knowledge, attitude and practice.

cialist Dietetic Networks of EFAD and all EFAD delegates during the summer of 2016. The EuHHAC group received 102 responses from a range of European countries. The survey found that 50% of respondents did not know the current EFSA TWI recommendations for adults and 49% were not aware that older people have similar requirements to adults. About half of respondents (45%) didn't know that a child's thermoregulatory mechanisms are not fully developed. There was confusion over the definitions of TWI and TFI with 31% of respondents unable to distinguish that TWI is the sum of water from fluids and food. There was great variation in defining the term "beverage". More than 50% of respondents had inadequate knowledge about the average sugar content of a fizzy drink. Finally, when asked about their country's water recommendations, 58% did not provide an answer.

Hydration Webinar

Based on the findings of the survey, dietetic experts of the EuHHAC group developed a hydration webinar, which was presented using the EFAD platform and supported by the European Network of Dietetic Students. The webinar consisted of 2 parts. The first covered the water content and its functions in the body, factors affecting hydration needs, recommended daily TWIs, epidemiological data regarding fluid intake, evidence relating hydration to health (kidney diseases, obesity), and the use of copeptin as a predictor for disease risk. The second webinar section presented the results of the questionnaire investigating the hydration awareness of dietitians. Over 400 people submitted applications to attend the webinar. Unfortunately, the system could only accommodate 100 attendees. As a result, 98 people across Europe watched the webinar of which 70 provided feedback through a follow-up online survey. Attendees were mainly dietitians and students in nutrition or/and dietetics. The feedback was positive, with 90% of attendees rating themselves as satisfied or very satisfied with the webinar. Queries were posed with regard to water intake and its impact on CKD, acute kidney disease, and stage 3 CKD. Attendees said it would be useful to receive further information about foods with a high water content. They also asked if it would be possible to pictorially or visually present the water intake of European countries. Also, participants viewed evidence-based information about the health benefits of water intake as useful tools for dietitians to inform patients. Those resources were sent to those who attended, and frequently asked questions were answered. The EuHHAC webinar (Water: The Forgotten Nutrient) can be viewed on the YouTube channel; it had been viewed over 550 times at the time of this publication.

Interactive Session

Following the feedback received from the attendees of the webinar, a registered dietitian and hydration expert of the EuHHAC group developed a session during the preconference Academy of the 10th Hydration for Health Scientific Conference in Evian, France, in 2018. Approximately 100 dietetic and nutrition students attended the session that lasted for 1 h and included both didactic lecturing and interactive learning. The content of the presentation included terminology, fluid recommendations, intake of SSB, assessment methods of hydration status and drinking behavior, practical advice to increase water intake, information about the use of intravenous fluids in dehydration, and optimal hydration in older people. The activities focused on the estimation of TFI and energy content via 24-h recall, as well as the visual presentation of the same volume of water using different shapes of glasses. Additionally, the attendees were asked to (a) suggest potential barriers to and facilitators of fluid intake in older people living in care homes and (b) suggest ideas to create a water-friendly environment and encourage people to drink water in community settings.

Twenty-seven attendees provided answers about barriers, 26 about facilitators, and 23 suggested ideas on promoting water intake in community settings. Regarding dietitians' perceptions about barriers, 2 main themes emerged. Theme 1 included barriers in relation to older people's physical dysfunction related to aging (e.g., incontinence, poor memory), dietary factors that might prevent fluid intake (e.g., prescribed low intake of salt), and individual attitudes/behavior (e.g., low awareness, tiredness). Theme 2 included barriers related to care home resources and facilities. Examples included the lack of staff or lack of staff time to perform tasks related to fluid intake, negative attitudes/behavior of staff such as unwillingness to assist older people to visit the bathroom and environmental barriers (e.g., lack of access to fluids). Regarding dietitians' perceptions of facilitators, 2 main themes emerged. Theme 1 included facilitators that related to older people's characteristics including the contribution of those who take care of older people (care givers), as well as attitudes, behavior, and social interactions with others. Theme 2 included facilitators that included resources/facilities of care homes (e.g., staff with positive attitudes and behaviors toward fluid intake), the resources of care homes (e.g., well-informed staff, pro-

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viding special cups/beakers/water bottles), and having a water-friendly environment (e.g., fluids are accessible in rooms and with meals). Regarding dietitian responses about encouraging people to increase their water intake in community settings, they reported giving tips and advice to individuals, acting as role models; they also suggested that community and policy makers could create social campaigns and provide easy access to safe water and toilets in public places. These themes and examples of responses of dietitians are summarized and presented in Table 2.

Hydration Tutorial

A hydration tutorial was designed for delegates attending the 40th EFAD conference in Rotterdam on September 28–29, 2018. The tutorial was a 4-minute video displaying, graphically and in text, information about water balance and water losses in the human body, an overview of the current EFSA water intake recommendations for various age-groups, definitions, and classifications of fluid types; a map depicting the fluid recommendations of various countries worldwide; the definition and symptoms of clinical dehydration; and "take-home" messages. The video played in a loop on a monitor displayed at a booth in the conference exhibition area. Leaflets with EFSA recommendations and urine color charts for assessing hydration status were also available. Two hydration experts supported this booth. These activities informed delegates about the launch and aims of the EuHHAC project, answered queries about hydration, distributed hydration leaflets, and answered delegate questions. By the end of the conference, the hydration experts concluded that many delegates were aware of the EuHHAC project and inquired when the outputs of the project would be available online. In particular, delegates were interested in methods of assessing hydration status, water intake of specific demographic groups (e.g., older people, children), and the impact of hydration and dehydration intake on health. They also mentioned that online resources such as webinars and YouTube videos are the preferred modes of learning and increasing awareness about hydration among dietitians.

Summary and Conclusions

The EuHHAC is a joint initiative of EFAD and the Hydration and Health Department of Danone Research, which attempts to increase awareness and provide evidence-based resources for dietitians to promote healthy hydration. Completed actions include an online survey to assess current gaps in hydration knowledge, a webinar to clarify the recommended intakes of fluids, an interactive session to provide tips and advice, collecting dietitian views and opinions about hydration topics, and an online tutorial to graphically present key messages.

The project is currently in Phase 3 (Fig. 1), presenting resources via the EFAD online Healthy Hydration Resources Center for members of EFAD (i.e., including clinicians, students, researchers, and academics). Subscribers will be able to access the resources at any time and download printed materials for use in their dietetic practice (e.g., fluid intake data of various countries, tools to assess fluid intake, and recommendations for different groups).

Based on experiences and feedback, the EuHHAC group acknowledges that dietitians were very keen to learn more about hydration, in particular for groups of people with varying needs or requirements. Also, they expressed interest in accessing user-friendly and validated tools to promote healthy fluid intake and assess TFI or hydration status of people in community and clinical settings. After completing Phase 3, the EuHHAC group will undertake a pilot study to test the feasibility of the newly created hydration resource center and creates focus groups among dietitians across Europe to evaluate the impact of the project and necessary future activities. Once completed, EuHHAC and its deliverables will be cascaded across Europe and worldwide via social media, conferences, and published outputs.

Several education programs for dietitians exist; some are fully based on mentoring [37] or e-learning [38]. The unique features of EuHHAC reside in the specificity of hydration science as its topic, the various modes of delivery, and its iterative building process.

Hydration science is an underappreciated topic in public health, even though scientific evidence exists that demonstrates an impact on health. Expanding research on hydration is key; however, concrete actions like EuHHAC are needed to implement this knowledge into practice. Because barriers exist (Table 2), there is a need to create water-friendly environments to encourage healthier hydration behaviors. Providing education to dietitians about hydration science and giving them access to user-friendly tools is a first step. Future public actions are needed in every country.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Table 2. Dietitian perceptions regarding barriers and facilitators of fluid intake and methods to increase water intake in older people who reside in care homes

Questions	Responses			
	main themes	sub-themes	number of responses, %	dietitian responses
Describe barriers of fluid intake in older people residing at care homes (*n* = 27)	1. Barriers related to older individuals	1.1 Aging-related characteristics	22 (81.5)	"Incontinence" "Low thirst" "Lack of motor ability to hold a cup, swallow, and so on." "Low memory"
		1.2. Dietary or disease-related characteristics	2 (7.4)	"Low intake of salty foods due to other conditions" "Increased medication- diuretics, low ADH"
		1.3. Personal (behavioural) characteristics	17 (63.0)	"Low literacy on how much to drink" "Uncomfortable to use elderly diapers" "Not asking for their preferred beverage"
	2. Barriers related to human resources/ facilities at care homes	2.1 Resources	5 (18.5)	"Time pressure of staff/ often times understaffed to ensure hydration for every single patient" "Availability of special beakers for safe swallowing (if not on thickened fluids but bed-bound) to drink unassisted"
		2.2. Staff attitudes/ behaviour	7 (25.9)	"Not willing to remind patients to drink/ help them/ care" "Lack of information/education" "…serving drinks that they (older people) do not like"
		2.3. Environment	4 (14.8)	"Unavailability of good water sources" "Toilet access"
Describe facilitators of fluid intake in older people residing at care homes (*n* = 26)	1. Facilitators related to individual characteristics	1.1 Care givers	6 (23.1)	"Carers can help" "Family"
		2.2. Individual attitudes and behaviour	3 (11.5)	"Remember to take water with their medication" "Education about benefits of hydration"
		2.3. Socializing/ interaction with others	6 (23.1)	"Find a way to link it to something fun" "Having someone to have a drink with"
	2. Facilitators related to human resources/ facilities at care homes	2.1. Staff attitudes/ behaviour	13 (50.0)	"Ask people what drink you prefer" "Give fluids with snack and medication" "Keep good temperature of fluids when served" "Encouraging to drink- helping with going to toilet more often" "Protected mealtimes" "Staff that is aware of the importance"
		2.2. Resources	7 (26.9)	"Having willing staff available" "Educate staff" "Secure cups – for example, beakers/using straws"
		2.3. Environment	12 (46.2)	"Tap water coolers" "Friendly design bathroom" "Water access"
Record ideas to create a water-friendly enviroment and encourage water intake in community settings (*n* = 23)	1. Actions that dietitians/health professionals could take in practice		16 (69.6)	"Keep patients record on intake- monitoring is key" "Be a role model" "Set fluid goals to work towards" "Adapting in house dietsheets- adding in info fluid" "Increase education regarding benefits" "Make water fun/interesting"
	2. Actions that community/policy makers could take		17 (73.9)	"Clean water fountains strategically placed" "Affordable water" "Campaign (visual, video)" "Public toilets" "Education" "Interesting bottle" "Make it a social event (5 a day drink)" "Awareness of nutritionists- community"

Disclosure Statement

R.Y.W. and L.L. are full time employees of Danone Research. J.G. is a member of the Fluid Intake Expert Group of Danone Research and has been employed as a consultant for Danone Research. K.B., J.G., A.G., J.L., and P.D. received travel expenses and registration fee from Danone Research to attend the 2018 Hydration for Health Scientific Conference.

Author Contributions

K.B. participated in the implementation of some project actions and prepared the manuscript. R.Y.W, L.L., J.G., and P.D. prepared and participated in the implementation of the actions of the project, reviewed the paper, and made critical comments to its content and structure. A.G. and J.L. contributed to the implementation of the overall project.

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Hydration in Children: What Do We Know and Why Does it Matter?

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Keywords
Hydration · Water intake · Children · School · Barriers · Interventions · Behavior change

Abstract
In children, maintaining adequate fluid intake and hydration is important for physiological reasons and for the adoption of healthy, sustainable drinking habits. In the Liq.In[7] cross-sectional surveys involving 6,469 children (4–17 years) from 13 countries, 60% of children did not meet the European Food Safety Authority (EFSA) adequate intake for water from fluids. Beyond fluid quantity, the quality of what children drink is important for health. In these surveys, the contribution of sugar-sweetened beverages and fruit juices to total fluid intake (TFI) in children exceeded that of water in 6 out of 13 countries. To assess the adequacy of children's fluid intake, urinary biomarkers of hydration such as urine osmolality, urine specific gravity, and urine color may be used. To date, while there are no widely accepted specific threshold values for urine concentration to define adequate hydration in children, the available literature suggests that many children have highly concentrated urine, indicating insufficient fluid intake. This is worrisome since studies have demonstrated a relationship between low fluid intake or insufficient hydration and cognitive performance in children. Furthermore, results of the Liq.In[7] surveys showed that at school – where children spend a significant amount of time and require optimal cognitive performance – children drink only 14% of their TFI. Consequently, it is pertinent to better understand the barriers to drinking water at school and encourage the promotion of water intake through multicomponent interventions that combine educational, environmental, and behavioral aspects to support adequate hydration as well as optimal cognition in children.

Introduction

In recent decades, research demonstrating an association between water intake and/or hydration and health has raised interest for this topic within the scientific community and in the eyes of public health professionals.

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While there is benefit in improving eating and drinking behaviors in adulthood, concentrating on the acquisition of healthy consumption habits in children may prove to be a more sustainable and successful strategy for the prevention of health risks. This article aims to provide an overview of research on water, fluid intake, and hydration in children and their importance for health both from a physiological and behavioral viewpoint, as well as to provide perspective of what may be needed to create and maintain a water-friendly environment at different levels, at the levels of family and school in particular.

Water Balance in Children

In children, maintaining adequate fluid intake and optimal hydration is essential for physiological and behavioral reasons. Water is the most abundant component of the human body. In newborns, who have developed in an aqueous milieu, body water content at birth is approximately 75% of body mass [1]. This is much higher than that of adults for whom water represents 50–60% of body mass. The relative water content of infants decreases rapidly throughout the first year of life to 60% and remains relatively stable throughout childhood until adolescence, after which changes in body composition and hormonal balance result in reduced water content, particularly in young women [2–4]. Physiologically, water supports many functions essential in daily life, such as thermoregulation and waste elimination; it also serves as a carrier and a solvent for numerous metabolic reactions. In children, physiological specificities of water balance, such as the progressive maturation of kidney function by around the age of 2, as well as a higher body surface-to-body mass ratio which translates into higher insensible water loss through the skin, explain in part why children have higher water requirements relative to their body mass when compared with adults [4, 5]. Voiding volume and frequency also reach their full maturity by adolescence only [6].

Water Intake in Early Childhood: A Driver of Sustainable Healthy Habits?

Beyond physiological differences, water is also an essential component of the adoption of healthy sustainable drinking habits in children. Acquiring healthy drinking habits is important from infancy because many dietary behaviors acquired during childhood persist into adulthood. For example, Fiorito et al. [7] demonstrated that consumption of sugar-sweetened beverages (SSB) at age 5 predicted the consumption of SSB at age 13. Similar associations were obtained in different countries and age categories [8, 9]. However, the association between early childhood and later life intake has never been demonstrated for drinking water, due to the scarcity of longitudinal studies assessing water intake. But if indeed drinking habits (i.e., plain water intake in particular) were sustained throughout life, children who drink little water would become adults who drink little water with potential consequences for kidney [10] and metabolic health [11, 12] as well as cognitive and mood impairments [13, 14]. During early childhood, the acquisition of eating and drinking behavior is mainly driven by adults since children depend upon them for the provision of food and beverages, and adults serve as role models which children copy and acquire habits from. Indeed, numerous studies support an association between parent and child food and beverage intake, including SSB in particular [15–17]. While there is no peer-reviewed published research on the association between parents' and children's water intake, results from a survey commissioned by the Natural Hydration Council, involving 1,000 parents from across the United Kingdom and one of their children, aged 4–8 years old, showed that children whose parents were drinking plain water often were more likely to drink plain water themselves; this demonstrated that parents can positively influence the drinking habits of their children [18]. In addition to parental influence on eating and drinking habits during childhood, school environment, rules, and policies also play a crucial role in the acquisition of healthy consumption behaviors. Regarding water intake, observational studies have shown that consumption of water in schools where water intake is encouraged (i.e., by ensuring water access, providing appropriate water fountains and toilet facilities, and education about the importance of hydration), is greater than in schools that do not have supporting rules and infrastructure in place [19, 20].

Water and Fluid Intake Habits of Children

To better understand drinking behaviors in children, studies have attempted to assess the quantity and quality of their fluid intake. However, assessing fluid intake in children involves multiple challenges (e.g., multiplicity of caregivers and/or locations throughout the day, bias in parental diet records, on-going cognitive capacity development, limited literacy skills, difficulties in estimating portion sizes, differences in child portion sizes compared with those of adults, and a tendency not to finish servings) [21]. Additionally, plain water intake is often overlooked in clinical and observational studies focusing on obesity because water contains no calories. Consequently, in a systematic review of studies reporting fluid intake published in 2014, Ozen et al. [22] found that of the 34 publications reporting fluid intake in children, less than half included any measure of plain water intake. In practice, the omission of water means that in the majority of studies investigating the associations between childhood nutrition and health outcomes, water is absent.

Recently, fluid intake data that include drinking water have become available with the publication of the Liq.In[7] survey results. The harmonized Liq.In[7] cross-sectional surveys, collected with 7-day fluid specific records, encompass data on the consumption of all types of beverages including plain water for 6,469 children (4–17 years) from 13 countries [23]. A first analysis of the data highlighted large discrepancies in total fluid intake (TFI; sum of all beverages including plain water) both between countries and within countries [24]. As an example, the mean TFI of 4–9-year-old children in Indonesia was 1.9 ± 0.8 L, twice the intake of Belgian children: 0.8 ± 0.4 L. In Brazil, there was a 6-fold difference of TFI between the 5th and 95th percentile. This suggests that, in order to identify individuals who have increased fluid intake-associated health risks, data should be analyzed at the individual level rather than at the mean population level. Therefore, comparing individual children's TFI to the daily adequate intake for water (i.e., from recommendations provided by health authorities such as the European Food Safety Authority, EFSA), the results demonstrated that 61% of children in the Liq.In[7] surveys did not meet the adequate intake for water from fluids derived from EFSA [24]. Focusing on the quality of fluid intake, these surveys demonstrated that the contribution of SSB and fruit juices to TFI in children exceeded that of water in 6 out of 13 countries [25]. Moreover, 55% of children and adolescents in the sample consumed more than 1 serving of SSB daily, while up to 21% did not drink water on a daily basis in some countries (unpublished data). This raises concern since the negative consequences of SSB consumption on children's health have been highlighted in numerous studies demonstrating that children who consume one or more SSB serving per week have a 50–80% increased risk of dental caries, overweight and obesity, and metabolic syndrome compared with non- or sporadic consumers of SSB [26–33].

Hydration Assessment of Children

As in adults, markers of urine concentration such as osmolality, specific gravity, and color may be used for day-to-day hydration assessment of children [34, 35]. Urine color, in particular, may be used for self-assessment of hydration since it can reliably be self-assessed by children above 8 years of age [36]. To date, however, there are no widely accepted specific threshold values for urine concentration to define adequate hydration in children. Previous studies have utilized cutoff values of 500, 800, and 830 mOsmol/kg, referring to different terminologies such as mild dehydration, euhydration, appropriate hydration, hypohydration, and underhydration, without any evidence for health benefit or risk [37–40]. This is mainly due to the scarcity of studies demonstrating an association between a quantified fluid intake or urine volume or concentration and a health benefit or risk in children. In fact, very few studies have investigated the effect of hydration on health outcomes in children. Preliminary evidence demonstrates a link between hydration and physical performance in children: improving hydration by providing education regarding the importance of hydration, a urine color scale [41] to assess the hydration before and after exercise, and by improving water access resulted in increased performance during an endurance run by athletic children [42]. This is relevant since some studies suggest that a majority of child athletes may be insufficiently hydrated before they start exercising [43, 44]. While there are limited data concerning preexercise hydration status of children from the general population, research suggests that many of them have elevated urine concentration on a given "normal" day across various countries [45–49]. Hydration has also been linked to cognitive performance in children in a number of studies [38, 39, 50, 51]. In a cross-sectional study, Bar-David et al. [38] demonstrated that insufficient hydration, indicated by elevated urinary markers of hydration, was associated with poorer short-term memory performance in children. Although limited, a handful of interventions have also indicated that providing children with water results in improved cognitive performance [39, 50, 51].

Water and Hydration at School: Running on Empty?

In this context, understanding the drinking behaviors of children during school, where optimal cognitive performance is essential, seems relevant. A more detailed investigation of fluid intake within 6 countries of the Liq.In[7]

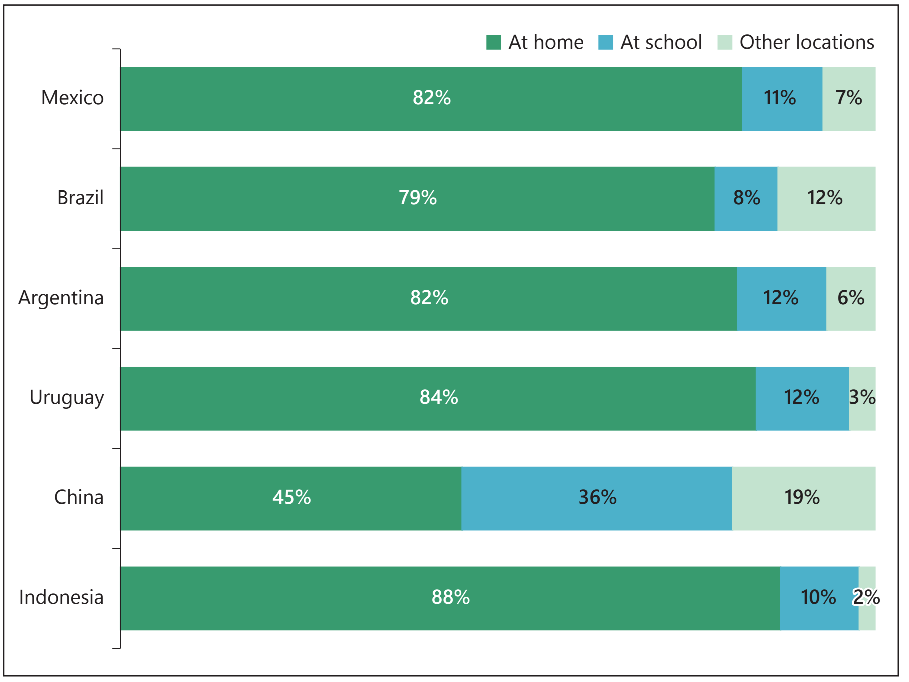

Fig. 1. Proportion of daily TFI in children by location in the Liq.In[7] surveys. Age of the children: 4–17 years old. Sample size for Mexico: $n = 669$; Brazil: $n = 340$; Argentina: $n = 392$; Uruguay: $n = 265$; China: $n = 649$; Indonesia: $n = 866$. Adapted from Morin et al., 2018 Eur J Nutr 57(Suppl 3):101–12.

surveys showed that children only consume 14% of their TFI at school, despite spending approximately half of their waking hours at school (Fig. 1) [52]. This is further confirmed by the results of clinical studies demonstrating that many children have highly concentrated urine before or during school [46, 48, 49, 53, 54] (Table 1), suggesting that a large proportion of children arrive at school already in a state of water conservation, and continue not to drink adequately during the school day. Understanding the barriers that prevent children from drinking at school is essential to promote water intake at school through successful behavior change interventions. Earlier research in this area highlighted barriers in teachers, including poor teacher knowledge of the effect of hydration on cognition, and a fear of disruption to class due to increased need to urinate [55]. Consequently, many teachers limit toilet use to specific times, which may be perceived by children as too short to use the toilet facilities [56]. Other barriers to toilet use reported by children include toilet dirtiness, unpleasant smell, and the fear of bullying [57–60]. As a result, studies highlight that up to 1 out of 4 children report not using the toilets at school to urinate, and 4 out of 5 children not using toilets to defecate [58–60]. Preliminary evidence from France also suggests that this may have consequences on a child's quality of life and ability to focus since 30% of children reported having trouble concentrating because of abdominal pain as a result of not using toilets [59].

Finally, results from the Liq.In[7] surveys demonstrate that many schools simply do not provide access to water for children [52]. This has obvious consequences on drinking behavior as demonstrated by a study of 6 schools in the United Kingdom in which children with limited access to water at school were almost twice as likely to drink below a recommended fluid quantity during school time (calculated from EFSA recommendations) as compared to children with free water access [20], confirming that access to water is a primary driver of water intake at school. In another study from Belgium, comparing hydration in children from 17 primary schools with different school policies on water, children's hydration, assessed by urine osmolality, was better in schools which supported water availability, toilet and hydration-related education, good toilet infrastructure, a formal agreement on drinking and toilet visits, as well as participation of parents and children during the development of policies [19].

Finally, in a toolkit analyzing data from 18 interventional studies, the European Commission joint research center focused on successful measures to promote water consumption and reduce SSB intake in schools. While success was relatively low globally across the studies, multicomponent interventions (i.e., education, changes in the drinking environment including water fountains and/or restricted access to SSB, and a behavioral component involving the family) were found to be

Table 1. Mean osmolality measured in urine samples collected before or during school in clinical studies

Reference	Year	Country	Number (male/female)	Age, years	School collection time	Urine osmolality, mOsmol/kg, mean (SD)	Range of urine osmolality values	Percentage of children with urine osmolality <500 (a) or <600 (b) mOsmol/kg	Percentage of children with urine osmolality >800 mOsmol/kg	Percentage of children with urine osmolality >1,000 mOsmol/kg
Michels et al. [46]	2015	Belgium	371 (176/195)	7–13	School start (around 10 a.m.)	888 (192)	94–1,262	8.9 (b)	76	
Michels et al. [46]	2015	Belgium	371 (176/195)	7–13	Pooling of all samples collected during school time	767 (310)	91–1,291	34 (b)	53.6	
Gouda et al. [48]	2015	Egypt	519 (260/259)	9–11	30 min after breakfast (37%) or fasting sample upon awakening if no breakfast (63%)	814 (250)	122–1,525		57	24.7
Bonnet et al. [47]	2012	France	529 (269/260)	9–11	30 min after breakfast or second void of the morning if no breakfast	823 (227)			62.2	22.7
Robers et al. [65]	1996	Germany	231 (231/0)	3–18	24 h	801				
Robers et al. [65]	1996	Germany	238 (0/238)	3–18	24 h	729				
Soto-Mendez et al. [66]	2015	Guatemala	78	2–7	24 h started from 7 to 8 a.m.	430 (median) 407–491 (95% CI)	115–1,102			
Philip et al. [67]	1993	Israel	200 (125/75)	2–6	Noon time	791 (201)			60.5	7
Bar-David et al. [54]	2009	Israel	428	8–10	Noon time	862 (211)		6.8 (a)	67.5	25
Bar-David et al. [38]	2005	Israel	51 (19/32)	10.1–12.4	Morning (8 a.m.)	856 (232)			62.7	25
Bar-David et al. [38]	2005	Israel	51 (19/32)	10.1–12.4	Noon (1 p.m.)	813 (294)			62.7	25
Kawauchi et al. [49]	1996	Japan	1,453	3–12	First morning urine sample immediately after waking	900 (233)				
Skinner et al. [68]	1996	United Kingdom	322 (170/162)	3–18	Early morning urine sample	845 (median)	275–1,344	17.8 (M) (b) 25.2 (F) (b)		
Stookey et al. [53]	2012	United States	337 (172/165)	9–11	8.30–9.30 a.m.	827 (250)	99–1,372		63	25
Stookey et al. [53]	2012	United States	211 (116/95)	9–11	8.30–9.30 a.m.	853 (219)	186–1,259		66	27

most successful. Indeed, while education and access to water are at the base of hydration, influences from peers, especially in teenagers, may be a key component of changing behaviors. Recent studies have shown that it is possible to increase water and decrease SSB intake in children through a social network-based intervention using the most influential children to promote water consumption [61, 62]. Testing different ways to nudge, enable, or motivate water intake by children may also be useful in identifying the most successful components for initiating and maintaining behavior change in the future [63, 64].

To support adequate intake and optimal hydration in children during school, it therefore seems relevant to: (1) identify barriers to drinking water in schools at the local level, (2) promote and facilitate access to free water access at school and during class as well as improve toilet facilities, (3) educate children, teachers and parents about the

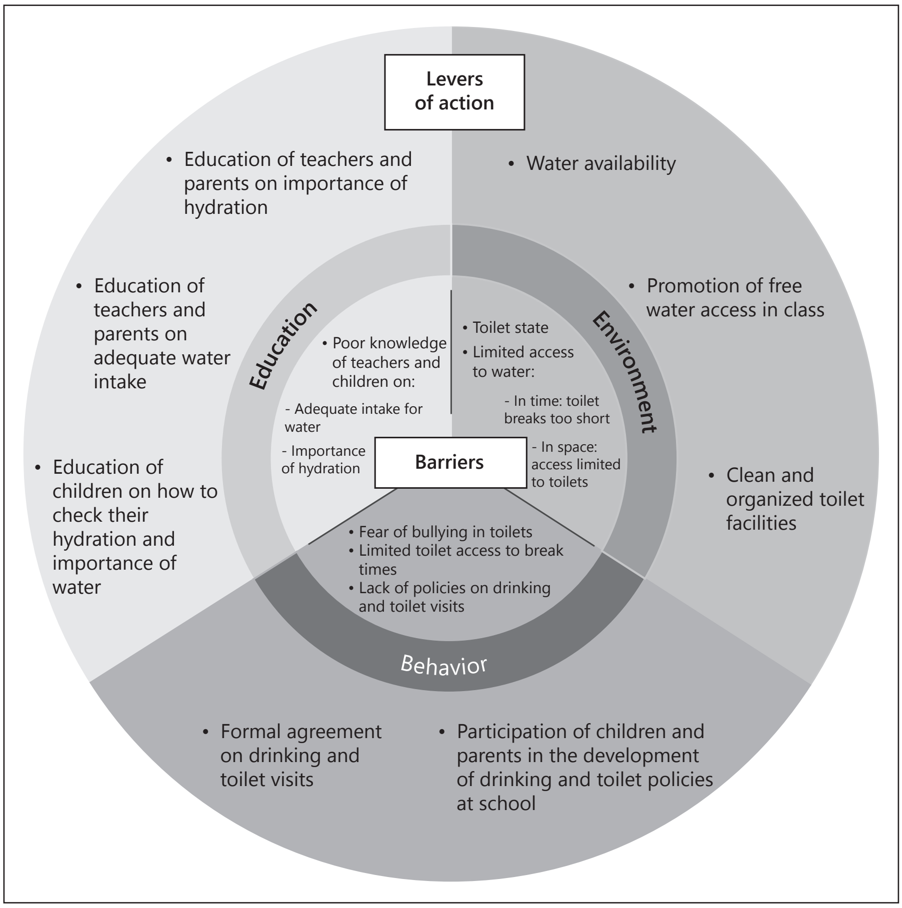

Fig. 2. Identified barriers of water intake in children and possible levers of action to overcome them at school.

importance of water intake and hydration for health, and (4) promote behavior change by motivating and nudging children to drink more water (Fig. 2). Taking inspiration from successful school initiatives as well as involving parents and children through every step of the process may ensure better success.

Conclusion

Maintaining adequate fluid intake and optimal hydration is important for children for physiological reasons and for the adoption of healthy, sustainable drinking habits. Yet, data from the Liq.In[7] cross-sectional surveys suggest that the majority of children do not drink sufficiently, particularly at school. This is further supported by studies in which urinary biomarkers of hydration were collected, showing that many children have highly concentrated urine. This situation is worrisome since studies have demonstrated a relationship between low fluid intake or insufficient hydration and cognitive performance in children. Introducing water to children early and encouraging healthy drinking habits from the youngest age are therefore essential to support adequate fluid intake and optimal hydration in childhood and in later life. Within the family and school context, some actions may be put into place by adults to support healthy drinking habits in children:

- Offering water to children regularly throughout the day without relying on one's own thirst;
- Associating water intake with "moments" such as wake up, breakfast, morning and afternoon breaks to establish a routine;
- Making water accessible to children, even the youngest, at all times by using age-appropriate cups or bottles that children can access and drink from independently;
- Providing a positive parental drinking model for children at home and at school;
- Making water fun by various means such as drinking straws, fresh herbs or sliced fruits, sparkling water, personalized glass, or bottle;

- Introducing children to urine color and hydration assessment from a young age;
- Encouraging and educating children to drink and check their hydration before and after exercise, for example, using urine color;
- Asking children about water access, toilets facilities, and water- and toilet-related education at school;
- Establishing or improving water- and toilet-related policies at school.

Future research is needed to better understand barriers to drinking water in children and to identify factors that successfully encourage water intake in different contexts.

Disclosure Statement

J.H.B., C.M., I.G., and E.T.P. are full-time employees of Danone Research.

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Perspective

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Hydration for Health: So What? Ten Advances in Recent Hydration History

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We have long understood that water is essential to life. From early experiments on water's importance for survival in extreme environments [1] to a thorough understanding of how hydration affects sports performance and safety [2–6], the importance of replacing body water losses is well-known and markers of water loss dehydration are well-understood. However, outside of sport and occupational health, water has remained to a large extent an essential but also an invisible nutrient [7–10]. The past decade marks a turning point in considering the importance of water and hydration for the general population, with significant advances in our understanding of water, hydration, and health. On this tenth anniversary of the Hydration for Health Scientific Conference, we offer the following "top ten list" describing key advances in the hydration and health sciences and present perspectives for the next decade.

The Concept of the *Low Drinker*

This concerns the physiological characterization of otherwise healthy adults who, despite free access to water and other beverages during their daily activities, routinely consume far less than the Adequate Intake for water as defined by European [11] or American [12] public health authorities. These *low drinkers* maintain a normal total body water volume and plasma osmolality and are thus not dehydrated. Yet, they remain in a state of near-

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constant water saving, as evidenced by consecutive days of low urine volume, high or approaching maximal urine concentration, with normal but elevated circulating arginine vasopressin (AVP) and cortisol [13–18], and, curiously, no evidence of increased thirst drive [17, 19] to stimulate increased drinking. This suggests that at least a segment of the general population is relatively insensitive to physiological cues to drink adequately, with possible implications to kidney or metabolic health (see below).

The First Acknowledgement of "Desirable" Urine Concentration in Setting a Dietary Reference Value for Water

The EFSA Scientific Opinion on Dietary Reference Values for water [11], published in 2010, considered for the first time that an adequate intake of water should provide a margin or buffer between "desirable" and maximal urine concentrating capacity. The committee concluded that it would be prudent to provide for a safe margin of "free water reserve" [8, 20]. The water requirement was thus targeted to achieve a urine osmolarity around 500 mosm/L, well below the maximum concentrating capacity of the kidneys.

A Heightened Interest in Accurately Recording Fluid Intake

A key aspect to understanding the relationships between water intake, hydration, and health begins with widespread and accurate recording of fluid intake in population surveys and clinical trials. As recently as 2014, a systematic review of fluid intake across age groups found that while most publications describing fluid intake in adults recorded water intake, more than half the publications involving teenagers or children did not record plain water consumption [21]. Recent work has highlighted that water and fluid intake are underestimated in combined food and beverage recording instruments [22, 23], suggesting the need for a fluid-specific tool. Recently a prospective, 7-day fluid-specific diary was validated against a gold-standard method of water turnover [24]. This validated tool, along with increasing publications describing fluid intake patterns worldwide [25–34], allows for a growing, global worldwide picture of what people drink, essential to understand the impact of fluid intake on health.

The Widespread Availability of an Ultrasensitive Copeptin Assay

AVP, or the antidiuretic hormone, is a key regulator of total body water. It acts via V2 receptors to modulate water reabsorption in renal collecting ducts and thus adjust urinary water losses to maintain body water homeostasis in response to changes in daily water intake. Beyond its role in body water homeostasis, AVP also has widespread central and peripheral effects that make it an interesting candidate in the study of many diseases [35]; however, its instability and rapid clearance have historically made reliable measurement difficult [36]. Copeptin, the C-terminal portion of the AVP prohormone, is released in equimolar concentration to AVP, and therefore would provide a quantitative measure of AVP release. The development and commercialization of an ultrasensitive sandwich immunoassay (B.R.A.H.A.M.S Copeptin pro-AVP, Thermo Scientific, Hennigsdorf, Germany) made possible an explosion of new research on AVP through its surrogate, copeptin. The research impact of this assay has already been profound: a full 3 quarters of scientific papers including copeptin have been published in just the past six years.[1] This includes explorations of the role AVP may play in the development of kidney and cardiometabolic disease (see below).

The Copeptin Explosion and the Rise of the Cohorts

The availability of the ultrasensitive copeptin assay has facilitated a surge of publications identifying copeptin, a surrogate marker of AVP, as an independent risk factor in kidney and cardiometabolic disease. More specifically, higher plasma copeptin (usually defined as the top quintile or quartile measured in population studies) has been independently associated with increased likelihood for incident impaired fasting glucose or type 2 diabetes mellitus (T2DM) as well as components of the metabolic syndrome including hypertension, high C-reactive protein, or abdominal obesity [37–40]. Moreover, in patients with existing T2DM, higher copeptin appears to be linked to higher risk for the onset of kidney pathology including a more rapid eGFR decline [41] or doubling of serum creatinine in addition to increasing risk for cardiovascular events [42]. This evidence, pooled with associations be-

[1] PubMed search on January 24, 2019 for "copeptin" in Title and/or Abstract. Of a total of 869 records returned in the search, 650 (75%) were published in 2013 or later.

tween low urine volume or low water intake and kidney or cardiometabolic disease [43–46], suggests that a combination of habitual low drinking, highly concentrated urine, and a higher circulating AVP may contribute to increased risk of metabolic disease in healthy individuals and may worsen comorbidities in those with existing T2DM.

New Statistical Approaches Help to Establish a Probable Causal Role of Vasopressin in Metabolic Disease

While large, prospective cohorts have documented associations between AVP and disease risk, these studies cannot establish whether higher circulating AVP plays a causal role in the development of metabolic dysfunction. A recent publication by Roussel et al. [39] attempts to shed light on the directionality of the relationship by exploring patterns of mendelian randomization. Briefly, the authors documented that participants (men and women) in the upper quartiles of copeptin had higher incidence of hyperglycemia and lower insulin sensitivity than those with lower plasma copeptin. They also found that specific variants of the AVP gene were also associated with increased risk for hyperglycemia, and that men expressing these variants also had higher plasma copeptin (no association was found in women, who, on average, tend to have lower plasma copeptin than men). This finding is consistent with previous preclinical evidence that AVP contributes to metabolic dysfunction via V1a and V1b receptors expressed in hepatocytes and pancreatic islets, respectively [47–50].

First Findings that Increasing Water Intake Lowers High AVP, a Risk Factor for Disease

If higher AVP (copeptin) is an independent risk factor for disease, might increasing daily water intake meaningfully lower circulating AVP? And would this reduction subsequently improve long-term health outcomes? Four recent, independent studies provide a convincing proof of concept that among low drinkers, and particularly in those with high baseline AVP, increasing water intake lowers AVP (or copeptin) over hours [51], days [17], or weeks [52, 53]. Promisingly, the copeptin-lowering effect appears to be most pronounced in individuals with higher baseline copeptin as well as other baseline signs of low drinking (such as low urine volume or high urine osmolality), suggesting a potential subpopulation of "water responders" for whom increased water intake may represent an attainable lifestyle intervention with real potential for health benefit. Important gaps still exist as to whether increasing water intake and subsequently lowering AVP would result in a reduction in disease incidence. A recent study by Enhörning et al. [53] found that in addition to reducing copeptin, 6 weeks of increased water intake resulted in a modest but significant lowering of fasting plasma glucose; furthermore, the reduction in glucose was predominantly driven by those with the highest baseline copeptin and the greatest reduction in response to the water intervention. Longer-term, larger-scale interventions are needed to verify whether increasing water intake to lower AVP reduces or slows the onset of disease.

Water Intake as a Potential Therapeutic Target for Renal Disease

Water intake has generated interest as a potential therapeutic agent for multiple kidney diseases including urolithiasis, chronic kidney disease (CKD), autosomal dominant polycystic kidney disease (ADPKD), and the mesoamerican nephropathy epidemic [54, 55]. In urolithiasis, low water intake and low urine volume are known risk factors for stone formation [56–60], and increasing water intake to promote the excretion of a large volume of dilute urine is recognized in secondary stone prevention [56, 61, 62]. Less is known about the potential therapeutic role of water intake and hydration in CKD and ADPKD. While a pilot study involving stage 3 CKD patients documented that increasing water intake increased urine volume and lowered plasma copeptin [63], a larger-scale randomized controlled trial failed to show that an increase in water intake slowed the progression of the disease [64]. However, the increase in urine volume was quite modest (+0.6 L.d) and the follow-up time relatively short. In ADPKD, the suppression of AVP by increased water intake may slow renal cyst growth; however, the limited human data available are conflicting. A large RCT is currently assessing the safety and efficacy of prescribed water intake to slow disease progression [65]. Finally, recurrent exposure to heat stress and dehydration has been identified as a key risk factor in the mesoamerican nephropathy [55], an epidemic of CKD of unknown etiology affecting young men working in Central American agricultural fields in the lower altitudes along the Pacific coast. Further investigation into these pathologies, the mechanisms by which water intake may alter the course of the disease, and the efficacy of water intake as a therapeutic agent, all represent exciting future research opportunities with the potential to impact public health.

The First RCT on Water Intake for the Prevention of Urinary Tract Infection

The recent publication of the first RCT on increased water intake to prevent urinary tract infection (UTI) recurrence demonstrated that water intake can play a powerful role in secondary prevention [66]. This 12-month study demonstrated that increasing water intake by 1.2 L/day cut UTI recurrence in half in women who suffered from recurrent UTI and who, at baseline, consumed <1.5 L of water and other beverages daily. This is especially relevant given the high prevalence of UTI (more than 60% of women worldwide); the widespread use of antibiotics to treat each recurrence or as prophylaxis; and the health-care costs associated with diagnosis and treatment. Moreover, this subject struck a chord with a decidedly nonscientific audience, generating mainstream media attention, a surge of activity on social media, in addition to becoming one of the most attended-to articles on the journal website,[2] suggesting widespread interest in the fact that something as simple as increasing water intake can measurably impact health.

Growing Academic Interest and Debate around What It Means to Be Well-Hydrated

The study of hydration is expanding, from its origins in dehydration, sports performance, and safety toward an increased understanding of how hydration plays a role in health. Until quite recently, however, the models, terminology, and biomarkers used to describe hydration remained rooted in the concept of body water gains and losses [67]. To be euhydrated was, for all intents and purposes, defined by the absence of dehydration (hypohydration) or measurable body water loss. Little attention was paid to the process by which euhydration was maintained, that is, by modulating urinary water losses as a function of water intake. Today, we see a growing interest and healthy debate over what it means to be well-hydrated that extends beyond simply replacing body water losses. Recent publications have weighed in on the distinction between the hydration state and the hydration process [18, 68–71]; have proposed cutoffs and criteria for defining underhydration, optimal hydration, and the question of daily water requirements [72–76]; have debated the validity of various hydration biomarkers in different circumstances [77–82]; and have introduced concepts for various beverage indices [83, 84]. Evidently, as in any academic field, there are differences of opinion, discrepancies that require clarification, conflicting evidence, and many subjects that have not been adequately addressed. However, the fact that the subject of hydration for health is now on the table and being vigorously debated is a positive development, which will encourage further scientific advances in the years to come.

Perspectives for the Next Ten Years

Today, we have a solid foundation upon which to build the next generation of hydration and health research. We have valid tools to measure fluid intake and easier access to measuring copeptin, a reliable surrogate for AVP and antidiuretic activity. We have a large body of epidemiological evidence that suggests that low water intake, low urine output, and high AVP are associated with kidney and metabolic disease risk. We have plausible mechanisms and supporting preclinical evidence for how low water intake or suboptimal hydration may contribute to disease. We have proof of concept studies which demonstrate that increasing water intake can lower high plasma copeptin, a key risk factor in disease, and a first large-scale randomized, controlled trial demonstrating that water is effective in secondary prevention of UTI. After ten years of developing the framework for research around hydration for health, where are the critical gaps? What still needs to be done? The following is a nonexhaustive list of opportunities to contribute to this growing field of research:

- Dig further into defining thresholds for copeptin that are predictive of disease risk and deepen our understanding of the apparent sex differences in the relationships between water intake, AVP, and disease.
- Need for large-scale, appropriate-length RCTs to determine under which conditions increased water intake may play a role in disease prevention or health maintenance.

[2] At the time of writing, the article has been viewed more than 42,000 times at the journal website, is ranked within the top 2% of all research reviewed by Altmetric for quality and quantity of online attention received, including news media, blogs, and social media.

- Support or improve thresholds or criteria for optimal hydration.
- Increase our knowledge of water intake, hydration, and health in underresearched populations, such as young children, pregnant and breastfeeding women, and the elderly.
- Understand the role water intake and hydration may play in modulating comorbidities (for instance, reducing the risk for diabetic nephropathy in T2DM).
- Dig deeper into water and fluid intake patterns of selected demographic groups and develop strategies to encourage healthier drinking habits.

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Table 1. Selected topics that were presented at previous Hydration for Health scientific conferences, 2009–2017

Effects of dehydration on brain function and cognitive performance
Cellular processes involved in total body water balance and movement of water between fluid compartments
Relationships between water consumption and renal diseases, including acute kidney injury, chronic kidney disease, kidney stones, urinary tract infections
Epidemiological links between low daily water intake and the following chronic diseases/disorders: diabetes, cardiovascular disease, obesity, metabolic syndrome
Chronic underhydration: habitual low-volume drinkers
Multiple factors that induce and regulate thirst
Self-assessment of daily hydration status: urine color, thirst, body weight change
Hormonal regulation of total body water via arginine vasopressin (AVP), angiotensin, and atrial natriuretic peptide
Hydration needs of pregnant and breastfeeding women
The relationship of daily water intake to weight loss
Teaching children to value healthy drinking habits
Positive parental role models of healthy drinking habits and beverage choices
Encouraging healthy drinking in schools by creating schedules that allow students to drink from fountains and use toilets
Programs that improve community water quality, sanitation, and waterborne illnesses

optimal drinking at school. Dr. Jeanne H. Bottin and colleagues promote water consumption in schools via multiple interventions that combine educational, environmental, and behavioral support for adequate drinking and optimal cognition. Expanding consideration of cognition, Daniel Westfall, Northeastern University, USA, notes that children are an understudied group and that the cognition literature provides inconsistent findings. In an effort to rectify this situation, he reviews the definition of cognition and the domains of which it is composed, explains how cognition has been measured in both field and laboratory studies, presents the results of neuroimaging studies, and describes the relationship between hydration and academic achievement in children. Third, Dr. Schätzer of the Institute for Preventive Cardiology and Nutrition in Austria describes efforts to improve nutrition education, student drinking behavior, and the local school environment (e.g., sugar sweetened beverages offered at vending machines). Due to the existing infrastructure, staff, facilities, and policies, he believes that schools provide a logical site to implement programs and interventions, which promote healthy hydration practices for 10- to 18-year-old pupils.

In the article by Belogianni and colleagues, a joint initiative is described that seeks to increase awareness of healthy hydration practices among dietitians and provide evidence-based resources for patients and clients. Named the European Healthy Hydration Awareness Campaign, this initiative combines the resources of EFAD and Danone Research to generate a webinar, a tutorial, and an online hydration resources center, among other benefits. Examples of these resources can be viewed by entering the term "European Healthy Hydration Awareness Campaign" into your search engine.

On a larger scale, community and international efforts to prevent kidney diseases are described in the 2 articles written by Professor Etienne Macedo, MD, PhD, Department of Medicine, University of California San Diego, USA. With the advent of disease classification systems, our understanding of acute kidney injury (AKI) has evolved. For example, the International Society of Nephrology in 2013 launched the 0 by 25 campaign with the goal that no patient should die from preventable or untreated AKI in low-resource areas by 2025. As a result, we now know that community-acquired AKI in low-income and low-middle income countries have common risk factors. A subsequent project, the Global AKI Snapshot study, provided insights into the recognition, treatment, and outcomes of AKI worldwide. In her first article, she comments on the main findings and lessons learned from the 0 by 25 initiative. Second, Professor Macedo describes a future study in 3 communities bordering Lake Chapala, Mexico. Before implementing this research, she and her colleagues will determine the water, sanitation, and hygiene characteristics of the target population and evaluate the incidence of diarrheal disease. The goals of this study will be to determine if consumption of unsafe water is associated with an increased incidence of gastroenteritis leading to episodes of AKI and to determine if the provision of clean water to the residents of these communities (i.e., as a research intervention) is associated with a decreased incidence of clinical complications.

The final 2 publications in this special supplement involve the increasing incidence of kidney disorders resulting from the combined effects of strenuous labor in a hot environment, inadequate water intake, and other lifestyle or work environment factors (e.g., nonsteroidal anti-inflammatory drugs, renal infections, diet, pesticides, heavy metals). Dietitian-Researcher Fabiana Nerbass, Nephrology Division, Pró-Rim Foundation, Brazil, examines the feasibility of conducting kidney health research in factories. Chronic kidney disease of unknown etiology was the focus of this pilot study. More than 25 hydration, kidney function, personal, circulatory, blood, and urinary variables were successfully observed. The authors declare industrial research of this type feasible, but also described the limitations of conducting research in a factory environment. In my opinion, such future research studies will have greater external and internal validity if the following features are incorporated into the experimental design: on-site measurements of environmental conditions, chronic changes of kidney function measurements across months and years, recorded histories of previous kidney disease or dysfunction, chest/wrist heart rate monitor values that describe the intensity of the work performed, verification of the extent of dehydration and hyperthermia in workers, and recording physiological measurements immediately before, during (i.e., lunch break), after the work shift. Dr. Richard Johnson, University of Colorado, USA, also considers industrial scenarios from the perspective of global warming, which may result in kidney disorders, disability, and loss of productivity. His previously published research focused on chronic kidney disease among Central American laborers. Given the increase of air temperatures worldwide, there is a great need to better understand how heat stress can induce kidney disease, how best to provide adequate hydration, and ways to reduce the negative effects of chronic heat exposure in work environments.

Since 2016, attendees have overwhelmingly expressed their enjoyment of the Young Researcher Competition; it generates excitement. Six invited speakers are allowed only 3 minutes each to present their research on stage; the audience then selects, by electronic vote, a winner for the Young Researcher Award. The 2018 recipient was Gabrielle Giersch, USA, for her project titled, “Mild Dehydration by 24 h Fluid Restriction Increases Evening Fatigue and Sleep Duration.” Her abstract appears with those of the five other invited contestants on the final pages of this journal supplement.

The breadth of the topics and the interchange of ideas that appear in this special supplement demonstrate that the 2018 conference in Evian, France, was as successful as the 9 previous Hydration for Health Scientific Conferences (Table 1). This event provided a fitting conclusion for the first decade of successful conferences and stimulated interest in future discoveries regarding human hydration.

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