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Dr. Widjaja Lukito serves as a member of Hydration for Health Scientific Committee.

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Editorial

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Current Evidence in Water and Hydration Science

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Introduction

Water constitutes a significant component of the human body. It accounts for 50–80% of body weight, depending on lean body mass [1]. The human body needs water as an essential medium for metabolism and various biochemical reactions. Many organ functionalities require the role of water. Therefore, water deficit in the forms of hypo- and dehydration leads to organ dysfunction, and, vice versa, many health problems and organ-based diseases contribute to body water imbalance and dysregulation.

Water and hydration are two sides of the same coin. In healthy individuals, water consumption significantly affects hydration status, and, vice versa, hydration status depends on water intake. These relationships are not applicable to overtly sick individuals, e.g., with ascites in liver cirrhosis, edema in nephrotic syndrome, and water retention in hypercortisolism. At this point, water has its functionalities beyond hydration, it has reached out to many dimensions of health and medicine [2]. Water, hydration, and health are three inseparable dimensions that have been comprehensively discussed for 13 years in Hydration for Health (H4H) conferences.

The evolution of H4H conferences has built on its own credibility. H4H conferences bring together experts from all disciplines with an interest in hydration for health to share cutting-edge research in this area. H4H started with a small, invited audience from a narrower range of disciplines and now involves more diverse experts in health, social, and environmental sciences. The 13th edition of H4H conferences presented, among other themes, emerging evidence on the potential roles of hydration on microbiome and immunity. The active participation of Early Career Researchers demonstrated a sustained capacity of professionals in water and hydration science. Overall, the event sustains more professionals and experts and young professionals and researchers.

The elaboration of the articles in the current proceedings can be at least clustered into five themes: thirst, physiology of hydration and aging; epidemiology of fluid intake patterns; psychology of thirst and hydration; hydration, metabolic responses, and kidney disease; and water, hydration, immune response, and gut microbiota.

Thirst, Physiology of Hydration, and Aging

Armstrong and Kavouras [3] have reviewed comprehensively the complexity of the thirst paradigm and the drive to drink water in 2019. In short, the understanding of thirst has undergone a long evolution, which has also involved various experts from different disciplines. Ad-

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vances in neuroscience with its imaging technologies have made a significant leap in explaining the phenomenon of thirst and motivation to drink water. In the present proceedings, Bichet [4] affirmed that two brain regions have already been defined to be important in drinking behaviors in animals, the subfornical organ and the organum vasculosum of the lamina terminalis, which can perceive two modes of thirst, osmotic and hypovolemic. Moreover, the peripheral sensory systems in the tongue, which have multimodal sensations, like taste and olfaction, can also taste water through the change in the pH of the saliva due to dilution by water.

Carroll [5] described four compartment-multidisciplinary models of thirst beyond a "conventional" physiological understanding of thirst, namely true thirst, which is primarily osmoregulated; contextual thirst like that induced by mouth-breathing; pharmacological thirst, as a consequence of drugs and excipients; and impulsive thirst like daily spontaneous drinking. Pharmacologic thirst and pharmacologic-induced hypohydration should become the focus of attention for clinicians and healthcare professionals in clinical settings. Pharmacologic thirst and pharmacologic-induced hypohydration have been reviewed comprehensively. Documented mechanisms of hydration status alteration by polypharmacy include decreased thirst sensation, diarrhea, increased urine volume, decreased appetite, increased sweat production, and central thermoregulatory affectation [6].

With aging, lean body mass and total body water decline. In aged individuals, many body functions, like cognition, mobility, and thirst sensation, decline [7]. On the other side of the coin, the aged are exposed to various health problems, such as, amongst others, metabolic syndrome and cardiovascular and chronic kidney diseases [8]. Johnson [9] suggested the cause-effect of low water intake in the aging process. It is plausible that improving water intake, to a significant extent, is a strategic interventional modality for healthy aging.

Epidemiology of Fluid Intake Patterns

Findings of various fluid consumption and its determinants using *Liq.In7* records in 13 countries worldwide [10, 11] have enriched the science of hydration for health. The use of harmonized *Liq.In7* records in those countries has demonstrated its reputation in minimizing unnecessary data variability due to inconsistency in methodologies [12, 13].

Two articles in the present proceedings describe further analyses of fluid intake habits and patterns in children and adolescents [14, 15]. Two findings can be emphasized: first, the finding that a high proportion of children and adolescents did not meet the European Food Safety's Adequate Intake recommendations for total fluid intake raised public health concerns about their hydration status and its related health and well-being outcomes; second, consumption of sugar-sweetened beverages (SSBs) in a significant proportion of children and adolescents, with low or high drinkers, raised the issue of future public health problems of noncommunicable diseases. The substantial contribution of SSBs consumption to daily sugar intake has raised concerns due to its adverse impacts on health [16]. SSBs consumption of adolescents at school strongly indicates the need to promote healthy drinking, aiming to prevent future unfavorable health outcomes and reduce the burden of noncommunicable diseases. Parental education holds its own importance. In many cases, responses to sweetness can originate from and form through repetitive exposure to foods and beverages prepared regularly at home, which are determined by family choices or parental preferences [17].

Psychology of Thirst and Hydration

Two articles in the present proceedings discuss perspectives of fluid intake, hydration, and mood changes, alertness, and drinking behavior using the COVID-19 lockdown model.

Yoder et al.'s [18] findings on the effect of hydration on self-reported thirst and alertness have added to the discourse on the importance of hydration status on several aspects of cognitive function. An earlier study by Pross et al. [19] with a different study design demonstrated that in individuals with high water intake, restricted water intake resulted in a significant increase in thirst and a decrease in contentedness, calmness, positive emotions, and vigor/activity. On the other hand, in those with low water intake, increased water consumption resulted in a significant decrease in fatigue/inertia, confusion/bewilderment, and thirst and a trend to lower sleepiness compared to baseline. Edmonds et al. [20] proposed that thirst moderates the effect of water, through centrally processing resources, on some aspects of cognitive performance. Their proposal was derived from their findings on the positive effects of water supplementation on the speed of responding, which may imply alertness.

For ~2 years, the COVID-19 pandemic has shown no signs of ending. Countries worldwide have implemented lockdown policies, and this policy has been implemented several times. Papies et al. [21] reported how drinking behavior changed during the UK lockdown. Water consumption during the lockdown did not increase. On the other hand, consumption of SSBs increased markedly, to the extent of negating the previous achievement of decreasing consumption of SSBs as part of a healthy lifestyle.

In their scoping review, Bennett et al. [22] reported that the effect of the COVID-19 lockdown both negatively and positively impacted dietary practices, and negative dietary habits were associated with other related poor lifestyles, including weight gain, mental health issues, and limited physical activity. These findings are of great concern given that unhealthy dietary behavior greatly affects the preexisting comorbidities [23] and the degree of severity of comorbid COVID-19 sufferers, which can aggravate inflammation and even increase the mortality rate [24].

Hydration, Metabolic Responses, and Kidney Disease

The previous proceedings have elaborated on the roles of the vasopressin system in the risk of diabetes and cardiorenal diseases [25, 26]. Available data showed that increased water intake led to a decline in plasma osmolality and copeptin, a surrogate biomarker for vasopressin. High plasma copeptin is a significant independent predictor of the development of new-onset diabetes [26]. By using an acute experimental model, Seal et al. [27] demonstrated the importance of adequate water intake for plasma gluco-cortisol regulation. Arginine vasopressin (AVP as indicated by copeptin) induces hypersecretion of adrenocorticotropic hormone (ACTH) and cortisol, and this does not have a negative feedback loop [28]. Further comprehensive studies are needed to determine whether the acute effect of delayed reduction of plasma glucose was due to vasopressin or ACTH pathway.

There is another mechanism reported by Andres-Hernando et al. [29] concerning vasopressin. Animal studies have shown that dehydration causes stimulation of the polyol pathway in the hypothalamus, thereby increasing fructose and vasopressin production, leading to fructose-induced obesity and metabolic syndrome. By increasing water intake in a fructose-fed mice model, they could demonstrate the reversal of obesity, which was associated with suppression of vasopressin levels.

Two articles address the relations between hydration and kidney health. Lartey et al. [30] analyzed the NHANES epidemiological dataset from 3 sample years 2005/2006, 2007/2008, and 2011/2012. The merged 3-period dataset revealed that participants with low total water intake were ~7% more likely than their counterparts with high total water intake to develop moderate to severe kidney dysfunction.

Battistone et al.'s [31] original animal studies have opened new insights into the timely management of dehydration-induced acute kidney injury. In principle, there are three elements that exert their significant contributions to renal inflammation, namely type A intercalated cells, P2Y14 receptors, and UDP-glucose (UDP-Glc) that are intertwined and mutually influencing each other, inducing an inflammatory cascade and, finally, leading to severe acute kidney injury, a potential medical complication with high mortality rate [32]. This study has raised a new hypothesis that blocking the UDP-Glc/P2Y14 pathway represents, therefore, a new therapeutic avenue for the prevention and or attenuation of dehydration-induced renal inflammation and dysfunction [33].

Water, Hydration, Immune Response, and Gut Microbiota

Universal and equitable access to safe and affordable drinking water is crucial for public health. Contaminated water and poor sanitation are linked to the transmission of preventable water-borne diseases, such as cholera, diarrhea, dysentery, hepatitis A, typhoid, and polio [34]. While the global burden of diarrheal disease remains high, continuous scientific interest in the effects of the drinking water microbiome and its sources and hydration status on the gut microbiota has attracted the attention of inter-disciplinary researchers [35, 36].

Vanhaecke [35] reported on the associations between the drinking water source and gut microbiota composition in the American Gut Project Database. Gut microbiota of 3,413 individuals was analyzed and categorized by the source of drinking water, namely bottled, tap, filtered, and well water. This study showed that drinking water source ranked among the key contributing factors explaining the gut microbiota variation both in alpha and beta diversity analyses, with effect sizes comparable to those of alcohol or diet type. Individuals drinking mostly well water also had higher fecal alpha diversity than the other groups. In addition, taxonomic differences were found in well water drinkers, with their potential of clin-

ically important taxa, such as *Bacteroides*, *Odoribacter*, and *Streptococcus*, being depleted and *Dorea* being increased as compared to the other groups.

These findings show the importance of drinking water sources as a confounding factor in examining the human microbiome. Combined with the report of a previous study on the diversity of the microbiome across different habitats [37], this current report has enriched the evidence pointing to an ecosystem strategy for drinking water sources, adequate hydration, and gut health, and also their link with each other [38].

Willis et al. [36], the winner of this H4H Early Career Researcher Award, reinforced the view of how hydration status affects the human fecal microbiota. This article presented three pathophysiological mechanisms that can lead to a clinical syndrome of gut dysfunction, including intestinal inflammation, gut barrier dysfunction, and fecal microbiota. Hydration status affects the dynamics of these three mechanisms. Two lessons can be learned from this study. First, the hypohydration state affects mucin production in the intestinal mucosal lining to the extent that the intestine becomes susceptible to inflammation [39, 40]. Intestinal inflammation contributes to impairment of gut barrier function. This mechanism can be concluded by the negative correlation between copeptin (substitute biomarker for hydration status) and protein-binding lipopolysaccharide. Second, there is a high plausibility that hydration status favors specific taxa of gut microbiota, which eventually contributes to its composition that favors the intestinal mucus barrier function.

The link between hydration and the immune system is an important future agenda in hydration for health [41, 42]. Innate and adaptive immunity play their parts in harmony and synergy against foreign and infectious agents. Eco-immunology research in reptiles has shown the role of hydration status on innate immunity using in vitro proxy parameters [43], and this phenomenon was not nutritional energy dependent. Many studies in exercise immunology showed the effect of strenuous exercise on the acute and chronic immune systems [44]. The immune system is very responsive to the workload of exercise. In individuals with intense exertion, several innate components, like natural killer cell activity and neutrophil oxidative burst activity, and adaptive components, like the T- and B-cell immune system, are functionally suppressed. At the same time, both plasma pro- and anti-inflammatory cytokines are elevated. Again, in this model of immune alteration, hydration status is not the only contributing factor; at the same time, energy balance, heat stress, and stress hormones make significant contributions [43, 45].

Observational Remarks

Sufficient scientific evidence on hydration for health in the present and previous proceedings confirmed the role of water and healthy hydration in a healthy life. We are faced with the question on how to monitor, evaluate, and appropriately correct our hydration status [46]. Monitoring and evaluating hydration status is important for athletes for their performance. However, there are strong relationships between hydration status and metabolic and kidney health; therefore, we also need to monitor it for our long-term health and well-being. One of the simplest methods is monitoring urine color [47]. The present proceedings have demonstrated the importance of measuring biochemical indicators, such as UDP-Glc, for early detection of organ disorders; an increase in UDP-Glc is an early sign of acute kidney injury due to dehydration.

Achieving adequate hydration in the elderly is a challenge in itself. Body composition changes markedly in the elderly by a decline in lean body mass and total body water and increased body fat mass. By virtue of physiological changes with aging, the level of euhydration in the elderly can differ from that of young adults. Multiple illnesses and polypharmacy often pose a higher risk for hypo- and de-hydration to the elderly than to young adults [48]. Declining brain health and prevailing neurodegenerative diseases [49] in the elderly, with their apparent neuron loss, may adversely affect the neural circuits controlling thirst. Therefore, it is vital not to forget healthy drinking practices in aged care in both community and institutional settings.

Epidemiological data regarding fluid consumption patterns in children and adolescents show that a reasonably high number among them are consuming SSBs. This situation constitutes a serious public health problem in the future. The World Health Organization (WHO) reported that the prevalence and incidence of type 2 diabetes remained high globally including in the developing countries [50]. Data are now accumulating demonstrating the relations between SSBs consumption and type 2 diabetes and cardiometabolic health [51], now including an association with early-onset colorectal cancer in women [52]. On the other hand, the development of the concept of sweetness in beverages will further affect the consumption patterns of SSBs in children and adolescents. The concept of sweetness was developed based on the understanding that sweetness in SSBs does not have to be due to sugar, but sugar can be replaced by sugar substitutes or low-calorie sweeteners. Switching sugar to sweet-

eners still raises a new dilemma: what are the consequences of high low-calorie sweeteners exposure in children and adolescents, considering that children and adolescents prefer sweet tastes compared to adults [53, 54]. The influence of parents on children and adolescents concerning the consumption of SSBs has raised the importance of household education on healthy drinking.

Findings regarding the role of water and hydration on the human gut microbiota deserve more attention. Two articles in the present proceedings provide strong evidence for the need for an ecological approach to water sources with the diversity of their microbiomes by their habitats. Many studies showed the importance of gut microbiota for better health outcomes, especially gastrointestinal health. An important lesson that we can learn from the two articles in this issue is that there is significant potential for orchestration between hydration, mucin production, and gut microbiota, which, if there is dysregulation of these three factors, may lead to inflammation, gut barrier dysfunction, and then, further negative implications for gut health.

Water is an essential element for biological function, and it is needed to achieve the required hydration status. The overall discussion points in the present proceedings have reinforced the value of hydration for health, which is fundamental but often ignored or forgotten and should be the focus of attention in many public-health interventions in both developed and developing countries.

Conflict of Interest Statement

W.L. has served as a Scientific Committee member of the Hydration for Health conference and received a consulting fee from Danone Research. He is also the Chair of the Indonesian Danone Institute Foundation and receives relevant honoraria.

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New Animal Data on Osmotic and Hypovolemic Thirst

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Keywords
Osmotic thirst · Hypovolemic thirst · Subfornical organ · Organum vasculosum of the lamina terminalis · Taste receptors

Abstract
Introduction: The group of Yuki Oka, working at Caltech, recently discovered unique populations of neurons in the mouse brain that separately drive osmotic thirst and hypovolemic thirst [1]. After eating salty chips, the concentration of salts and minerals in blood becomes elevated which induces a state called osmotic thirst. On the other hand, after exercising and losing water and some electrolytes, a different thirst called hypovolemic thirst occurs since extracellular fluid volume is reduced. Two brain regions have already been defined to be important in drinking behaviors in animals, the subfornical organ and the organum vasculosum of the lamina terminalis. ***Methods:*** With a technique called single-cell RNA-seq, single cells were found to be involved in specific behavior states, that is, either drinking pure water and avoiding salty water, osmotic thirst, or, appetite for mineral-rich liquids for hypovolemic thirst (Fig. 1). ***Discussion/Conclusion:*** Thirst is therefore a multimodal, many ways, 2 or more, of doing things, sensation, activated by 2 different stimuli, osmotic and hypovolemic. Multimodal means having, or using, a variety of modes, or methods to do something. Multimodal teaching is a style in which students learn material through a number of different sensory modalities. For example, a teacher will create a lesson in which students learn through auditory and visual methods. For thirst, the 2 circumventricular sensory group of neurons, that is, the subfornical organ and organum vasculosum of the lamina terminalis, are able to perceive 2 modes of thirst. Other peripheral sensory systems are also characterized by multimodal sensations like taste and olfaction. The fungiform papilla of the anterior tongue involved in water and salt tasting is also described as a complex multimodal sensory organ for taste, tactile, and temperature modalities [2]. The instantaneous and simultaneous sensations of taste, touch, and temperature when solid or liquid stimuli contact the tongue tip are necessary for eating and drinking. Oka and his team [3] also found that the tongue has a taste for water: applying deionized water to mouse tongues caused specific taste nerves to fire owing to a change in the pH of the saliva as it was diluted by the water. Water is detected only by acid-sensing taste receptor cells (type III cells). The appetitive sodium responses are mediated through the sodium-selective ENaC pathway (type III cells), whereas the rejection of high salt results from the recruitment of the sour- and bitter-taste-sensing pathways (type II cells) [4]. It is therefore inferred that our brain senses internal states by using similar strategies.

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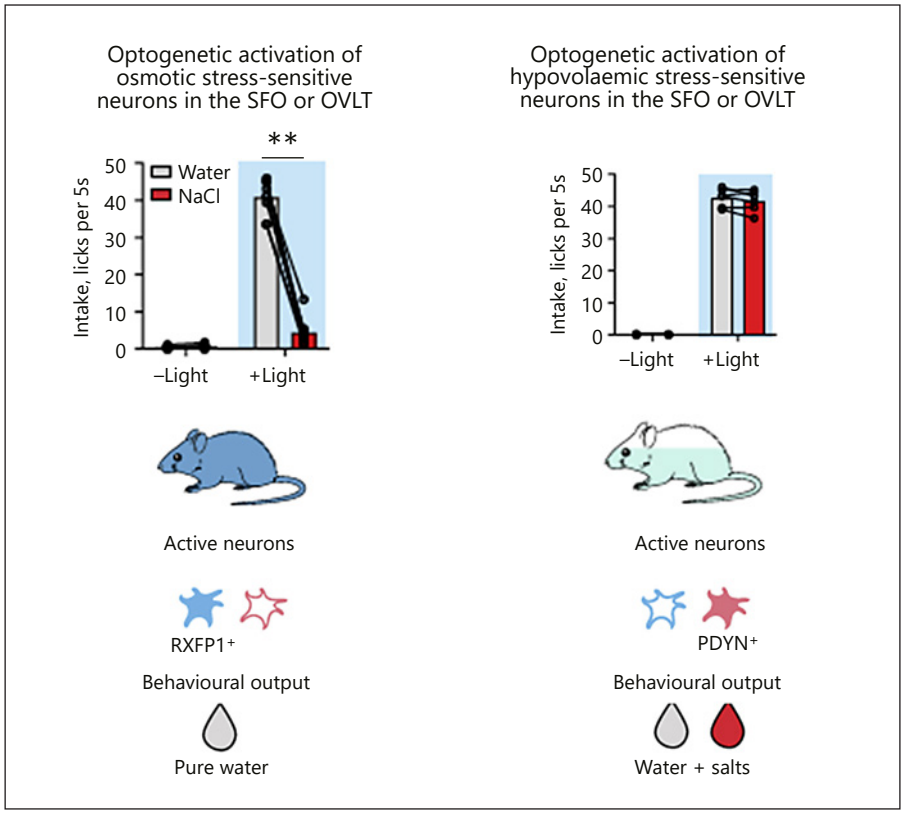

Fig. 1. Optogenetic activation of RXFP1 (relaxin/insulin-like family peptide receptor 1) neurons drive selective drinking of pure water (left). Conversely, stimulation of prodynorphin neurons drives consumption of both water and hyperosmotic salt solution (right) Modified and redrawn from [1].

Statement of Ethics

This work is based on previously published data and therefore does not require ethical approval.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

Funding Sources

This study was supported by Research Center, Hôpital du Sacré-Cœur de Montréal.

Data Availability Statement

The data referred to in this abstract can be found in reference [1].

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Abstracts

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Redefining Thirst: Beyond Dehydration and toward a Holistic Biopsychological Model

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Keywords
Appetite · Acetylcholine · Hydration · Osmolality · Thirst · Xerostomia

Abstract
Introduction: Currently, the conceptualization of thirst is based nearly entirely on osmoregulation, with some acknowledgment of anticipatory-thirst, though with no testable mechanism. Such a model of thirst is unable to explain many thirst-related phenomena, such as why drinking can occur with hypoosmolality or how quantity of intake at a drinking occasion is regulated. ***Discussion:*** This model aimed to unify various lines of thinking from different disciplines surrounding thirst by presenting a 4-compartment model comprising true-thirst (primarily osmo-regulated), contextual-thirst (e.g., mouth-breathing), pharmacological-thirst (induced from drugs), and impulsive-thirst (everyday spontaneous drinking). Within this framework, xerostomia (dry mouth) is the primary regulator of drinking, with a further differentiation between a literal dry mouth ("true-xerostomia," hyposalivation) and the sensation of dry mouth ("sensational-xerostomia," a typically nonoverwhelming desire to drink based on a feeling of dry mouth without hyposalivation). Based on pharmacological-thirst mechanisms, the cholinergic system is proposed to initiate impulsive-thirst by triggering a (sensation of) dry mouth in everyday life. Food-appetite constructs that are centrally regulated (sensory-specific satiety, palatability, and pleasantness) are applied to thirst to explain everyday drinking patterns. ***Conclusion:*** This model helps to explain some anomalies that are thus far unexplained by true-thirst, though there are several other factors which may need to be included after further exploration in the future.

Statement of Ethics

This is a theory paper; no human or animal participants were used as no study was conducted.

Conflict of Interest Statement

H.A.C. has received research funding from the Economic and Social Research Council, the European Hydration Institute, and the Esther Olssons stiftelse II & Anna Jonssons Minnesfond; has conducted research for Tate & Lyle; has received speakers fees from Danone Research; has a scientific advisory role at Hyduro; and holds an honorary research position at the University of Aberdeen.

Funding Sources

No funding was acquired for this work.

Data Availability Statement

No data were collected for this theory paper; as such there are no accompanying data. Full paper available from doi: 10.31232/osf.io/q7gvd.

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Fluid Intake Habits of Spanish Children and Adolescents: An Update of the Liq.In7 Survey

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Luis A. Moreno-Aznar[a, b, e]

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Keywords
Hydration habits · Spanish youths · Liq.In7 survey · Beverages intake

Abstract
Introduction: Insufficient and unhealthy total fluid intake (TFI), especially in early stages of life, may have negative health impact [1]. Understanding how fluid consumption may differ throughout the day or as a function of location could help drive policy initiatives to encourage healthier drinking habits, especially in young population groups, so this study assesses current patterns of fluid consumption in children and adolescents in Spain, including drinking occasions and locations and to compare TFI with the adequate intake of water from fluids recommended by the European Food Safety Authority (EFSA) [2]. ***Methods:*** Our analyses were based on a Spanish cross-sectional study assessing TFI from all sources of fluid consumption according to occasions of the day and location, using a validated liquid intake 7-day record (Liq.In7), details of which can be found elsewhere [3]. Data collection occurred in spring 2018. A sample of 146 (63% boys) children (4–9 years old) and adolescents (10–17 years old) was included (Table 1). Parents reported such information in case children were younger than 16 years. The header categories of fluid consumption were water, milk and derivatives, hot beverages, sugar-sweetened beverages (SSBs), fruit juices, artificial non-nutritive sweetened beverages, alcoholic beverages, and others. Regarding occasions, the analyzed categories were main meals (breakfast, lunch, and dinner), snacks (mid-morning, mid-afternoon, after-dinner) and outside meals. Considered occasions were home, school/university/work, and other. ***Results:*** A high proportion of children and adolescents did not meet EFSA-derived reference values for fluid intake (73% and 72%, respectively) (Fig. 1). Forty percent of children and around 50% of adolescents consumed at least one serving of SSB per day, while about 20% consumed only one or less serving of water per day. Consumption during main meals was most important for both children and adolescents (representing 50% and 54% of TFI, respectively) and was mainly driven by water (62%). The consumption at home in children (70% of TFI) was made of water (47%). In the same way, at school, water was contributing to half of the intake. However, adolescent girls at school drink more SSB (41%) than water (34%), being the highest consumed fluid. At other locations, adolescent boys also drink more SSBs (51%) than either water (29%) or milk and derivatives (10%). ***Conclusion:*** Drinking habits of Span-

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ish young populations are far away from current recommendations because a low fluid intake, specifically water, and a high proportion of SSB consumption in children and adolescents. Interventions that assure achieving EFSA TFI recommendations are of special importance for children and adolescents, with, according our results, a special focus in male adolescents.

Table 1. General overview of the sample

	4–9 years	10–17 years
Sample size, *N* (%)	65 (45)	81 (55)
Females	27 (42)	27 (33)
Males	38 (58)	54 (67)

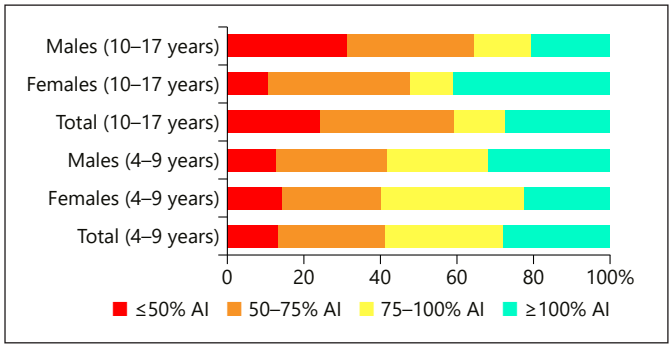

Fig. 1. Percentage (%) of participants according to their adherence to the EFSA AI recommendations for water from fluids. EFSA, European Food Safety Authority; AI, adequate intake.

Acknowledgements

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Statement of Ethics

No Ethical Committee was required. Individuals who agreed to participate in the study received detailed information about the survey's objectives (expectations, confidentiality rules, etc.). Following these additional information and the principles of informed consent, parents or the caregivers were asked for their approval to participate. Moreover, for children and adolescents under the age of 16 years, a single parent was responsible for completion of the questionnaires. The participants or their parents could fill in the questionnaire up to 48 h from the actual time of drinking.

Conflict of Interest Statement

Clementine Morin is a full-time employee of Danone Research. Maria Luisa Miguel Berges reports no conflicts of interest, while Luis A. Moreno is a member of the Scientific Committee of Danone Institute (Spain) and received consultancy fees from Danone Waters Spain. Iris Iglesia-Altaba has received fees from Danone Research for the lecture at the conference.

Funding Sources

The survey was funded by Danone Waters Spain.

Data Availability Statement

The datasets used in the current study are available from the corresponding author on reasonable request.

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What Characterizes Fluid Intake Patterns across the World?

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Keywords
Cluster analysis · Drinking patterns · Children · Beverages intake · Hydration

Abstract
Introduction: Total fluid intake and the type of fluids consumed have been reported by many studies [1–3] and have shown that while an individual may be drinking sufficiently, in terms of volume, to meet or exceed recommendations on fluid intake, there may be a wide variety of combinations of fluids within that total volume [4–6]. Moreover, considering only volume and fluid types may limit the interpretation of the data [7]. In a novel approach, we propose to analyze and understand fluid intake patterns as opposed to only fluid volume or types. The primary aim of this study was to identify patterns of fluid intake in children and adolescents from 6 countries: Argentina, Brazil, Mexico, Uruguay, China, and Indonesia. The secondary aim was to characterize those fluid intake patterns. ***Methods:*** A validated 7-day fluid specific record (Liq.In7 record) [8] was used to collect primary data on fluid intake amongst children and adolescents (10–17 years; $N = 1{,}781$). To identify relatively distinct clusters of subjects based on 8 fluid types (water, milk and its derivatives, hot beverages, sugar-sweetened beverages [SSB], 100% fruit juices, artificial/nonnutritive sweetened beverages, alcoholic beverages, and other beverages), a cluster analysis (partitioning around k-medoids algorithm) was used. Clusters were then characterized according to their socio-demographic and lifestyle indicators. ***Results:*** The 6 clusters identified (Fig. 1) were low drinkers – SSB ($n = 523$), low drinkers – water and milk ($n = 615$), medium mixed drinkers ($n = 914$), high drinkers – SSB ($n = 513$), high drinkers – water ($n = 352$), and very high drinkers – water ($n = 264$). Country of residence was the dominant characteristic, followed by socioeconomic level, in all 6 patterns. ***Conclusion:*** Fluid intake patterns among children are primarily driven by water and SSB. In addition to country, socio-demographic and lifestyle factors determined the characteristics of each cluster. Therefore, interventions aiming to encourage healthier fluid intake behavior need to target and be tailored to a particular subpopulation.

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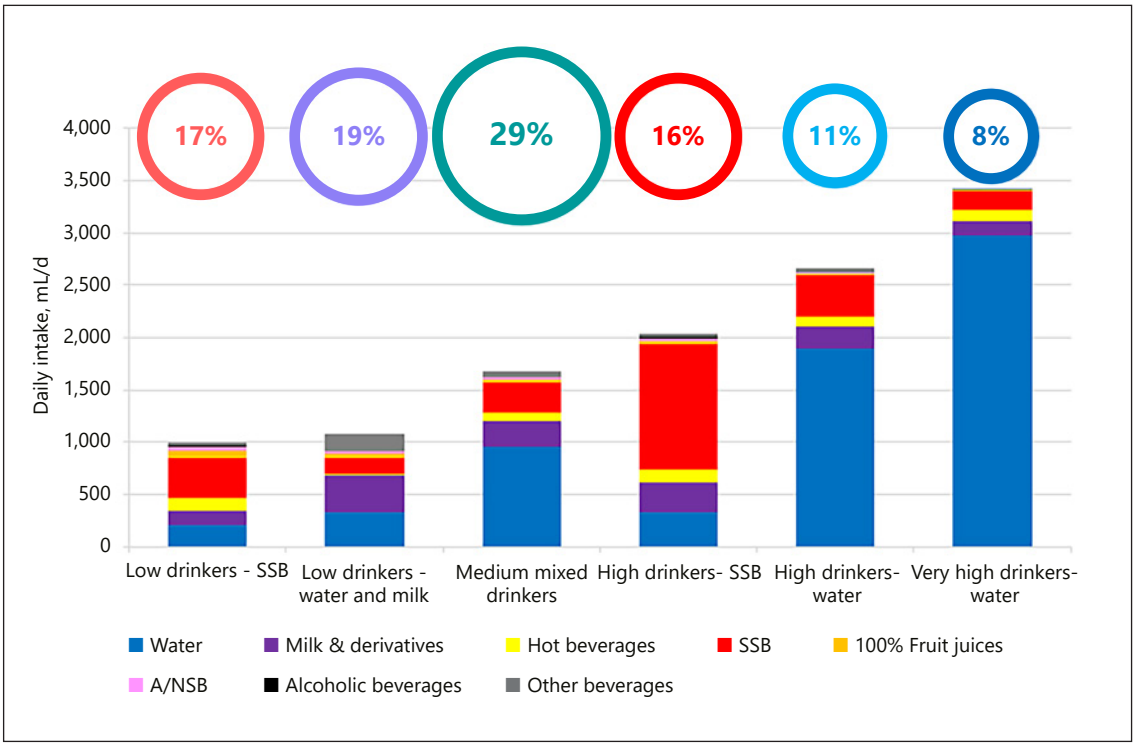

Fig. 1. Mean daily intake of different fluid types (mL/day) of each cluster among children and adolescents. SSB, sugar-sweetened beverages.

Acknowledgment

The authors wish to thank the participants who took part in the original data collection and to acknowledge the role of IPSOS in participant recruitment and data collection. They also thank Isabelle Guelinckx and Rémi Brazeilles for their support in the conduct of this analysis and the critical review of the manuscript.

Statement of Ethics

Study approval statement: The protocol of the surveys was reviewed and approved by the Institutional Review Board, Office of Research Compliance of the University of Arkansas (IRB Protocol # 14-12-376). Consent to participate statement: All the participants gave their written informed consent prior the inclusion in the study. All data were recorded and analyzed anonymously.

Conflict of Interest Statement

C.M. and J.B. are full-time employees of Danone Research. J.G. is a member of the Scientific Committee of Hydration for Health and received consultancy fees from Danone Research. J.S.-S. partially supported by ICREA under the ICREA Academia programme. S.A.K., L.M., and H.M. have received research grants from Danone Research.

Funding Sources

The study received no funding.

Data Availability Statement

The datasets used for the purpose of this analysis are available from the corresponding author upon reasonable request.

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Abstracts

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Recent Findings on the Psychology of Hydration Habits

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Keywords
Habits · Hydration behavior · Sugar-sweetened beverages · Water · Reward

Abstract
Introduction: This synthesis addresses the psychology of habits in hydration behavior, and presents recent insights about water drinking habits. Habits play a key role in most health behavior, and they allow us to act automatically and without much deliberation or effort. Habits also play a key role in hydration behavior, and are among the strongest predictors of the consumption of water, sugar-sweetened beverages (SSBs), hot beverages, and alcoholic drinks. ***Methods:*** We synthesized novel findings from recent in-depth qualitative interviews, a qualitative survey, and a quantitative survey on the role of habits in the consumption of water and sugar-sweetened beverages. ***Results:*** Qualitative data show that water drinking is not a simple behavior, and reward plays an important role in water drinking. Participants described numerous barriers to drinking water, including forgetting, lack of access, perceived effort, and others. In addition, our analyses show that water drinking habits are unlikely to emerge or be maintained unless consumers expect experiencing reward from drinking water, for example, because of its taste, cognitive, or physical consequences. Our quantitative study of the effect of the UK pandemic lockdown on drinking behavior points to the effects of reward in drinking habits as well. Situations that typically afford the consumption of SSBs and water outside of the home (e.g., eating out, socializing, parties for SSBs, gym, office, and travel for water) were less frequent during lockdown. Nevertheless, overall consumption of SSBs, but not water, increased in this period, especially among strongly habitual SSB consumers. This was driven by SSB consumption at home, suggesting that participants established new, rewarding consumption habits when their typical consumption situations had disappeared. ***Conclusion:*** These findings suggest that experiencing reward from consumption is essential in hydration habits, which may further inform applications to increase healthy hydration.

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Statement of Ethics

This abstract paper does not present empirical data, but a synthesis of recent findings. In all studies underlying the synthesis presented here, participants have given their written informed consent. All study protocols were approved by the University of Glasgow College of Science and Engineering Ethics Committee (application numbers 300200029, 300190043, 300200055).

Conflict of Interest Statement

E.P. received travel expenses and registration fee from Danone Research to attend the 2019 Hydration for Health Scientific Conference, for the European Federation of the Associations of Dietitians 2019 Conference, and the 2020 and 2021 European and International Congress on Obesity (online). The University of Glasgow has received speaker fees for E.P. from Danone Research. Danone Research co-funds the ESRC/SGSSS PhD studentship of A.R.

Funding Sources

The research reported in this presentation was supported by an ESRC/SGSSS studentship to A.R., and by ESRC Research Grant ES/R0055419/1 awarded to E.K.P. The funders had no role in the study design or analysis, or the decision to present these findings.

Author Contributions

This synthesis was developed by E.K.P., with contributions from A.R., M.A.C., and M.L., who are authors on the original empirical studies synthesized here.

Data Availability Statement

This abstract paper does not present empirical data. However, 2 of the studies from which findings are synthesized are available online with open access to all underlying data on the Open Science Framework, here https://psyarxiv.com/grndz and here https://psyarxiv.com/kg367/.

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Associations between Drinking Water Source and Gut Microbiota Composition in the American Gut Project Database

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Keywords
Drinking water · Gut microbiota diversity · 16s rRNA gene

Abstract
Introduction: The gut microbiome exerts a fundamental role in host physiology. Extrinsic factors such as lifestyle and diet are widely recognized as the main drivers of gut microbiota composition [1, 2]. While drinking water is among the food items consumed in the largest amount, little is known about its potential impact on gut microbiota structures [3–5]. ***Objective:*** We explored the associations between plain drinking water source and gut microbiota compositions in a large microbiota-based cohort. ***Methods:*** Participants in the American Gut Project database provided fecal samples and completed health, lifestyle, and food records which included plain drinking water source (bottled, tap, filtered, or well water). Associations between drinking water source and gut microbiota were evaluated using models adjusted for anthropometric, diet, and lifestyle factors in 3,413 individuals [6]. Index of intra-individual fecal microbial diversity, inter-individual differences in composition, and taxa abundance were estimated by 16S rRNA sequencing. ***Results:*** The type of drinking water was associated with fecal microbiota composition. Drinking water source ranked among the key contributing factor explaining the gut microbiota variation both in alpha and beta diversity analyses, with effect sizes comparable to that of alcohol or diet type [6] (Fig. 1). Subjects drinking different sources of water had differences in gut microbiota signatures, as revealed by beta diversity analyses ($p < 0.05$; Bray-Curtis dissimilarity, Weighted UniFrac distance) [6]. Subjects drinking mostly well water also had higher fecal alpha diversity than the other groups ($p < 0.05$; Faith's PD, Observed OTUs) [6]. Taxonomic differences were found in well water drinkers, with clinically important taxa, such as *Bacteroides*, *Odoribacter*, and *Streptococcus* being depleted and *Dorea* being increased as compared to the other groups [6]. ***Conclusions:*** Our results reveal that drinking water may be an important factor in shaping the gut microbiome. Future research investigating the gut microbiota in relation to environmental factors may benefit from integrating drinking water source as a covariate in the analyses.

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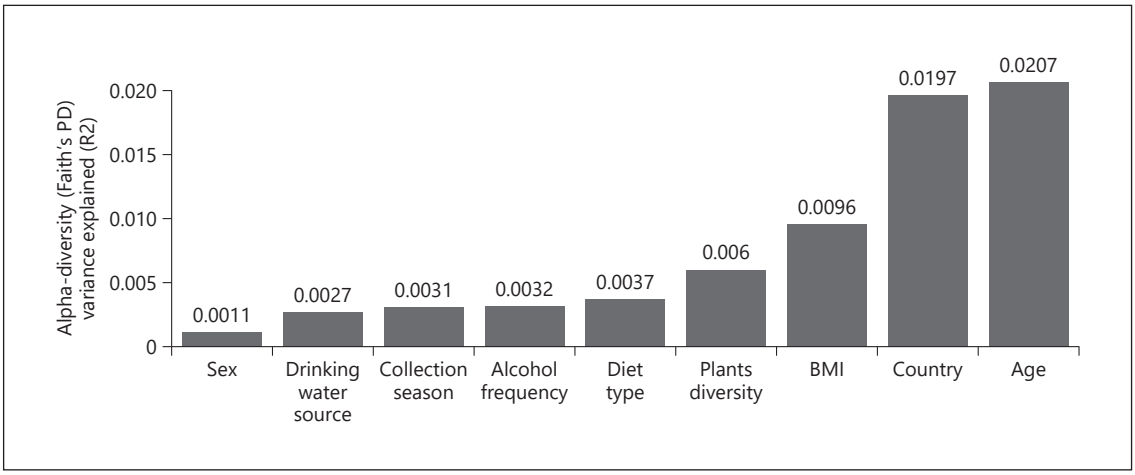

Fig. 1. Effect sizes of α Diversity as measured by Faith's PD. Proportions of variance captured by significant variables in model adjusted models for age, sex, BMI, infant feeding, level of education, country, collection season, exercise frequency, diet type, plant diversity (number of types of plants consumed per week), alcohol, and sugar-sweetened beverage consumption. Adapted from Vanhaecke et al. [6].

Statement of Ethics

Ethical Committee approval for the collection of AGP data was obtained either from the University of Colorado Boulder Review Board (protocol No. 12-0582; December 2012–March 2015) or from the University of California Review Board, San Diego (protocol No. 141853; February 2015–present), in accordance with the Declaration of Helsinki, and all participants provided written informed consent. Return of results to participants, public deposition of de-identified data, and subsequent analyses are allowed by the IRB-approved protocol [7].

Conflict of Interest Statement

T.V. is a full-time employee of Danone Research.

Funding Sources

The author reported no funding received for this study.

Data Availability Statement

Data for this research originate from the AGP database, a self-selected citizen-scientist cohort initiated by the University of California, San Diego [7]. It contains analyses of fecal, oral, and skin samples sent by >24,000 volunteers worldwide. After contributing USD 99, participants receive a kit to collect their biological samples and mail them for 16S rRNA gene sequencing to establish their microbial composition. Self-reported metadata are collected through a web portal (https://microsetta.ucsd.edu/). Surveys, methodology, sampling, and laboratory test procedures have been described elsewhere [7].

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Influence of Suboptimal Hydration on the Immune Response

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Keywords
Hydration · Hypertonicity · Immunity · Multiple sclerosis

Abstract
Background: A healthy immune system is a subtle orchestration of the innate and adaptive immune systems that efficiently detect and process foreign antigens while tolerating the self. The influence of hypertonicity on the immune system is poorly understood [1–16]. ***Summary:*** In vitro studies suggest that hypertonicity influences innate and adaptive immunity on several cellular and molecular levels. This influence tends to be pro-inflammatory, but not always. Other cofactors include the duration of exposure to hypertonicity (chronic versus acute), the location in the body, and the timing with priming of the immune system. Recent publications about high salt diet in vitro and in animal models of multiple sclerosis (MS) suggest an influence on the TH17 autoimmune pathway, that does not translate into the human disease in vivo. ***Key Messages:*** The influence of hypertonicity on the immune system is complex and depends on multiple factors, such as temporality with immune priming and length of exposure. Since findings in animal models did not always translate into human diseases, further studies are needed to specify the consequences of acute or chronic hypertonicity in healthy subjects or patients with autoimmune diseases such as MS. Further studies need to be conducted in animal models and in humans to better understand the influence of suboptimal hydration on the immune system and on autoimmune diseases, and address its clinical relevance.

Acknowledgements

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Conflict of Interest Statement

Dr. Dorothée Chabas was hired as a consultant by Danone to prepare and present this work at the 2021 Hydration for Health conference.

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Abstracts

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Hippocrates Was Right: Now What? Water As a Part of Healthy Aging

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Keywords
Aging · Disease · Metabolism · Water recommendations

Abstract
Background: Aging is defined as the progressive organism change leading to debility, disease, and death [1]. We know that as we age, our risk increases for diseases such as diabetes, cancer, and chronic kidney disease, and many of our homeostatic processes change as well, such as cell signaling, metabolism, and proteostasis [2]. The data clearly show that water intake decreases with aging, especially after age 60 years [3]. However, the question becomes "Do we drink less because we age, or do we age because we drink less?" (Fig. 1). ***Summary:*** There are data to support both directions of this hypothesis. One example supporting that water intake decreases due to aging is that in older adults, the thirst response to hyperosmotic and hypovolemic stimuli is blunted in comparison to younger adults [4]. However, we are increasingly gathering data to also support that low water intake can be a contributor to both disease and altered cellular processes, potentially accelerating aging related dysfunction. For example, in older adults, low water intake has been shown to be associated with working memory [5], blood glucose regulation [6], incidence of stroke [7], and falls [8] (i.e., dementia, diabetes, cardiovascular disease, and mobility). Additionally, processes such as metabolism [9], cell signaling [10], and muscle damage following exercise [11] have also been linked to hydration. Key messages are that it is clear that water intake changes as we age, primarily due to changes in thirst. However, what is our duty as hydrationists is to begin to evaluate both directions of the aging, dysfunction, and water intake relationship (Fig. 1). Just as we have begun to realize the influence as water as a nutrient, we can hopefully demonstrate how a simple intervention like drinking to recommendations can be a part of healthy aging for all.

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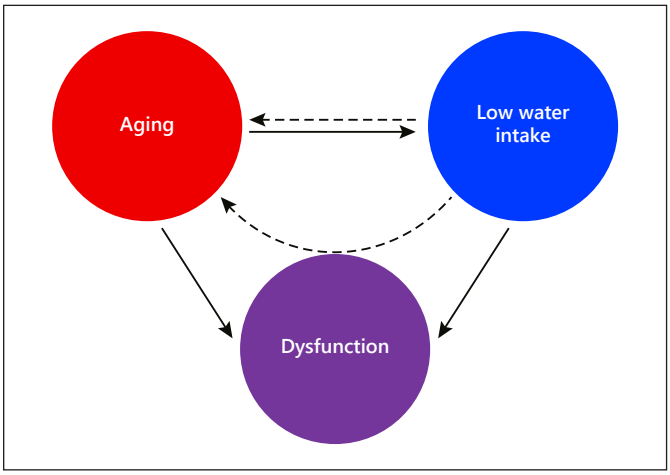

Fig. 1. Solid lines represent established causal relationships between different physiological states and behaviors. Dashed lines represent proposed, supported, but unproven relationships.

Conflict of Interest Statement

E.C. Johnson is a member of the scientific advisory board for Danone. In the past, E.C. Johnson has received research funding, travel expense reimbursement, and consulting fees from Danone.

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Modeling Hydration Status Given Daily Measures of Body Mass, Urine Color, and Thirst

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Keywords
Machine learning · Copeptin · Vasopressin · Hydration monitoring · Health

Abstract
Background: The ability to monitor changes in daily hydration status is critical for human health and performance. Monitoring changes in body weight (W), urine color (U), and thirst (T) was proposed as a simple, low-cost method for daily hydration monitoring [1]. However, the ability of these metrics to accurately predict 24-h hydration status is yet to be fully tested. ***Objective:*** The purpose of this study was to assess the degree to which daily monitoring of W, U, and T (i.e., the WUT model) could accurately predict 24-h hydration status. ***Methods:*** Thirty-five male and female adults (age: 23.4 ± 4.1 years, height: 173.0 ± 10.3 cm, mass: 77.2 ± 18.2 kg, body fat: 18.4 ± 8.4%) were monitored for 8 consecutive days. Assessments on each morning included a 24-h urine sample for urine osmolality (UOSM24), a first void spot urine for urine color (U), nude body weight (W), and perceived thirst (T) using a 1–9 Likert scale. On days 7 and 8, a blood sample was taken for copeptin assessment [2]. If UOSM24 was >800 mOsm•kg^{-1} on any day, the participants were classified as hypohydrated. Multiple research questions were explored. First, models tested the degree to which W, U, and T could predict UOSM24 (RQ1). Classification models assessed the ability to predict whether an individual was hypohydrated (UOSM24 >800 mOsm•kg^{-1}; RQ2). Last, models tested the degree to which W, U, and T could predict concentrations of copeptin (RQ3). For each question, 4 separate modeling approaches were used: linear regression (LR), elastic net regression (EN), extreme gradient boosted random forests (XB), and a single hidden layer neural network (NN). Eighty percent of the data (RQ1/RQ2 $n = 207$, RQ3 $n = 49$) were used to train the models, while 20% of the data were held out (RQ1/RQ2 $n = 51$, RQ3 $n = 10$) for model validation. Within the training data, bootstrap samples (XB) and cross-fold validation (EN and NN) samples were used to optimize model hyperparameters. Prediction accuracy for regression analyses were assessed via R^2 and root mean square error (RMSE), and for classification analyses via area under the curve of the receiver operating characteristic. ***Results:*** The results demonstrated that the NN model performed best when predicting UOSM24 ($R^2 = 0.532$, RMSE = 228 mOsm•kg^{-1}), but all models had relatively poor fit and large errors during validation. All classification models were moderately effective at discriminating between the binary hydration status of individuals (area under the curve of the receiver operating characteristic range: 0.661–0.696). Linear regression (Fig. 1; R^2 = 0.929, RMSE = 1.49 pmol•L^{-1}), XB ($R^2 = 0.834$, RMSE = 3.11 pmol•L^{-1}), EN (R^2 = 0.890, RMSE = 2.13 pmol•L^{-1}), and NN (R^2 = 0.930,

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RMSE = 1.84 pmol•L^{-1}) were able to predict copeptin concentrations with relatively low error. ***Conclusions:*** The WUT model accurately predicts copeptin concentrations on out of training data observations, suggesting that first morning measures of W, U, and T are effective for tracking hydration status by indirectly monitoring arginine vasopressin. More research is needed to determine potential cut-scores of predicted copeptin levels to aid practitioner decisions.

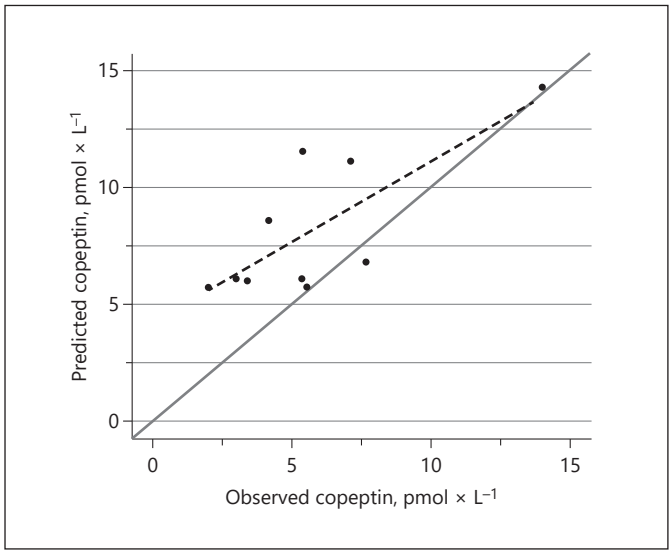

Fig. 1. Predicted copeptin from the LR model compared to observed copeptin in the out of training sample observations. The solid gray line represents perfect prediction. LR, linear regression.

Statement of Ethics

All subjects gave their written informed consent, and this study protocol was reviewed and approved by the Institutional Review Board at the University of North Carolina at Greensboro (IRB #18-0063).

Conflict of Interest Statement

Travis Anderson has received speakers fees from Danone Research.

Funding Sources

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Author Contributions

Travis Anderson contributed to data collection, conceptualization, data analysis, primary author, critical review, and editing. William M. Adams is the principal investigator and contributed to data collection, conceptualization, critical review, and editing. Laurie Wideman is the senior investigator and contributed to conceptualization, critical review, and editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ongoing analysis but are available from T.A. (t_ander2@uncg.edu) upon reasonable request.

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Abstracts

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Urinary UDP-Glucose as a Novel Actionable Biomarker of Dehydration-Induced Acute Kidney Injury

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Keywords
Inflammation · Dehydration · Acute kidney injury · UDP-glucose

Abstract
Background: People working in "extreme" conditions termed as sugar cane workers, firefighters and military personnel are subjected to significant dehydration. Prolonged episodes of dehydration may result in acute kidney Injury (AKI). AKI is associated with inflammation and is usually diagnosed only after the kidneys have gone through significant and often irreversible damage. We showed that the P2Y14 receptor mediates renal inflammation, leading to AKI following ischemia-reperfusion-injury [1]. P2Y14 is activated by the danger molecule UDP-glucose (UDP-Glc). Here we hypothesized that UDP-Glc is released by cells throughout the body after dehydration-induced stress. UDP-Glc is filtered by the kidney and concentrated in collecting ducts where it activates P2Y14 in intercalated cells. This would trigger renal inflammation and contribute to dehydration-associated AKI. ***Objective:*** The aim of this study was to characterize the participation of UDP-Glc in pro-inflammatory cell recruitment and renal dysfunction following dehydration. ***Method:*** Mice were subjected to water deprivation for 24, 48, and 72 h. Kidney function was assessed via serum creatinine (SCr), blood urea nitrogen (BUN), and urine albumin. To study proximal tubule (PT) damage, aquaporin 1 (AQP1) localization was analyzed by immunofluorescence (IF). Urinary UDP-Glc concentration was measured by LC-MS, and renal recruitment of immune cells by flow cytometry and IF. ***Results:*** Water deprivation induced elevations in SCr and BUN after 48 h and 72 h, relative to control. Dehydration also induced albuminuria and the redistribution of AQP1 from the plasma membrane into the PT cell body indicating PT injury. An increase in urinary UDP-Glc concentration and renal recruitment of macrophages were detected at 48 h and 72 h of dehydration. ***Conclusion:*** This study supports the hypothesis that UDP-Glc, released by damaged cells during severe dehydration, induces the renal recruitment of inflammatory macrophages leading to PT injury and kidney dysfunction (Fig. 1). Blocking the UDP-Glc/P2Y14 pathway represents, therefore, a new therapeutic avenue for the attenuation of dehydration-induced renal inflammation and injury. In this context, urinary UDP-Glc is a promising actionable biomarker for dehydration-induced AKI.

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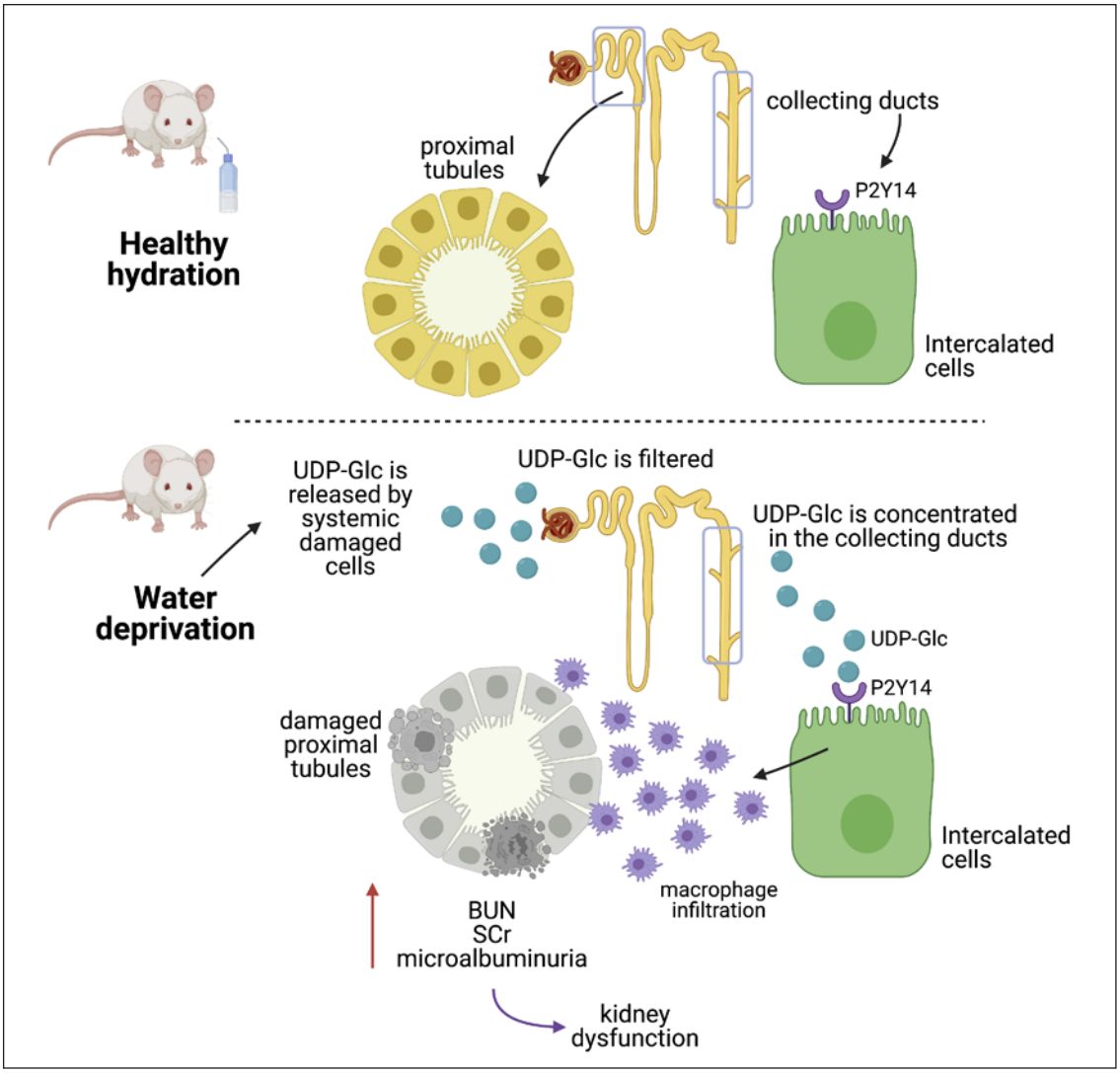

Fig. 1. Proposed mechanism of action of UDP-Glc in mediating renal inflammation following dehydration. UDP-Glc is released by systemic damaged cells, is filtered by the kidney, and is then concentrated in the lumen of collecting duct, where it reaches higher levels due to the concentrating ability of the kidney. UDP-Glc binds to the P2Y14 receptor located on the apical surface of intercalated cells. This receptor-ligand interaction stimulates the production of chemokines, which attract macrophages into the kidney. The newly recruited immune cells aggravate renal tubular injury and kidney dysfunction. UDP-Glc, UDP-glucose; PTs, proximal tubules; BUN, blood urea nitrogen; Scr, serum creatinine.

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Statement of Ethics

All preclinical procedures were approved by the Massachusetts General Hospital (MGH) Subcommittee on Research Animal Care and were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals (National Academies Press, 2011; protocol 2018N000127).

Conflict of Interest Statement

S.B. is a cofounder of Kantum Pharma (previously "Kantum Diagnostics Inc."), a company developing a diagnostic and therapeutic combination to prevent and treat acute kidney injury. S.B. and her spouse own equity in the privately held company. S.B. and D.B. are inventors on a patent (US Patent 10088489) covering technology that has been licensed to the company through Massachusetts General Hospital (MGH). S.B. and D.B. interests were reviewed and are managed by MGH in accordance with their conflict-of-interest policies.

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Author Contributions

M.A.B., D.B., and S.B. designed the study. M.A.B. and A.C.M performed the experiments and analyzed the data. M.A.B., D.B., and S.B. wrote the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Abstracts

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Self-Reported Changes in Thirst and Alertness during Variable Prescribed Fluid Intake

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Keywords
Water intake · Euhydration · Thirst

Abstract

Background: Maintaining euhydration is beneficial for health, safety, and physical performance [1]; however, it may also improve subjective feelings [2, 3]. ***Objective:*** The aim of this study was to evaluate the relationship between changes in self-reported thirst and alertness in people undergoing changes in drinking water volume. ***Methods:*** Subjects (mean ± SD) (n = 115, 59 males, 32 ± 10 years; 24.6 ± 4.4 kg·m^{-2}) visited the lab 3 times over 10 days: V1, a baseline visit prior to participants were drinking ad libitum; V2, following 3 days of fluid restriction (1 L·d^{-1}, 250 mL was consumed in the morning prior to the visit); and V3, the morning following a prescribed increase in water intake. The increase in water intake at V3 varied by group assignment: control group (CON) maintained 250 mL, while LOW and HIGH groups (n = 45 each) consumed 496 ± 82 mL and 878 ± 125 mL, respectively. At each visit, subjects indicated on an open-ended visual analog scale (VAS) how thirsty and alert they felt and were measured in millimeters (mm). Four, two-way ANOVAs (group × visit) for change in thirst and alertness between V1–V2 and V2–V3 were completed. A repeated-measures correlation (r_{rm}) procedure was completed for change in alertness and thirst from V1 to V2 and V2 to V3 [4]. The study was approved by the University of Wyoming's Institutional Review Board (protocol #20160524EJ01208), and all subjects provided written informed consent. ***Results:*** Groups were similar at baseline (V1) for fluid intake, thirst, and alertness (all $p \geq 0.17$). Fluid restriction (V2) resulted in a main effect of visit for thirst and alertness (both $p < 0.01$), with no main effect of group. Thirst increased (35 ± 35 mm) and alertness decreased (−19 ± 31 mm) from V1 to V2. The prescribed increase in water intake (V3) revealed a significant interaction of visit and group for thirst and alertness (both $p < 0.01$) (Table 1). Independent-samples t tests with a Bonferroni correction revealed that HIGH reduced thirst (−38 ± 37 mm) and increased alertness (18 ± 25 mm), while no change was observed for LOW (thirst, −7 ± 37 mm; alertness −1 ± 24 mm) and CON (thirst, −6 ± 23 mm; alertness 0 ± 23 mm; all $p < 0.01$) (Fig. 1). There was no difference between LOW and CON (both $p > 0.92$). Repeated-measures correlation analysis revealed an inverse relationship between change in alertness and thirst (r_{rm} [114] = −0.53, 95% CI [−0.65, −0.38], $p < 0.01$). ***Conclusion:*** A reduction in water intake resulted in an increase in thirst and decrease in alertness. Following 3 days of fluid restriction, 750–1,000 mL of water intake was needed to decrease thirst and increase alertness. Overall, an inverse relationship was observed between self-reported thirst and alertness.

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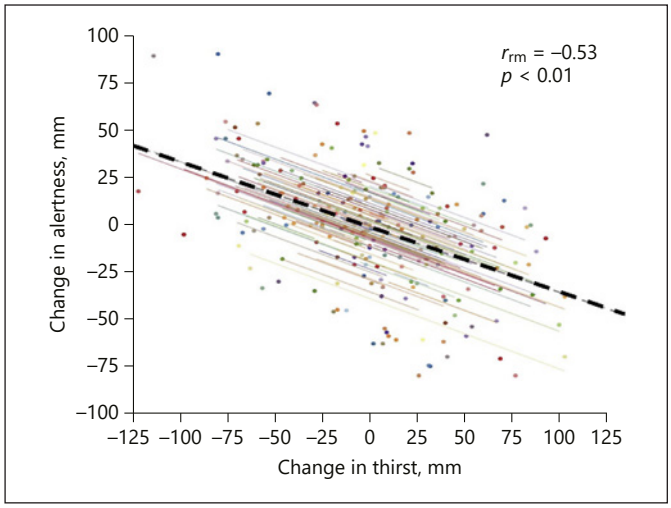

Fig. 1. Repeated measures correlation for self-reported change in thirst and alertness from V1 to V2 and from V2 to V3 ($r_{rm} = -0.53$, $p < 0.01$). Black dashed line represents overall correlation.

Table 1. Change in thirst and alertness from visit 1 (V1) to visit 2 (V2) and V2 to visit 3 (V3) in millimeter

Group	ΔV1–V2		ΔV2–V3	
	Thirst, mm	Alertness, mm	Thirst, mm	Alertness, mm
CON	35±23	–21±23	–6±23	0±23
LOW	34±35	–15±33	–7±37	–1±24
HIGH	37±41	–21±33	–38±37**	18±25**

** Indicates significant difference from CON and LOW.

Statement of Ethics

The study was approved by the University of Wyoming's Institutional Review Board (protocol #20160524EJ01208) and all subjects provided written informed consent.

Conflict of Interest Statement

E.C.J. received this grant and was partially funded during his graduate studies by similar grants from Danone Research. H.A.Y. has received speakers fees from Danone Research.

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Author Contributions

E.C.J. was the principal investigator and developed the project. H.A.Y., A.E.H., and S.M. completed the data collection and data entry. E.C.J. and H.A.Y. completed the statistical analysis and wrote the abstract with input from A.E.H. and S.M.

Data Availability Statement

Data are not available because we are working on a manuscript based on this project and want to keep the data confidential for the time being.

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Estimating Differences in Risk of Chronic Kidney Disease Based on Water Intake in a National Sample

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Keywords
Kidney disease · National health and nutrition examination survey · Hydration · Chronic kidney disease of unknown origin · Human nutrition

Abstract
Background: In agricultural communities in Central and South America, Egypt, India, and Sri Lanka, an unexplained form of chronic kidney disease affects agricultural workers. Termed chronic kidney disease of unknown origin (CKDu), it disproportionately affects young men in their 30s–40s and is unrelated to the traditional risk factors of diabetes, hypertension, and obesity [1–3]. Recent investigations suggest that agricultural work in the USA carries similar risks, as reduced kidney function has been found among those working in US agriculture [4–5]. However, researchers are yet to determine the etiology of the disease [6–8]. Central to the hypotheses of CKDu is the reduced blood flow to the kidneys due to inadequate hydration during periods of intense physical labor. ***Objectives:*** The primary aim of the current investigation was to identify if a relationship between hydration and kidney function exists among the general population by using the data from the National Health and Nutrition Examination Survey (NHANES). We hypothesize that reduced hydration will be associated with reduced kidney function. ***Methods:*** Data were retrieved from the NHANES dataset from 3 sample years 2005/2006, 2007/2008, and 2011/2012. Data were merged across all 3 periods with survey weights adjusted for combining across multiple years. Participants were excluded if they had missing data for hydration or kidney function, or if they were <19 year. Kidney function was categorized low risk, moderate risk, or high risk for impaired function based on estimated glomerular filtration rate and albumin creatinine ratio according to the National Kidney Foundation [9]. Hydration was classified based on total water intake (TWI) extracted from plain water intake and water from food. Participants were labeled as high if they met or exceeded sex-specific water recommendations, 3.7 and 2.7 L/day for men and women, respectively; otherwise they were labeled as low. A survey-weighted proportional odds logistic regression model was fitted to assess the association between water intake and kidney function, while controlling for other demographic, socio-economic, behavioral, and socio-economic risk factors [10–12]. ***Results:*** Of the 13,056 participants initially sampled, 10,651 participants are included in the analysis after cleaning and including survey weights. 9,125 (85.67%) of participants were in the low-risk group,

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1,128 (10.59%) were classified as medium-risk, while the remaining 398 (3.74%) were high risk (Fig. 1). Adjusting for survey weights, results suggest that the estimated rate of high-risk kidney function was 5% more for low water drinkers compared to high water drinkers (Fig. 2). There is strong evidence of a difference in CKD risk categories based on TWI ($\chi^2(1) = 13.1$, p value <0.0001) from a survey-weighted proportional odds logistic regression model, but only moderate evidence of a difference when controlled for sodium/potassium ratio, education, age, gender, ethnicity, income, BMI, blood pressure, diabetes, smoking, and alcohol consumption ($\chi^2(1) = 3.3$, p value = 0.067). ***Conclusions:*** Not meeting recommended daily TWI was associated increased presentation of high-risk kidney function. Even though the NHANES data are not focused on areas where chronic kidney disease is prevalent, results from this are an indication that hydration does play a role in kidney function.

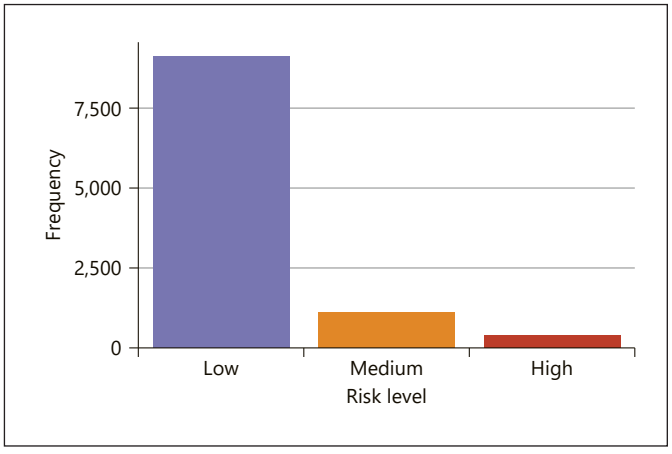

Fig. 1. Distribution of kidney function risk by study participants using survey weights.

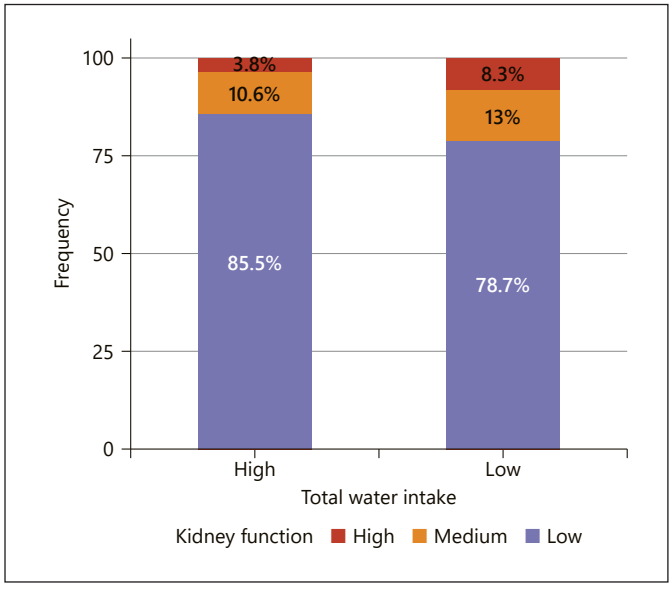

Fig. 2. Association between TWI and kidney function after adjusting for survey weights. TWI, total water intake.

Statement of Ethics

This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors. Study approval statement: No review by the Institutional Review Board was required because the analysis of de-identified, publicly available data does not constitute human subjects research as defined at 45 CFR 46.102 and that it does not require IRB review. Consent to participate statement: Health information collected in the NHANES is kept in strictest confidence. During the informed consent process, survey participants are assured that data collected will be used only for stated purposes and will not be disclosed or released to others without the consent of the individual or the establishment in accordance with section 308(d) of the Public Health Service Act (42 U.S.C. 242m).

Conflict of Interest Statement

Author Evan C. Johnson has previously received grant funding from Danone Research. All other authors have no conflicts of interest to declare.

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Author Contributions

David Lartey contributed to acquisition, analysis, and interpretation of data; drafting the work; and final approval of the version to be published. Mark Greenwood and Greta Linse contributed to acquisition, analysis, and interpretation of data; critical revision of the work; and final approval of the version to be published. Sally Moyce, Evan C. Johnson, and Cynthia Curl contributed to the design of the work and interpretation of data; critical revision of the work; and final approval of the version to be published. – Meredith Spivak contributed to acquisition and interpretation of data; critical revision of the work; final approval of the version to be published.

Data Availability Statement

The data that support findings of this study are publicly available. Reasonable requests for coded and weighted data should be addressed to the corresponding author, D.L.

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Abstracts

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The Acute Effect of Adequate Water Intake on Glucose Regulation in Low Drinkers

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Keywords
Glucose regulation · Hydration · Vasopressin

Abstract

Background: Arginine vasopressin (AVP), a key hormone in fluid balance, may be a modifiable contributor to hyperglycemia [1]. Low daily water drinkers often exhibit increased urine concentration and copeptin, a surrogate marker for AVP [2, 3]. ***Objective:*** The primary purpose was to investigate the acute effect of adequate water intake on daily glucose concentration in low drinkers. Secondarily, the study examined if adequate water intake could improve glucoregulatory hormonal profiles in low drinkers. ***Methods:*** Seven healthy (5 males, 2 females; age 43 ± 7 years, BMI 31 ± 3) low drinkers were recruited using a water frequency questionnaire and a 24-h urine sample. Participants were recruited using social media channels and flyers in local community. Classification of a low drinker was defined by a fluid intake (water and other beverages) <1.5 L·day^{-1} in males or <1.0 L·day^{-1} in females and a 24-h·UOsm of >800 mmol·kg^{-1}. In a crossover counterbalanced design, participants remained in the laboratory for 11 h (07:00–18:00) and were provided either the Institute of Medicine's recommended amount of water excluding fluid from food (males: 3 L·day^{-1}, females: 2 L·day^{-1}; high water intake, HWI) or an amount representing the bottom quartile of water consumption observed in the National Health and Nutrition Examination Survey (males: 0.5 L·day^{-1}, females: 0.4 L·day^{-1}; low iater intake, LWI) (Table 1) [4, 5]. Caloric intake was standardized to body weight (100 kJ·kg^{-1}) with an identical ratio of macronutrients and time of consumption between trials (Table 1). At 07:00, fasted baseline blood was drawn. Subsequent blood draws performed across the next 11 hours were analyzed for copeptin, glucose, insulin, glucagon, cortisol, and GLP-1 (Table 1). All urine voids during the 11-h protocol were pooled and analyzed for osmolality and glucose (n = 4). A two-way (water intake × time) repeated-measures ANOVA was used to determine differences in hydration and glucoregulatory measures. Dependent t tests were used to measure differences in urine samples. Statistical significance was determined a priori at an alpha of 0.05. ***Results:*** Participants were confirmed as low drinkers according to daily fluid intake, 24-h·UOsm, and copeptin (water frequency questionnaire volume: 823 ± 403 mL·day^{-1}, 24-h·UOsm: 961 ± 105 mmol·kg^{-1}, copeptin: 8.17 ± 3.05 pmol·L^{-1}). During the experiments, 11-h·UOsm (HWI: 224 ± 48 mmol·kg^{-1}, LWI: 956 ± 120 mmol·kg^{-1}), plasma osmolality, and copeptin were lower in HWI as than in LWI (p = < 0.05, Fig. 1). There was a borderline significant main effect of water intake on plasma glucose (p = 0.07, Fig. 2) and total urinary glucose output (HWI: 51.4 ± 6.9 mg, LWI: 40.1 ± 10.4 mg, p = 0.07). Cortisol was significantly higher in LWI as than in HWI (p = 0.009, Fig. 2); however, no pairwise differences were observed in post hoc analysis. Glucagon, insulin, and GLP-1 were similar between trials (p > 0.05). ***Conclusion:*** Acute increases in water intake may mildly reduce daily plasma glucose concentrations in low drinkers. This may be due to acutely increased urinary glucose output when low drinkers are given adequate amounts of water. Increased water intake also led to decreased cortisol concentration.

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Table 1. Water intake, meals, and blood draws during experimental protocol

Time	Water intake, mL				Meal	Blood draw
	male		female			
	HWI	LWI	HWI	LWI		
07:00	500	100	250	50	Breakfast	Yes
08:00	250	–	125	–	–	Yes
09:00	250	100	125	100	–	Yes
10:00	250	–	250	–	Snack 1	–
11:00	250	–	125	–	–	–
12:00	250	50	250	50	Lunch	Yes
13:00	250	–	125	–	–	Yes
14:00	250	100	250	100	Snack 2	Yes
15:00	250	–	125	–	–	–
16:00	250	50	250	50	Dinner	Yes
17:00	250	100	125	50	–	Yes
18:00	–	–	–	–	–	Yes

HWI, high water intake; LWI, low water intake.

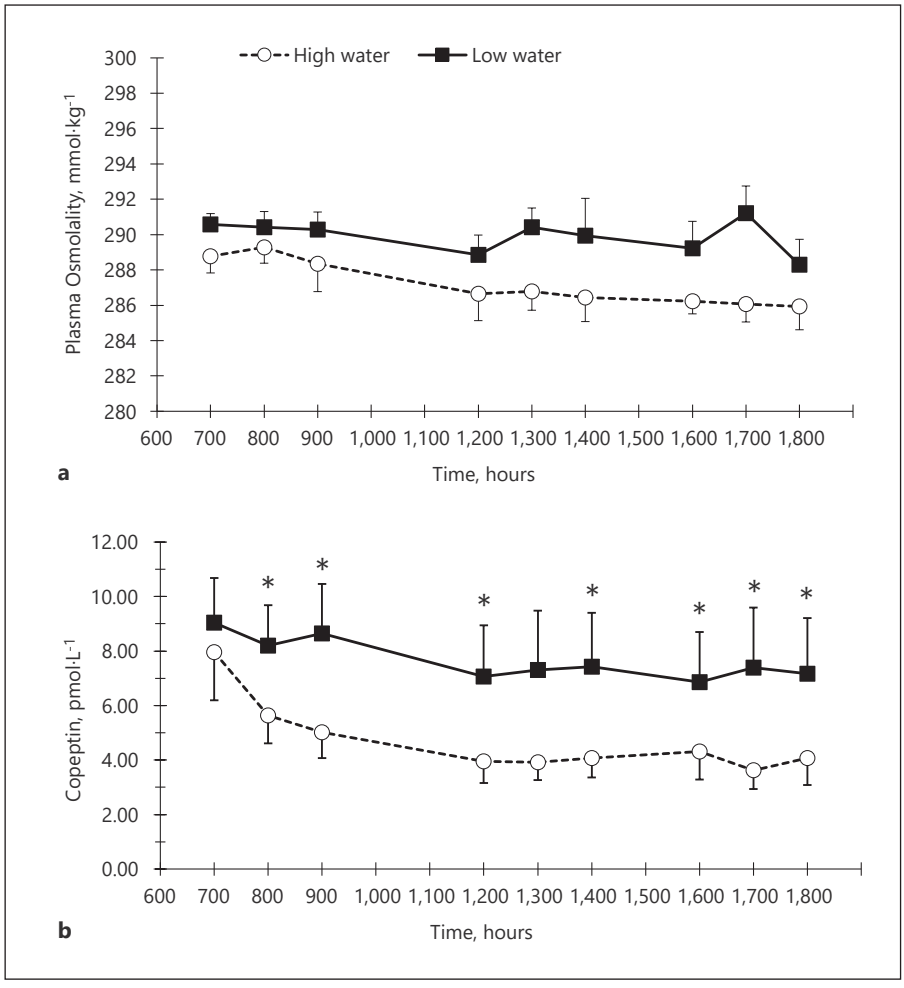

Fig. 1. Plasma osmolality (**a**) and copeptin (**b**) during HWI (males: 3 L; females: 2 L) and LWI (males: 1 L; females: 0.5 L) trials. *Represents significantly different from HWI for time point ($p < 0.05$). Error bars = SE. HWI, high water intake; LWI, low water intake.

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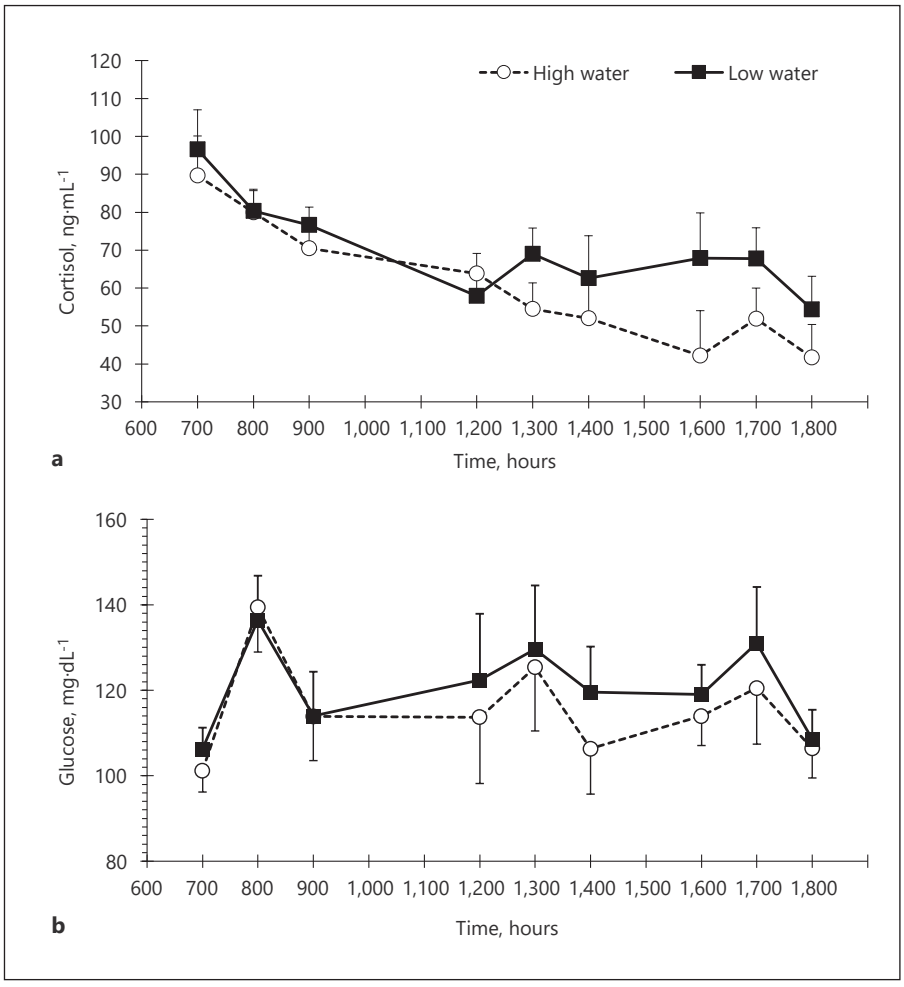

Fig. 2. Significant main effect of water intake on cortisol ($p < 0.05$) (**a**) and borderline significant main effect of water intake on plasma glucose ($p = 0.07$) (**b**) during HWI (males: 3 L; females: 2 L) and LWI (males: 1 L; females: 0.5 L) trials. Error bars = SE. HWI, high water intake; LWI, low water intake.

Acknowledgement

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Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects gave their written informed consent and the study protocol was approved by the Arizona State University Institutional Review Board, approval number STUDY00010276.

Conflict of Interest Statement

S.A.K. has served as scientific consultant for Quest Diagnostics, Standard Process, and Danone Research and has received grants from Danone Research and Standard Process. A.S. has received speakers fees from Danone Research.

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Author Contributions

All authors designed the study; A.S., A.T.C., and H.S. conducted data collection and sample analysis; A.S. and S.A.K. analyzed the data; A.S. wrote the paper; S.A.K. was the principal investigator. All authors read, critically revised, and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, A.S., upon reasonable request.

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Original Paper

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Hydration Biomarkers Are Related to the Differential Abundance of Fecal Microbiota and Plasma Lipopolysaccharide-Binding Protein in Adults

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Keywords
Copeptin · Vasopressin · Gastrointestinal microbiota · Hydration · Water · Obesity

Abstract
Introduction: Prevalence of chronic hypohydration remains elevated among adults in the USA; however, the health effects of hypohydration in regards to human gut health have not been explored. ***Methods:*** This study examined the relationship between total water intake, hydration biomarkers (first-morning urine specific gravity [FMU_{sg}], first-morning urine volume [FMU_{vol}], and plasma copeptin), fecal microbiota, and plasma lipopolysaccharide-binding protein (LBP) in adults (25–45 years, 64% female). Fecal microbiota composition was assessed using 16S rRNA gene sequencing (V4 region). Immunoassays quantified plasma copeptin and LBP in fasted venous blood samples. Dietary variables were measured using 7-day food records. Linear discriminant analysis effect size (LEfSe) analyzed differentially abundant microbiota based on median cutoffs for hydration markers. Multiple linear regressions examined the relationship between LBP and copeptin. ***Results:*** LEfSe identified 6 common taxa at the genus or species level that were differentially abundant in FMU_{sg}, total water (g/day), or plasma copeptin (μg/mL) groups when split by their median values. Uncultured species in the *Bacteroides*, *Desulfovibrio*, *Roseburia*, *Peptococcus*, and *Akkermansia* genera were more abundant in groups that might indicate poorer hydration status. Multivariate linear analyses revealed a positive relationship between plasma copeptin and LBP when controlling confounding variables ($F(6,52) = 4.45$, $p = 0.002$, $R^2 = 0.34$). ***Conclusions:*** Taxa common between markers are associated with the intestinal mucus layer, which suggests a potential link between hydration status and intestinal mucus homeostasis. The relationship between LBP and copeptin indicates that copeptin may be sensitive to metabolic endotoxemia and potentially gut barrier function.

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Introduction

Water is one of the most important but often overlooked essential nutrients for humans [1, 2]. As an integral component of all living cells, water is the single largest component of the human body and accounts for over 60% of adult body weight [3]. However, up to 65% of adults are chronically under-hydrated due to low daily water intake [4]. A 2% body weight loss from water depletion can contribute to cognitive and physical deficiencies and has been associated with obesity and chronic disease in adults [5].

Several plasma and urinary markers are sensitive to variable water intake. Body water balance is regulated by arginine vasopressin (AVP), which rises in circulation during water deprivation and preserves blood osmolality and volume by increasing renal water reabsorption. Pooled urine collected over a 24 h period is the ideal marker for measurement of daily hydration status, accounting for the diurnal variability of AVP [6]; however, spot urine samples, including first-morning urine (FMU), are also sensitive to variable water consumption [7]. As part of the AVP prohormone, copeptin is secreted in equimolar concentrations and can be used as a surrogate marker for AVP [8]. Beyond its role in hydration signaling, AVP is known to stimulate glycogenolysis [9], and influence gastrointestinal motility [10], while copeptin is sensitive to infection [11], and has been linked to elements of metabolic syndrome [12]. This indicates the diagnostic potential of copeptin as a marker of cardio-metabolic stress.

Lipopolysaccharide (LPS), a component of gram-negative bacteria, induces metabolic stress and systemic inflammation [13], and like copeptin, the concentration of plasma LPS has been linked to elements of metabolic syndrome [14]. However, to our knowledge, the concentration of plasma LPS or the LPS binding protein (LBP) [15], in the context of hydration status remains a novel inquiry. In fact, the effect of hydration status on gut health and relative abundance of gastrointestinal microbiota is largely unexplored.

Considering that hydration markers, LPS, and the gastrointestinal microbiota have all been implicated in metabolic regulation; this study aimed to investigate hydration biomarkers in relation to the relative abundances of fecal microbiota and plasma LBP. We hypothesized that we would observe fecal microbiota that would be differentially abundant across hydration markers (total water, first-morning urine specific gravity [FMU_{sg}], FMU_{vol}, and plasma copeptin). Additionally, we hypothesized that there would be a statistically significant relationship between plasma concentrations of LBP and copeptin.

Materials and Methods

Participants and Study Protocol

Participants were excluded from this study based on pregnancy or lactation, history of metabolic or neurological disease, and food allergies or intolerances. Participants were included in the primary analyses if they provided FMU samples, dietary intake information, and fecal samples (n = 156). This sample was then analyzed for normally distributed variables and outliers >3 SD from the mean were omitted (n = 10) resulting in a final sample size of 146. A subsample of participants provided fasted venous blood samples that were assayed for plasma copeptin (n = 85) and plasma LBP (n = 95); 59 samples were assayed for both markers (Fig. 1).

Plasma Copeptin and LBP Analysis

Blood was drawn from the antecubital vein following a 10-h overnight fast (with ad libitum water intake permitted), centrifuged, and stored at −80°C until later analyses. Plasma biomarkers were assessed in K_2EDTA treated plasma with commercial EIA kits for copeptin (Copeptin Kit No: EK-065-32; Phoenix Pharmaceuticals, Inc. Burlingame, CA, USA), and LBP (LBP: Hycult Biotech; HK315) in duplicate and according to manufacturer instructions. Samples with intra-assay coefficients of variation >20% were omitted from the analysis.

Urine Biomarker Analyses

FMUs were provided by participants, and all analyses were performed on fresh, nonfrozen samples. First-morning urine volume (FMU_{vol}) was measured in a graduated beaker, and FMU_{sg} was assessed using a digital handheld pen refractometer (ATAGO Co., Tokyo, Japan).

Fecal Microbiota Analyses

Participants provided a fresh fecal sample within 15 min of defecation. Samples were homogenized, flash-frozen, and stored at −80°C until analysis. Following fecal DNA extraction utilizing the PowerLyzer PowerSoil DNA Isolation Kit (MO BIO Laboratories Inc., Carlsbad, CA, USA), the V4 region of the 16S rRNA gene was amplified on a Fluidigm Access Array. Sequencing was performed on an Illumina MiSeq or HiSeq (Illumina Inc., San Diego, CA, USA) at the W.M. Keck Center for Biotechnology, University of Illinois at Urbana-Champaign. Sequence data were analyzed with DADA2 [16] and QIIME 2 [17]. Quality score was screened at a threshold of 20 and taxonomy was assigned to the amplicon sequence variants (ASV) with the SILVA 132 reference database. Fecal microbiota diversity analyses were conducted using R version 4.0.0 and Phyloseq package v1.16.2 [18].

Dietary Intake

Participants recorded food and beverage intake in a 7-day food diary. Laboratory staff under the supervision of a registered dietitian entered the food records into the Nutrition Data System for Research Version 2015 (Nutrition Coordinating Center, University of Minnesota) software. Diet records were entered, separately checked for quality, and any discrepancies were resolved by a third party inspecting the original record. Mean values for total water (comprising all dietary water from food and beverage sources), total dietary fiber, and total energy intake were extracted. Normalized dietary fiber was calculated as total dietary fiber per 1,000 kcal.

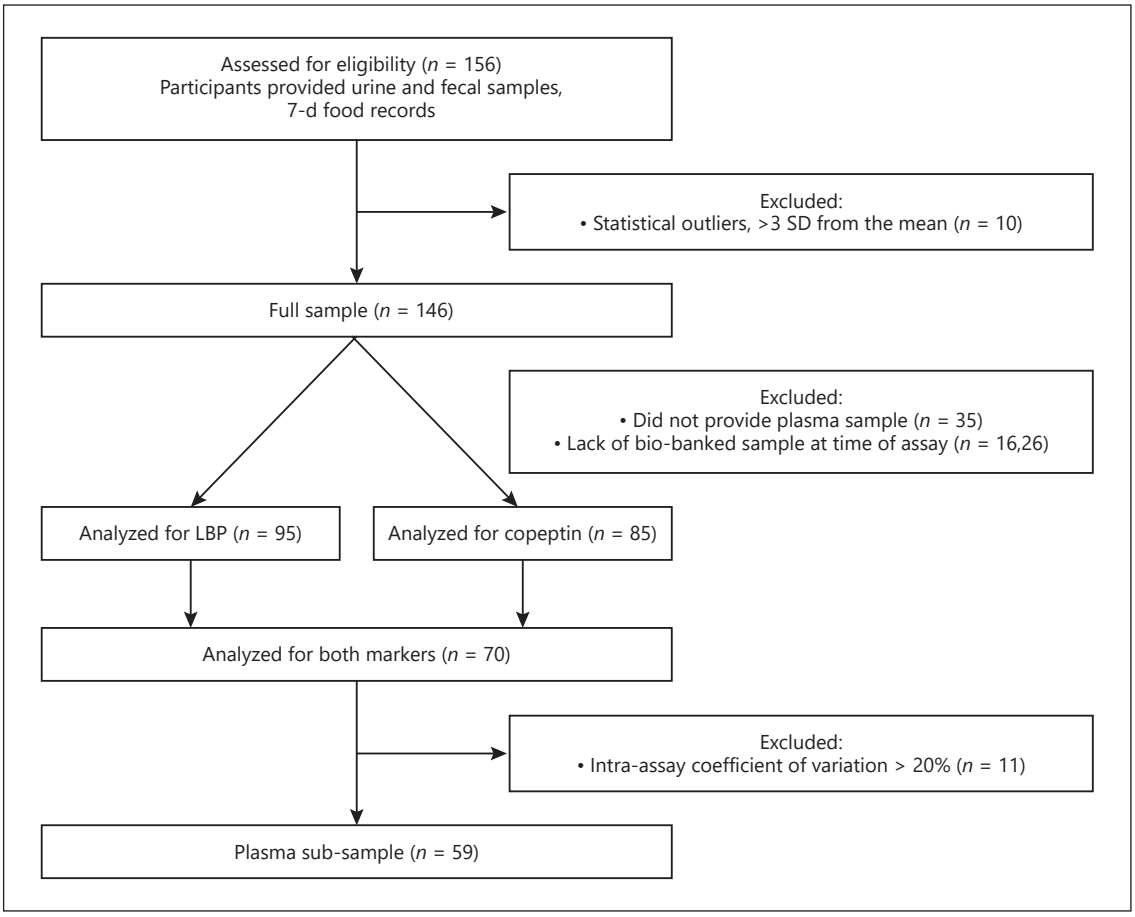

Fig. 1. Sample inclusion and analysis flowchart.

Anthropometrics

Height and weight were measured in triplicate and averaged to calculate body mass index (BMI). A stadiometer (model 240; SECA, Hamburg, Germany) and a digital scale (WB-300 Plus; Tanita, Tokyo, Japan) were used to measure height and weight, respectively.

Statistical Approach

Variables of interest were inspected for normality and a natural log transformation was used for the non-normally distributed variables to be included in linear analyses. Two-tailed Pearson correlations were conducted amongst variables including age, sex, BMI, total water, FMU_{sg}, FMU_{vol}, copeptin, normalized dietary fiber, and *Firmicutes* to *Bacteroides* ratio (F:B). A Pearson partial correlation was then conducted to adjust for age, sex, BMI in this analysis. Hydration variables (total water, FMU_{sg}, FMU_{vol}, and copeptin) were then split by their respective medians to examine above/below median group differences in demographic variables via Student's *t* test, and in the relative abundance of microbiota between groups via linear discriminant analysis effect size (LEfSe).

Alpha diversity was measured via pairwise comparisons using the Wilcoxon rank-sum test with continuity correction and the Holm *p* value adjustment method. Beta diversity was measured with principal coordinate analysis and permutational multivariate analysis of variance. Microbiota taxa summaries were formatted for input into LEfSe (Huttenhower Lab Galaxy Server) and analyzed for differential abundance based on above and below median groups for hydration markers of interest. Differentially abundant taxa were ranked by LEfSe; those with a Kruskal-Wallis threshold below $\alpha = 0.05$ and an LDA log score of at least ±2 were visualized in plots. LEfSe was conducted on both the full sample ($n = 146$) and the copeptin subsample ($n = 85$). Finally, multiple linear regression was conducted to explain variability in plasma copeptin by LBP in a model controlling for age, sex, BMI, normalized dietary fiber, and total water/day ($n = 59$).

Results

The full sample was split separately by the median total water (2,438 g/day), FMU_{sg} (1.018), and FMU_{vol} (258 mL) to observe differences between groups (Table 1). Copeptin median (1.14 ng/mL) group comparison was also observed for subjects with plasma samples. Above/below

Table 1. Sample descriptive data with mean and standard deviation values for variables of interest

	Full sample (N = 146)	Plasma subsample (N = 59)
Female sex, %	63.5	65.8
Age, years	34±6	34±6
BMI, kg/m^2	30±7	30±8
Underweight, *n* (%)	1 (0.7)	1 (1.7)
Normal weight, *n* (%)	33 (22.6)	12 (20.3)
Overweight, *n* (%)	58 (39.7)	24 (40.7)
Obese, *n* (%)	54 (37.0)	22 (37.3)
Total water[a, b, e], g/day	2,640±1,090	2,354±939
Total fiber[a, e], g/day	21±10	20±9
Normalized fiber (g/1,000 kcal)	9.84±4.46	9.32±2.85
F:B[b]	2.42±2.21	2.18±1.20
FMU_{sg}[a, b, c]	1.018±0.007	1.019±0.007
FMU_{vol}[b, c], mL	255±111	264±118
Plasma LBP[d, f], µg/mL	5.34±5.69	6.11±6.29
Plasma copeptin[d, g], ng/mL	1.17±0.24	1.18±0.24

BMI, body mass index; F:B, *Firmicutes* to *Bacteroides* ratio; FMU_{sg}, first-morning urine specific gravity; FMU_{vol}, first-morning urine volume; LBP, lipopolysaccharide-binding protein. Significant difference ($p < 0.05$) between variables when split by their respective medians are noted with the superscripts. [a] Total Water Intake, [b] FMU_{sg}, [c] FMU_{vol}, [d] Copeptin, [e] Sex. A subsample of participants provided plasma samples, in which analyses were conducted for LBP, in [f] 95 participants and copeptin in [g] 85 participants.

Table 2. p Values for above/below median group comparisons of alpha diversity and beta diversity across hydration variables

Diversity metric	Total water	FMU_{sg}	FMU_{vol}	Copeptin
Alpha diversity				
Observed ASVs	0.12	0.11	0.03*	0.65
Chao1	0.12	0.12	0.03*	0.65
ACE	0.12	0.12	0.03*	0.66
Shannon	0.24	0.26	0.12	0.37
Simpson	0.51	0.73	0.10	0.37
Beta diversity				
Weighted uniFrac	0.19	0.85	0.99	0.53
Unweighted uniFrac	0.23	0.65	0.62	0.52

Alpha diversity metrics were analyzed via Wilcoxon rank-sum test with a holm p value adjustment. Beta diversity metrics were analyzed via PERMANOVA and p values are presented for the respective models. ASV, amplicon sequence variant; FMU_{sg}, first-morning urine specific gravity; FMU_{vol}, first-morning urine volume; PERMANOVA, permutational multivariate analysis of variance. * $p < 0.05$.

median group sizes can be found in the supplementary materials (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520478).

Pearson Partial Correlations

When controlling for age, sex, BMI, and normalized dietary fiber; FMU_{sg} was negatively correlated with total water ($r = -0.18$, $p = 0.03$) and FMU_{vol} ($r = -0.26$, $p = 0.002$) and had a trend level relationship with F:B ($r = 0.16$, $p = 0.06$). There was also a trending relationship between total water and FMU_{vol} ($r = 0.16$, $p = 0.06$), but no other significant relationships were found between these variables.

Microbiota Analyses

Alpha and Beta Diversity Analysis

Alpha diversity was analyzed for within-sample richness using Observed ASVs, Chao1, and ACE richness estimators; and within-sample diversity using Shannon and Simpson diversity indices. These analyses revealed a higher degree of microbial richness in the above median FMU_{vol} indicated by observed ASVs ($p = 0.03$), Chao1 ($p = 0.03$), and ACE ($p = 0.03$). There were no significant differences between median groups when split by FMU_{sg}, total water, or copeptin (Table 2).

Beta diversity between groups was analyzed using weighted and unweighted UniFrac matrices [19]. We observed no statistically significant differences in beta diversity between above/below median groups (total water; unweighted $p = 0.23$, weighted $p = 0.19$: FMU_{sg}; unweighted $p = 0.65$, weighted $p = 0.85$: FMU_{vol}; unweighted $p = 0.62$, weighted $p = 0.99$: copeptin; unweighted $p = 0.52$, weighted $p = 0.53$) (Table 2).

Linear Discriminant Analysis Effect Size

LEfSe was conducted to assess differentially abundant taxa based on median splits for total water, FMU_{sg}, and FMU_{vol} independently. There were 37, 60, and 22 ASVs that were differentially abundant, respectively. Several of these features were redundant (i.e., the class, order, and family for a statistically significant genus were also significant); thus, we chose to include only taxa at the genus or species level in the discussion. This reduced the list of differentially abundant taxa to 24 (total water), 35 (FMU_{sg}), and 14 (FMU_{vol}) unique taxa. LEfSe analyses were then conducted on the copeptin subsample and revealed 23 unique taxa at the genus or species levels. The 10 genera with the highest LDA scores are presented in Figure 2. A full listing of the LEfSe output for each vari-

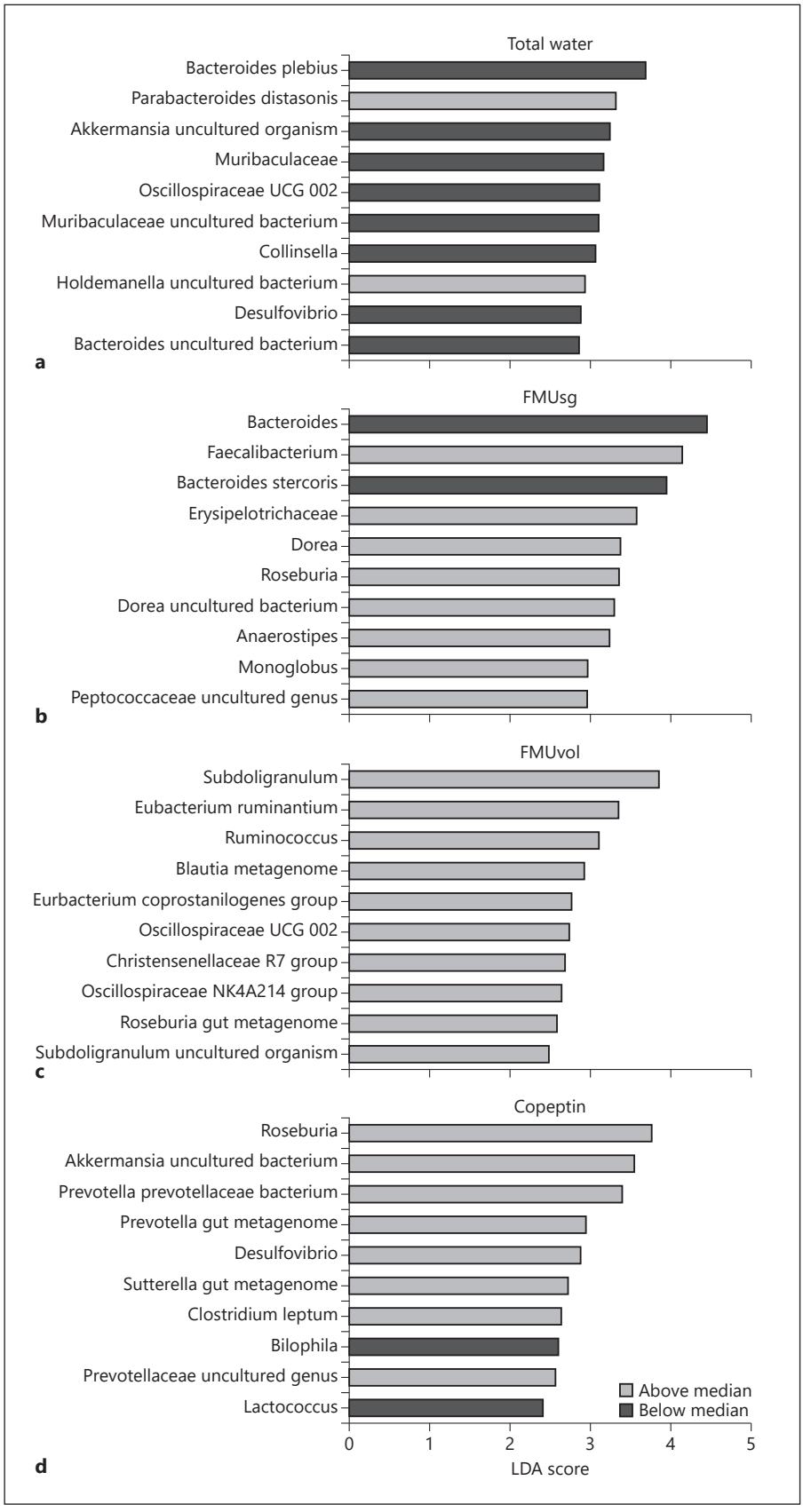

Fig. 2. Top 10 LEfSe LDA scores of fecal taxa at the genus or species level in groups based on median splits of total water intake (**a**), FMU_{sg} (**b**), FMU_{vol} (**c**), copeptin (**d**). The score indicates differential abundance of taxa and statistically significant magnitude of effect size (at $\alpha = 0.05$) to the difference between groups. The bars are shaded according to the above (light) or below (dark) median group in which individual taxa were found at greater relative abundance. FMU_{sg}, first-morning urine specific gravity; FMU_{vol}, first-morning urine volume; LEfSe, linear discriminant analysis effect size.

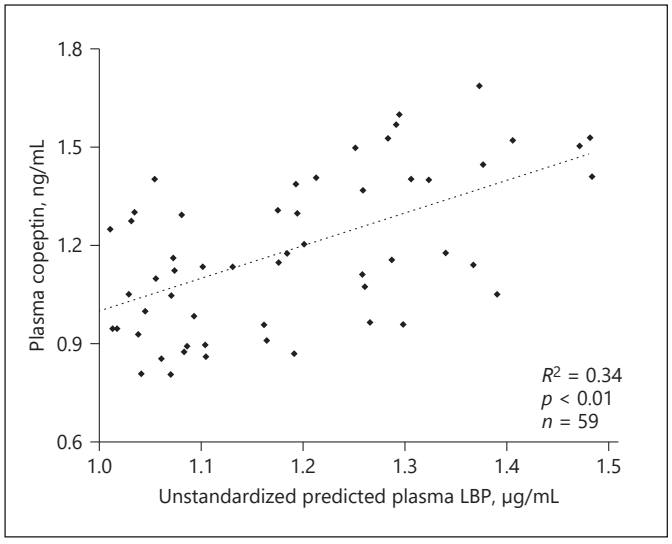

Fig. 3. Scatter plot of copeptin regressed over predicted plasma LBP (controlling for age, sex, BMI, total water, and normalized dietary fiber). Unstandardized residuals from the multiple regression models were used for this plot. LBP, lipopolysaccharide-binding protein; BMI, body mass index.

able may be found in the online supplementary materials (online suppl. Tables 2–5).

Copeptin and LPS Binding Protein

A regression model comprised of the covariates age, sex, BMI, total water, and normalized dietary fiber explained a significant amount of variance in plasma copeptin values ($F(5,53) = 2.65$, $p = 0.03$, $R^2 = 0.20$). Addition of LBP to the model explained an additional 14% of the variance in copeptin ($F(6,52) = 4.45$, $p = 0.002$, $R^2 = 0.34$; LBP $\beta = 0.018$, $p = 0.002$) (Fig. 3).

Discussion

This study examined relations between hydration biomarkers and fecal microbiota. Uncultured species of several bacterial genera were differentially abundant across median FMU_{sg}, plasma copeptin, and total water. Further, plasma copeptin explained variance in a marker of gut barrier dysfunction as evidenced by a statistically significant association with circulating LBP. To our knowledge, these findings are the first to characterize relations between hydration biomarkers and fecal microbiota and link copeptin to LBP in humans. Uncultured species in the *Bacteroides*, *Desulfovibrio*, *Roseburia*, *Peptococcus*, and *Akkermansia* genera were found at greater relative abundance in groups that might indicate poorer hydration status (Table 3).

The *Bacteroides* genus has been a popular target for analysis with a great deal of work specifically examining the polysaccharide degradation capabilities of *B. thetaiotamicron*. These bacteria express enzymes that coordinate the breakdown of multiple specific glycans on the human intestinal epithelium. In fact, 18% of the *B. thetaiotamicron* genome is dedicated to glycan degradation, evidenced by the discovery of 88 individual polysaccharide utilization loci's in the genome [20]. There is a known relationship between these metabolic generalists and mucin-specialists like *Akkermansia muciniphila* and *Bacteroides caccae* such that when dietary fiber is scarce, *A. muciniphila* and *B. caccae* increase in abundance, cleaving mucin glycans and presumably providing sugar residues for other microorganisms [21]. Interestingly, we observed species in the *Akkermansia* genus at greater abundance in those with below-median total water intake and above-median copeptin (Table 2). Recently, *A. muciniphila* has been shown to have improved probiotic traits in response to mucin depletion, inducing mucin secretion and improving barrier function in mice [22]. *Roseburia* also colonizes the luminal mucus layer and is known for butyrate production [23]. Further, *Roseburia* have been found in decreased abundance in persons with obesity and type 2 diabetes mellitus [24]; conditions that are also associated with hypohydation.

Desulfovibrio is unique in this group as a genus of sulfate-reducing bacteria. Sulfate reduction yields hydrogen sulfide which can both positively and negatively impacts mucus layer integrity, depending on concentration [25]. Further, *Desulfovibrio* c21_c20 has been found at greater relative abundance pre-clinically in male Brattleboro rats with AVP gene deletion, when compared to the heterozygous group [26]. While this finding was sex-specific, it does provide interesting evidence as to the potential extent of AVP-microbiota interactions in the gut.

Why these genera were differentially abundant is not immediately clear and will require further investigation to elucidate causal mechanisms. However, that the taxonomic units in common across these hydration markers were all associated with the intestinal mucus layer implies the potential impact of hydration signaling on intestinal barrier function. Indeed, there is evidence that AVP induces mitogenic signaling in response to epithelial injury, and this cell proliferation is posited to play a role in maintaining or recovering mucus and barrier integrity [27].

These findings are especially interesting considering our multiple regression model showing a moderate positive association between plasma copeptin and LBP concentrations. Circulating LPS leads to metabolic endotoxemia, and LPS could have a causal relationship with both intestinal barrier dysfunction and obesity-induced inflammation [14]. While our sample contained persons with overweight and obesity, participants were otherwise screened for metabolic and digestive disorders that frequently contribute to intestinal barrier dysfunction (e.g., inflammatory bowel disease). That LBP accounted for 14% of the variance of copeptin in this sample suggests that copeptin could be sensitive to metabolic endotoxemia. We cannot offer causal inferences based on these results; however, these findings suggest a novel line of inquiry into the role of AVP and/or copeptin in the modulation of intestinal barrier function that warrants further investigation.

The lack of statistically significant correlations among copeptin and self-reported water consumption was surprising. Copeptin, as a surrogate marker of AVP, has known relationships with hydration markers [28], is elevated in habitually low water consumers [29], and can be attenuated with increased plain water consumption [28]. Thus, we anticipated a negative relationship between plasma copeptin and total water intake; however, this is not unprecedented since the present investigation was not the first to observe such a relationship [28]. The inclusion of urine osmolality based on 24-h samples would have provided interpretive utility beyond FMU and self-reported dietary water intake.

Limitations and Future Directions

Given the exploratory nature of these aims, we did not posit a directional hypothesis. Nevertheless, establishing links between fecal microbiota and hydration biomarkers serves as a necessary first step in conducting larger studies examining the effects of hydration practices on gastrointestinal and metabolic health. While this study provides novel results linking hydration markers to fecal microbial profiles and plasma LBP, several limitations are worth considering. This was a cross-sectional analysis, and intervention studies are needed to investigate the causal effects of water consumption on gastrointestinal microbiota and barrier integrity. Body water turnover is complex, and ideal biomarkers are context dependent [30]; thus a gold-standard hydration biomarker has yet to emerge. As such, we are unable to make normative claims regarding hydration status based on FMU values alone, though previous work suggests an average FMU_{sg} of 1.018 (Table 1)

Table 3. Taxanomic units at the genus and species level found in common across multiple markers

Taxanomic unit	Marker			
	C	W	S	V
d__Bacteria.p__Bacteroidota.c__*Bacteroidia.o__Bacteroidales.f__Bacteroidaceae.g__Bacteroides. s__*uncultured_bacterium				
d__Bacteria.p__Desulfobacterota.c__Desulfovibrionia.o__*Desulfovibrionales.*f__Desulfovibrionaceae. g__*Desulfovibrio._*_				
d__Bacteria.p__*Firmicutes.*c__*Clostridia.o*__Oscillospirales.f__Oscillospiraceae.g__NK4A214_group				
d__Bacteria.p__*Firmicutes.*c__*Clostridia.o*__Lachnospirales.f__*Lachnospiraceae.*g__*Roseburia._*_				
d__Bacteria.p__*Firmicutes.*c__*Clostridia.o*__Peptococcales.f__*Peptococcaceae.*g__*Peptococcus. s*__uncultured_bacterium				
d__Bacteria.p__Verrucomicrobiota.c__Verrucomicrobiales.f__Akkermansiaceae.g__*Akkermansia.s*__uncultured_bacterium				*

Dark-shaded cells indicate that the taxa were found in above/below median groups indicating relatively poorer hydration status (i.e., below median water, above median copeptin, etc.), while light-shaded cells indicate that taxa were found in groups indicating the opposite. Hydration variable abbreviations: C, copeptin; W, total water; S, FMU_{sg}; V, FMU_{vol}. FMU_{sg}, first-morning urine specific gravity; FMU_{vol}, first-morning urine volume; LEfSe, linear discriminant analysis effect size. * *Akkermansia* uncultured organism was found in the total water LEfSe analysis. Variable prefixes indicate taxanomic level with p__ indicating phylum, c__ indicating class, and so forth.

falls between 1.2 and 2.0 L of daily plain water consumption [7]. Continued work should examine both the relationships between additional biomarkers of hydration (e.g., 24 h urine osmolality), plain water consumption, and the intestinal microbiota; while also considering other confounding factors (e.g., habitual physical activity) to better inform water intake recommendations and public health initiatives.

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Statement of Ethics

Primary study protocols were conducted according to the Declaration of Helsinki, and all procedures were approved by the Institutional Review Board of the University of Illinois (Protocol numbers 16840, 16277, 16071). All participants provided written consent before enrollment which included consent to secondary analyses of these data.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

The followings are the authors' contributions: conceptualization: N.B.W. and N.A.K.; formal analysis: N.B.W. and A.R.M.; funding acquisition: H.D.H. and N.A.K.; investigation: C.G.E. and N.A.B.; writing – original draft: N.B.W., C.X.M., and N.A.K.; writing – review and editing: A.R.M., C.G.E., P.W., C.H.H., N.A.B., and H.D.H.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary files. Further enquiries can be directed to the corresponding author.

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