Hydration, Kidney Injury and Clinical Outcome

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Abstract

Studies in health care professional (HCPs) have demonstrated a high prevalence of dehydration, which has been linked with morphological brain changes as well as cognitive impairment in other groups. Moreover, many age-related pathophysiological changes result in increased susceptibility to fluid and electrolyte imbalance, rendering older adults vulnerable to dehydration which may be associated with poor outcome.

This thesis investigates the prevalence of dehydration and impact on cognitive function amongst HCPs. It also investigates the prevalence of dehydration in hospitalised older adults and the association between dehydration, acute kidney injury (AKI) and clinical outcome.

Hydration status and cognition were objectively assessed in nurses and doctors working on emergency medical and surgical wards. This study demonstrated that a significant proportion of HCPs were dehydrated at the start and end of their shifts and many were oliguric. The prevalence of dehydration varied with level of experience and speciality and was associated with short-term memory impairment.

Using serum osmolality, the key regulated variable in fluid homeostasis as a measure of hydration status in hospitalised older adults, prospective assessment of 200 patients demonstrated that over a third had hyperosmolar dehydration (HD) at admission, two-thirds of which were dehydrated 48 hours later. Dehydration at admission was independently associated with a six-fold increase

in 30-day mortality. Subsequent retrospective assessment of 32,980 hospitalised older adults demonstrated that dehydration was diagnosed clinically in 8.9% of patients and was independently associated with a two fold increase in mortality. Nearly half of those dehydrated had a concomitant diagnosis of AKI and the median length of hospital stay (LOS) was nearly three times greater than those without the condition.

Despite the widespread use of serum osmolality in human physiology studies, it is rarely used clinically to assess hydration. Analysis of published equations estimating osmolality, demonstrated that an equation by Khajuria and Krahn was 90% sensitivity and 97% specificity at diagnosing hyperosmolar dehydration. Using this equation, we demonstrated that 27.2% of 6632 older adults had HD at admission to hospital and the risk of developing AKI 12-24 hours after admission in these patients was five times those euhydrated at admission. Moreover, the 30-day mortality was nearly twice that of euhydrated patients, independent of key confounders. The median LOS in dehydrated patients was almost double.

This work has highlighted the need to educate both patients and HCPs on the importance of hydration. Further work is required to prospectively assess the use of serum osmolality as a predictor of dehydration, AKI and outcomes. Given that hydration and nutrition are the hallmarks of compassionate care, there is clear room for improvement with findings from this thesis suggesting the need for further investigation and intervention in both community and hospital settings.

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Finally, to my wife Hannan, thank you for believing in me and for your endless support, patience and your never wavering encouragement on this journey. Without your commitment and sacrifices this thesis would not have been possible.

List of Abbreviations

ACE	Angiotensin converting enzyme
ACE-i	Angiotensin converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
ADL	Activities of daily living
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ANP	Atrial natriuretic peptide
BIA	Bioelectrical impedance
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CAM	Confusion Assessment Method
CCI	Charlson Comorbidity Index
CHD	Coronary heart disease
CHKS	Caspe Healthcare Knowledge Systems
CI	Confidence interval
CRP	C-reactive protein
CRT	Capillary refill time
CSHA	Canadian Study of Health and Ageing
DM	Diabetes mellitus
DVT	Deep vein thrombosis
ECF	Extracellular fluid
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
FBC	Full blood count
Glu	Glucose
HCPs	Health care professionals
HD	Hyperosmolar dehydration

HR	Hazard ratio
Hz	Hertz
ICD	International Classification of Disease
ICF	Intracellular fluid
K	Potassium
kg	Kilograms
LOS	Length of stay
MAP	Mean arterial pressure
MMSE	Mini Mental State Examination
MVP	Mitral valve prolapse
Na	Sodium
NEWS	National Early Warning Score
NICE	National Institute of Health and Care Excellence
NRS	Nutrition Risk Screening
NSAIDs	Non-steroidal anti-inflammatory drugs
PPG	Photoplethysmographic
PR	Pulse rate
RASS	Renin angiotensin aldosterone system
RCT	Randomised controlled trial
RIFLE	Risk, Injury, Failure, Loss of function, and End-stage kidney disease
SCr	Serum creatinine
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SR	Systematic review
SSRI	Selective serotonin reuptake inhibitor
TBM	Total body mass
TBW	Total body water
U&Es	Urea and electrolytes
UTI	Urinary tract infection
WHO	World Health Organisation

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Declaration

Except where acknowledged in the acknowledgment and text, I declare that this dissertation is my work and is based on research that was undertaken by me at the Division of Gastrointestinal Surgery from November 2013 to February 2015.

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Publications and presentations arising from this work

Publications

1. **El-Sharkawy AM**, Sahota O, Maughan RJ, Lobo DN. The pathophysiology of fluid and electrolyte balance in the older adult surgical patient. Clini Nutr 2014; 33(1): 6-13. [PMID:24308897]
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3. **El-Sharkawy AM,** Watson P, Neal KR, *et al.* Hydration and outcome in older patients admitted to hospital (The HOOP prospective cohort study). Age Ageing 2015; 44:943-7. [PMID: 26316508]
4. **El-Sharkawy AM**, Bragg D, Watson P. Sahota O, Maughan RJ, Lobo DN Hydration Amongst Nurses and Doctors On-call (The HANDS On Prospective Cohort Study). Clin Nutr 2015 Jul 16. [PMID: 26216194]
5. Benton D, Braun H, Cobo JC, Edmonds C, Elmadfa I, **El-Sharkawy AM** *et al.* Executive summary and conclusions from the European Hydration Institute expert conference on human hydration, health, and performance. Nutr Rev 2015 Sep; 73 Suppl 2:148-50. [PMID: 26290300]

Presentations

International meetings:

1. Hydration and Outcome in Older Patients Admitted to Hospital – **El-Sharkawy AM**, Sahota, O, Maughan R, Lobo DN. The European Society for Clinical Nutrition and Metabolism (ESPEN), poster presentation, Leipzig 2013.
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3. Hydration amongst nurses and doctors oncall - **El-Sharkawy AM**, Bragg D, Sahota, O, Maughan R, Lobo DN. The European Society for Clinical Nutrition and Metabolism (ESPEN), poster presentation, Geneva 2014.
4. Hydration and public health- **El-Sharkawy AM**, Sahota, O, Lobo DN. III World congress on public health and nutrition, oral presentation, Las Palmas de Gran Canaria 2014.
5. Hydration Amongst Nurses and doctors oncall- the HANDS On Study. **El-Sharkawy AM**, Bragg D, Sahota, O, Maughan R, Lobo DN. III World congress on public health and nutrition, oral presentation, Las Palmas de Gran Canaria 2014.
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1. Introduction

1.1 Fluid homeostasis in the healthy adult

Water is the most abundant compound in the body. It is a regulator of the internal environment and is essential for optimal cellular function. Total body water (TBW) makes up approximately 60% of body mass in healthy young adults of stable weight, divided into the intracellular (ICF) and extracellular fluid compartment (ECF) (Edelman and Leibman, 1959, Rush *et al.,* 2009). These compartments are separated by the cell membrane that is permeable to water but not solutes. The ICF compartment accounts for approximately 40% of the total body mass and the ECF compartment approximately 20% of the total body mass. The ECF compartment is further divided into intravascular space containing circulatory blood volume (approximately 5% of TBW) and the extravascular space, which includes interstitial fluid (approximately 15% of the TBW) (Figure 1). Interstitial fluid surrounds cells and includes other pockets of fluid such as that within connective tissues as well as cerebrospinal fluid and fluid within the gastrointestinal tract (Cheek, 1961).

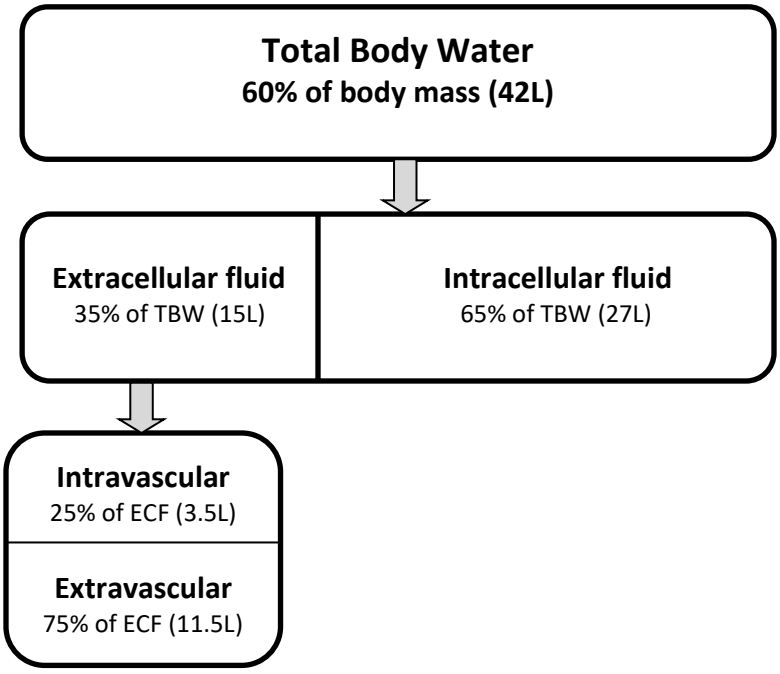


Figure 1: Schematic representation of fluid compartments and body water distribution. Total body water (TBW) makes up approximately 60% of total body mass (TBM) in healthy young adults of stable weight. This is divided into the intracellular (ICF), approximately 27 litres, 40% of the TBM and the extracellular fluid compartment (ECF), approximately 15 litres, 20% of the TBM. These compartments are separated by the cell membrane that is permeable to water but not solutes. The ECF compartment is further divided into intravascular fluid approximately 3.5 litres and extravascular fluid approximately 11.5 litres.

The volume of TBW fluctuates on a daily basis by up to 5% in healthy weight stable adults as a result of food and fluid consumption as well as climate and physical activity (Rush *et al.,* 2009, Rush *et al.,* 2010). Variations in TBW have also been reported with gender, age and race, often attributed to differences in body composition (Rush *et al.,* 2010, Rush *et al.,* 2009, Baumgartner *et al.,* 1995, Chumlea *et al.,* 2001, Jiang *et al.,* 1991, Watson *et al.,* 1980, Cohn *et al.,* 1985, Kyle *et al.,* 2001). The FELS longitudinal study (Chumlea *et al.,* 1999), reported that the mean TBW in men aged 20 to 29 years was approximately 42 litres compared with 31 litres in women of the same age group, using deuterium as a measure of TBW. Sequential decline in mean TBW was also reported in association with increased age (Chumlea *et al.,* 1999, Steele *et al.,* 1950, Norris *et al.,* 1963, Watson *et al.,* 1980, Baumgartner *et al.,* 1995, Cohn *et al.,* 1985). This is likely a result of the overall reduction in the proportion of fat free mass (FFM) and is associated with increased body fat which is relatively anhydrous, therefore leading to a reduction in TBW (Kyle *et al.,* 2001)-(Hume, 1971). Race related differences in TBW have also been reported (Townsend *et al.,* 1983, Schutte *et al.,* 1984, Jiang *et al.,* 1991), with the mean TBW in African-American men being approximately five litres more than age-matched Caucasian males (Chumlea *et al.,* 2001). Similar findings were also reported between age-matched Caucasian and African-American women (Chumlea *et al.,* 2001). These differences in TBW are thought to be related to higher proportions of FFM in the African-American subjects (Townsend *et al.,* 1983, Schutte *et al.,* 1984, Chumlea *et al.,* 2001).

1.1.1 Fluid movements across compartments

The distribution of TBW across the compartments will vary depending on the balance of osmotic, oncotic and hydrostatic forces. The osmotic pressure is the pressure required to oppose the movement of water by osmosis across the cell membrane. This is proportional to the number of particles in the solution (Landau *et al.,* 1970) and is created by the presence of high concentrations of solutes, most commonly sodium and potassium on one side of a membrane. The cell membrane is impermeable to solute but allows the free movement of water which will then move by osmosis across the membrane into the area with a high solute concentration until a balance or steady state has been reached.

The oncotic pressure is exerted by complex molecules such as proteins which are usually located within the intravascular space and cannot easily cross competent capillary walls (Evans, 2002, Adamson *et al.,* 2004). These large proteins act to draw water into the intravascular space and oppose the hydrostatic pressure that exists within the vessel acting to force water out of the intravascular space (Adamson *et al.,* 2004). The intravascular hydrostatic pressure increases with blood pressure (BP) and is influenced by cardiac output and vascular tone (Gertz *et al.,* 1966). The balance between the intravascular oncotic and hydrostatic pressure exert the greatest influence on the net movement of water across the capillary bed as described in Starling's equation (Woodcock and Woodcock, 2012). Interstitial hydrostatic pressure which increases with volume and is affected by tissue compliance can also effect the direction of fluid shift.

Encapsulated organs such as the kidneys tend to have low interstitial tissue compliance compared with non-encapsulated organs such as the skin. Consequently, small changes in interstitial volume within the kidneys results in significant interstitial hydrostatic pressure increase and therefore, greater influence on the net movement of fluid between the compartments.

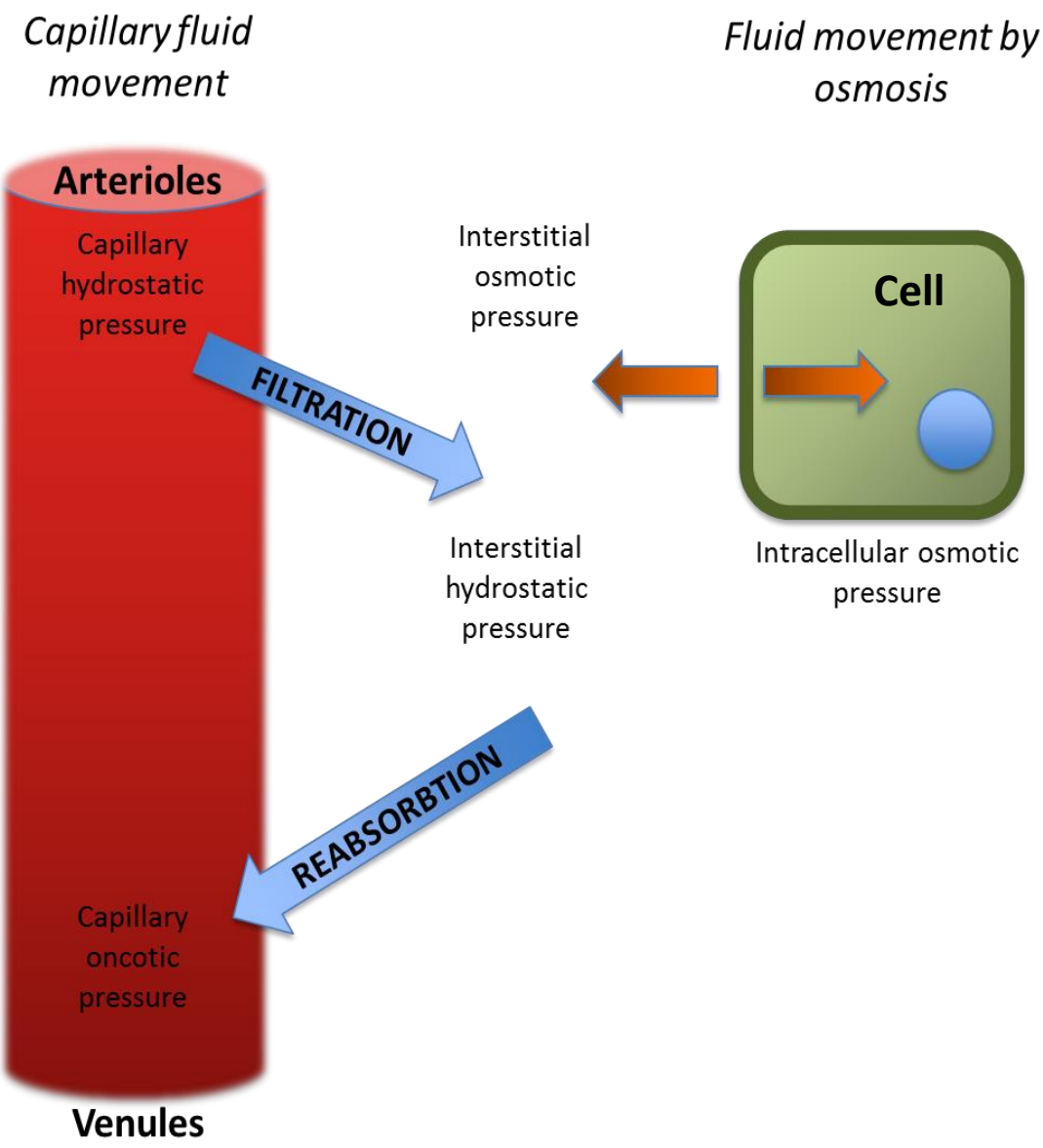


Figure 2: Schematic representation of the forces influencing the movement of fluid between compartments**.** The distribution of TBW across the compartments will vary depending on the balance of osmotic, oncotic and hydrostatic forces. The osmotic pressure is the pressure required to oppose the movement of water by osmosis across the cell membrane. The balance between the intravascular oncotic and hydrostatic pressure exert the greatest influence on the net movement of water across the capillary bed as described in Starling's equation. Interstitial hydrostatic pressure which increases with volume and is affected by tissue compliance can also affect the direction of fluid shift.

1.2 Regulation of fluid balance

Fluid balance is regulated tightly by neurohormonal mechanisms that result in conservation of salt and water as well as the activation of the thirst mechanism that stimulates ingestion of fluid. Osmoreceptors and baroreceptors are the regulators of fluid homeostasis, key to maintaining intravascular fluid volume and organ perfusion.

1.2.1 Osmoregulation

Osmoregulation is key to maintaining adequate cell volume, sensitive to as little as a 1% change in serum osmolality (Fitzsimons, 1963). This sensitivity to change in osmolality helps avoid large fluctuations in cell volume, which can be detrimental to cell function and can result in cell rupture. Osmoregulation is mediated by changes in water balance detected by osmoreceptors located within the vascular organ of the laminar terminalis (OVLT) in the hypothalamus, which sits outside the blood brain barrier (Thrasher *et al.,* 1982). Increase in plasma osmolality results in osmoreceptor activation, which stimulates the release of antidiuretic hormone (ADH) from the posterior pituitary (Stocker *et al.,* 2006, Benarroch, 2005, Robertson *et al.,* 1976, Mckinley *et al.,* 1992). ADH acts directly on receptors located on the basolateral membrane of the principal cells of the renal collecting tubules to increase the number of aquaporin channels (Figure 3) (Robertson *et al.,* 1976, Birnbaumer, 2000). Aquaporin channels allow selective

water reabsorption (Birnbaumer, 2000, Harris *et al.,* 1994), resulting in low urine volume and concentrated urine.

Increase in plasma osmolality by 1 to 2% also stimulates thirst, with animal models demonstrating that a further increase in plasma osmolality is associated with a proportional increase in water consumption (Fitzsimons, 1963).

Other osmoreceptors outside the hypothalamus have also been identified including the hepatoportal osmoreceptors (Ishiki *et al.,* 1991). Although their exact role is yet to be fully defined, animal models support their involvement in controlling and mediating the thirst response to plasma hyperosmolality (Ishiki *et al.,* 1991).

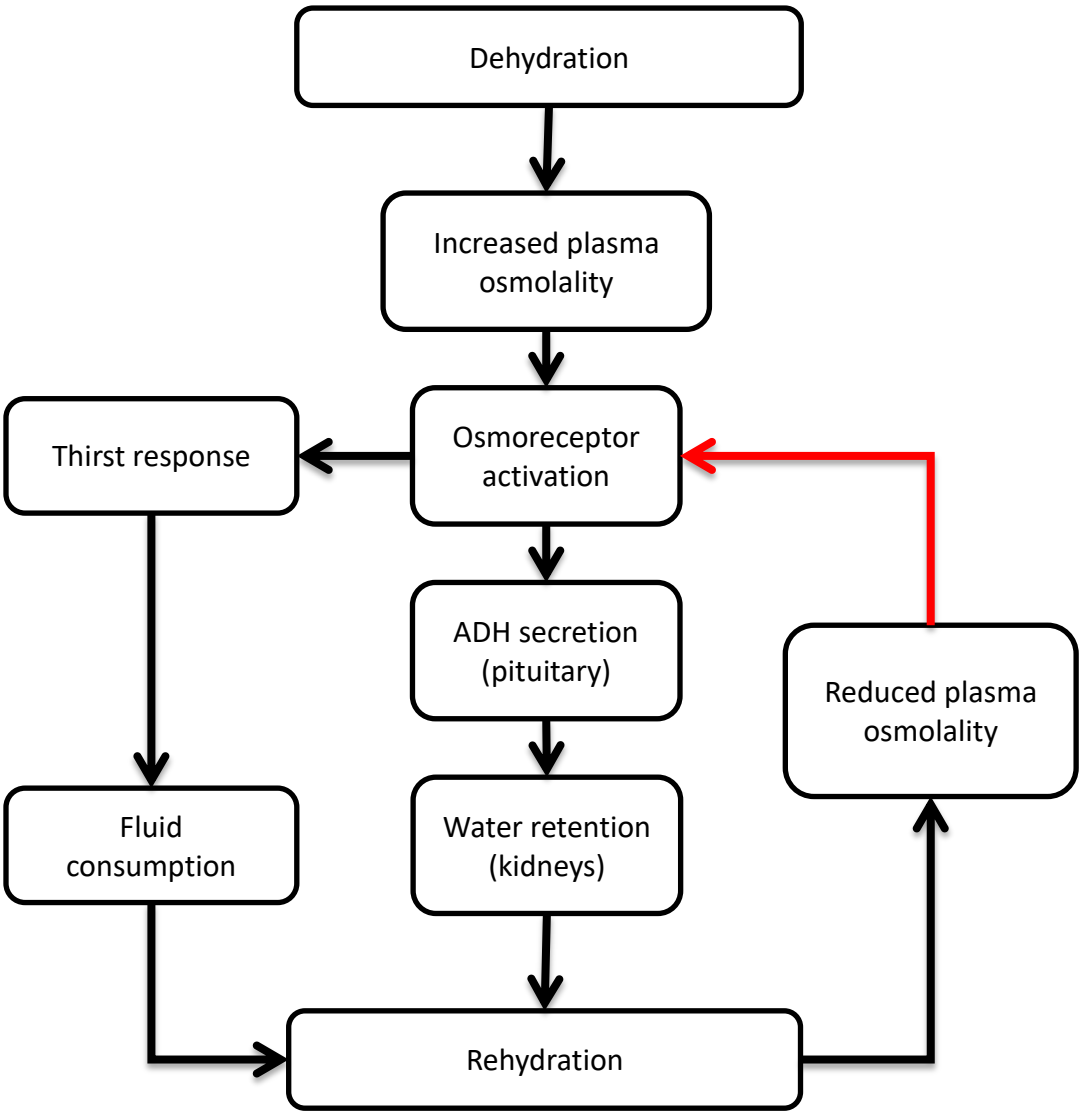


Figure 3: Summary of processes that results from serum hyperosmolality. Water loss dehydration can causes an increase in plasma osmolality resulting in hypothalamic osmoreceptor activation, which stimulates the thirst response as well as the release of antidiuretic hormone (ADH) from the posterior pituitary. ADH acts directly to increase the number of aquaporin channels in the distal convoluted tubules and cortical collecting ducts, allowing selective water reabsorption. Other osmoreceptors outside the hypothalamus have also been identified including the hepatoportal osmoreceptors thought to mediate the thirst response following fluid ingestion.

1.2.2 Baroreceptor activation

Baroreceptors are distributed throughout the circulatory system and detect changes in volume. The baroreceptor sensory endings are located within the tunica adventitia of the vessel and measure change in stretch and luminal pressure that accompanies changes in circulatory volume. Low pressure baroreceptors are found in the great veins as well as the right atrium (Zoller *et al.,* 1972, Abboud *et al.,* 1979). High pressure baroreceptors are located in many of the arteries with the greatest density found in the carotid body and the aortic arch. They are also found in the kidney, located in the juxtaglomerular apparatus of the afferent arterioles and the macula densa.

Baroreceptor neural activity has an inhibitory effect on efferent sympathetic nerve activity. Efferent baroreceptor nerves are continuously firing; when volume depletion is detected, baroreceptor activity decreases. This in turn reduces the inhibitory effects on the sympathetic centres in the brain stem (Guyenet, 2006, Dampney *et al.,* 2002, Strack *et al.,* 1989). The result is a neurohormonal response mediated by autonomic and sympathetic nervous system and activation of the renin angiotensin aldosterone system (RAAS) (Koganezawa *et al.,* 2008). This triggers ADH secretion from the posterior pituitary, activation of the thirst centre, salt and water retention as well as an increase in heart rate and vascular tone (Figure 4) (Johns *et al.,* 2011, DiBona and Kopp, 1997, DiBona, 1994, Janig and Habler, 2003). However, a substantial fall in intravascular volume by approximately 10% is required before baroreceptors are activated (Dunn *et al.,*

1973), and although less sensitive than the osmoreceptors, the hypovolaemic response mediated by baroreceptors results in a much greater surge of ADH.

1.2.3 Activation of the renin angiotensin aldosterone system

Stimulation of the RAAS occurs indirectly through baroreflex via the sympathetic afferent nerves, but also directly through the renal baroreceptors. The juxtaglomerular cells release renin when a reduction in arterial pressure is detected. Renin converts angiotensinogen into angiotensin I which is converted by angiotensin converting enzyme (ACE) into angiotensin II. Angiotensin II leads to central stimulation of the sympathetic nervous system and arterial vasoconstriction resulting in increased BP. Angiotensin II also triggers adrenocorticotrophic hormone (ACTH) release from the anterior pituitary and therefore stimulating the release of glucocorticoids (Gaillard *et al.,* 1981). ADH secretion is also stimulated by angiotensin II, resulting in water reabsorption from the collecting tubules. Angiotensin II also acts directly on the proximal tubules of the kidney resulting in sodium and water retention. Furthermore, it acts on the adrenal cortex to stimulate the production and release of aldosterone, from the zona glomerulosa. Aldosterone, a mineralocorticoid acts mainly on the distal convoluted tubule and the principle cells of the cortical collecting tubules in the distal nephron increasing permeability of the luminal membrane to sodium. It also promotes sodium-hydrogen exchange and activation of the sodium potassium ATPase pump on the basolateral membrane, thus increasing the

extracellular sodium concentration and the excretion of potassium leading to increased extracellular fluid and TBW (Linas *et al.,* 1979, Bauer *et al.*, 1979).

1.2.3.1 The thirst response

Hypovolaemia is also known to stimulate the thirst response mediated through the baroreflex, however, the exact mechanism is yet to be fully defined. In animal models where intravascular hypovolaemia was induced by administering extravascular colloids, water consumption was proportional to volume loss, thought to be mediated through activation of the RAAS (Stricker, 1983, Stricker, 1968, Stricker, 1981, Stricker and Jalowiec, 1970, Gauer and Henry, 1963, Stricker, 1966, Kozlowski *et al.,* 1968, Fitzsimons, 1961). Animal models have also demonstrated that angiotensin II acted as a dipsogenic hormone mainly with small circulatory volume loss (Johnson *et al.,* 1981). However, hypovolaemia appears to be a weak stimulant of thirst given that a 2% to 3% dilution of plasma osmolality has been shown in rats to abolish water intake with 35% plasma-volume deficits (Stricker, 1969). It is important to note, when plasma hyperosmolality and hypovolaemia coexist there is an additive effect on water intake (Corbit, 1968, Stricker and Verbalis, 1986). However, in the presence of arterial hypertension, inhibitory effect on water intake was observed in animal models, even in the presence of plasma hyperosmolality or hypovolaemia (Kirchheim, 1976, Stocker *et al.,* 1999).

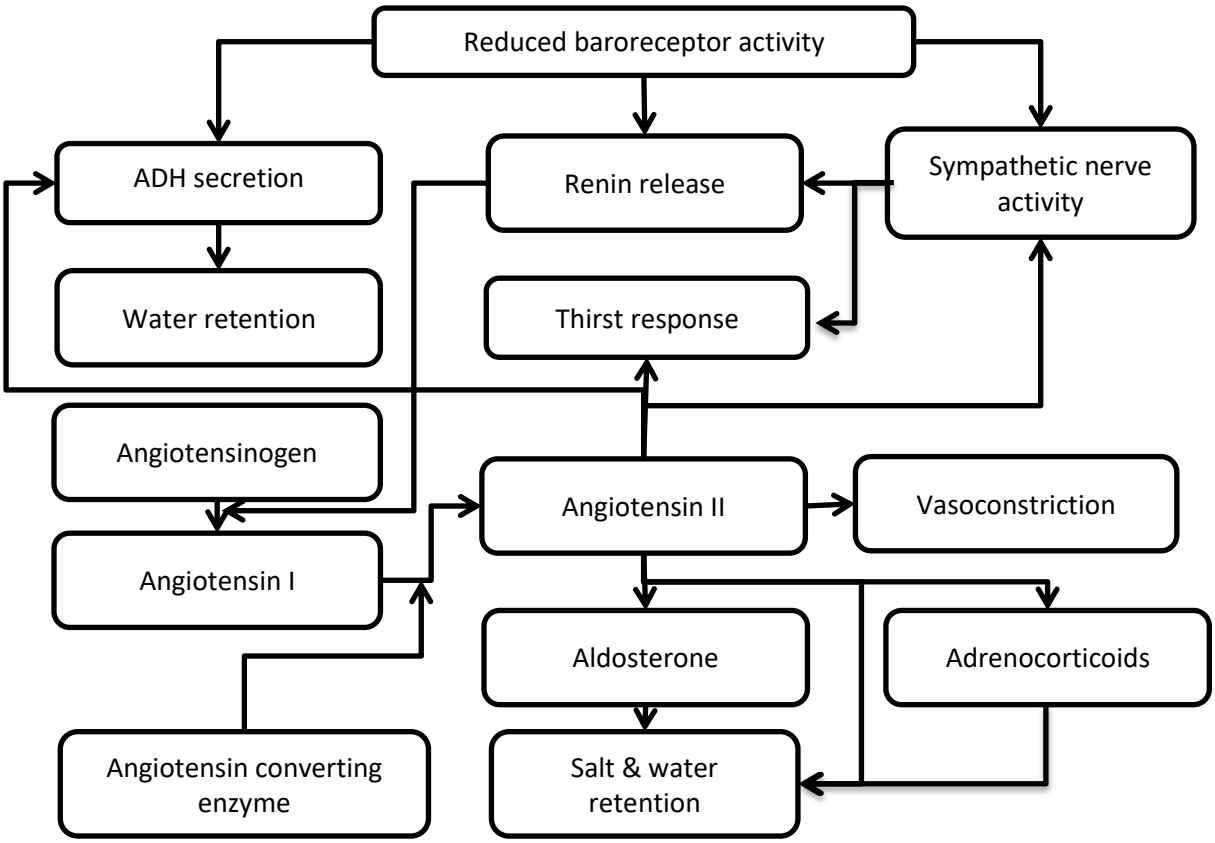


Figure 4: Schematic representation of processes involved in volume regulation in healthy adults. Baroreceptor neural activity decreases when volume depletion is detected. This in turn reduces the inhibitory effects on the sympathetic centres in the brain stem and results in a neurohormonal response mediated by the autonomic and sympathetic nervous system as well as activation of the renin angiotensin aldosterone system. Renin converts angiotensinogen into angiotensin I which is then converted by angiotensin converting enzyme into angiotensin II. Angiotensin II leads to central stimulation of the sympathetic nervous system and arterial vasoconstriction as well as stimulation of the thirst response. Angiotensin II also triggers adrenocorticotrophic hormone release from the anterior pituitary and therefore stimulating the release of mineralocorticoids. Furthermore, it acts on the adrenal cortex to stimulate the production and release of aldosterone which acts to increase sodium reabsorption. Antidiuretic hormone (ADH) secretion from the posterior pituitary is also stimulated by angiotensin II, resulting in water reabsorption.

1.3 The pathophysiology of fluid and electrolyte balance in older adults

The number of adults aged 65 years and over has increased significantly across the developed world; a likely result of advances in medical care. Between 1999 to 2000 and 2009 to 2010, there was a 66% rise in hospital stay across England in the over 75-year age group (HSCIC, 2012). The UK government estimates that the number of people aged 65 years and over will double by the year 2050, with an associated increase in public cost burden (Cracknell, 2010).

Older adults are susceptible to dehydration and electrolyte abnormalities. The causes are multifactorial, ranging from physical disability restricting access to adequate fluid intake to iatrogenic causes including polypharmacy and the unmonitored use of diuretics and other drugs (Allison and Lobo, 2004). Physical disability can limit older adults access to water (Gaspar, 1999), whilst incontinence-associated embarrassment may lead older adults to restrict their oral fluid intake. Furthermore, those from lower socioeconomic backgrounds, living alone, with pre-existing comorbidities, or receiving multiple drugs are more susceptible to dehydration and electrolyte disturbances. They are also at increased risk of associated morbidity and mortality (Foroni *et al.,* 2007). Poor patient education has also been reported to lead to high rates of dehydration-related hospital readmissions after discharge, particularly in surgical patients

(Hari and Rosenzweig, 2012, Khan *et al.,* 2012, Messaris *et al.,* 2012). Dehydration has been shown to be the main reason for readmission following formation of a defunctioning ileostomy, with those on diuretics being at increased risk (Messaris *et al.,* 2012). Higher mortality rates have been noted at one year associated with those readmitted to hospital after surgery for hip fracture, a significant proportion of which were related to dehydration (Khan *et al.,* 2012).

The ageing process is associated with physiological changes in water balance. TBW is reduced by 10-15%, owing to reduced lean body mass, leading to an increased extracellular to intracellular water ratio (Kyle *et al.,* 2001, Baumgartner *et al.,* 1995, Watson *et al.,* 1980, Steele *et al.,* 1950, Cohn *et al.,* 1985, Chumlea *et al.,* 1999). This, coupled with reduced glomerular filtration rate and a reduced ability to concentrate urine, can predispose older adults to dehydration as well as fluid retention and iatrogenic overload (Allison and Lobo, 2004, Lindeman *et al.,* 1985), further increasing their vulnerability during periods of physiological stress associated with illness or the perioperative period.

1.3.1 Renal senescence

Renal senescence reflects irreversible structural and functional changes associated with the ageing kidney (Melk, 2003). Amongst other changes, there is a loss of renal mass due to glomerular sclerosis and glomerular loss (Lindeman *et al.,* 1985, Nyengaard and Bendtsen, 1992, Epstein, 1996). This impairs the ability

to retain sodium, and therefore water, thus predisposing the patient to dysnatraemia and hypovolaemia (Hawkins, 2003). In addition, the ability to secrete potassium and excrete hydrogen is also impaired (Musso *et al.,* 2006, Frassetto and Sebastian, 1996, Berkemeyer *et al.,* 2008). The creatinine clearance in the aged kidney is also reduced. Reduction in the mean creatinine clearance was reported in two-thirds of the population studied in the Baltimore Longitudinal Study of Aging, with an estimated reduction in estimated glomerular filtration rate (eGFR) by 50-63% from the age of 30 to 80 years (Lindeman *et al.,* 1985). Furthermore, reduced tubular function and the medullary concentration gradient are also impaired in an aged kidney, diminishing the ability of the kidney to concentrate urine. Age-related reduction in renal blood flow has also been reported; this contributes to loss of nephrons as a result of ischaemia (Lindeman *et al.,* 1985, Messerli *et al.,* 1983, Hollenberg *et al.,* 1974, Beck, 2000). These changes impair the ability of the kidney to control water and electrolyte balance, predisposing to dehydration and electrolyte abnormalities, particularly in situations of physiological stress.

1.3.2 Hormonal changes and ageing

Hormonal changes that affect fluid and electrolyte homeostasis have been reported in older adults. There is an age-related reduction in the serum concentrations of renin and aldosterone as a result of increased atrial natriuretic peptide (ANP) activity, usually released in response to increased BP and right

atrial filling. This, coupled with age-related reduction in tubular response to aldosterone, predisposes to dehydration and electrolyte abnormalities (Beck, 2000, Kenny *et al.,* 1987). Serum ANP concentrations were shown to be nearly five-times greater in older adults than in the young (Ohashi *et al.,* 1987). ANP inhibits renin secretion from the juxtaglomerular cells, therefore limiting the conversion of angiotensinogen to angiotensin I, and inhibiting the RAAS (Figure 5) (Kurtz *et al.,* 1986). These changes result in a decreased ability to retain sodium in a hypovolaemic state and a reduced ability to excrete potassium (Ling *et al.,* 1990, Musso *et al.,* 2006), making it difficult to adapt to extracellular fluid depletion and sodium loss.

It is also important to consider the role of ADH in older adults, where there is conflicting evidence suggesting increased as well as decreased serum concentrations. The normal diurnal variation results in increased plasma concentrations of ADH at night, but in older adults this is attenuated contributing to the high prevalence of nocturia (Asplund and Aberg, 1991). This, along with reduced renal sensitivity to ADH, limits the ability to respond to extracellular fluid depletion (Beck, 2000, Stachenfeld *et al.,* 1996, Phillips *et al.,* 1984a). Furthermore, decreased plasma ADH concentrations have been reported in patients with Alzheimer's disease, limiting the ability to conserve water (Albert *et al.,* 1989).

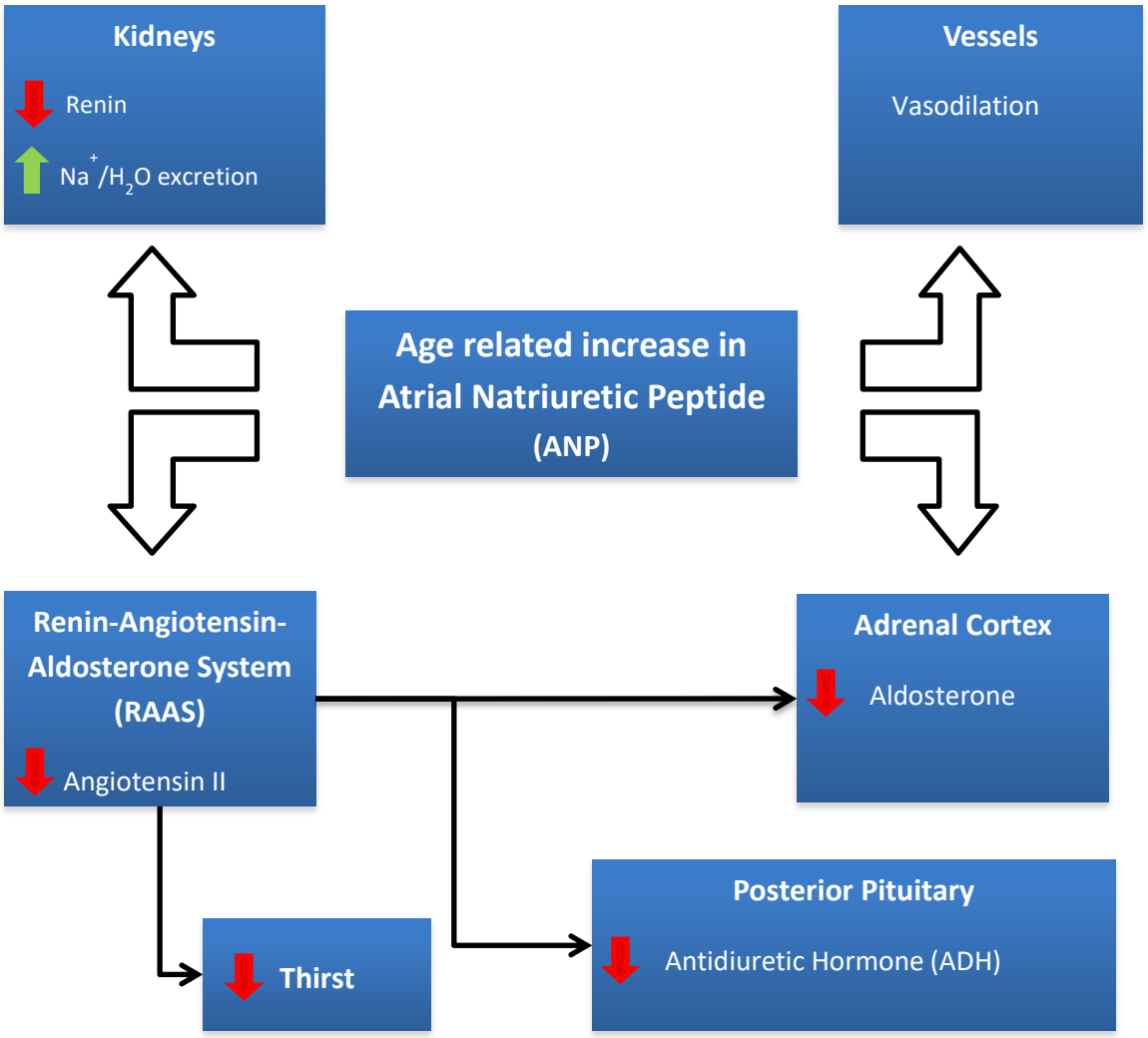


Figure 5: Age-related changes in the hormonal control of fluid and electrolyte homeostasis. There is an age-related reduction in the serum concentrations of renin and aldosterone as a result of increased atrial natriuretic peptide (ANP) activity. ANP inhibits renin secretion from the juxtaglomerular cells, therefore, limiting the conversion of angiotensinogen to angiotensin I, ultimately resulting in reduced angiotensin II, therefore inhibiting the renin angiotensin aldosterone system (RAAS). Consequences of this include; reduced aldosterone, impaired thirst response, reduced antidiuretic hormone. These changes result in a decreased ability to retain sodium and water making it difficult to adapt to extracellular fluid depletion and sodium loss.

1.3.2.1 The thirst response in older adults

The thirst response is blunted in older adults resulting in a persistent hyperosmolar state (McAloon Dyke *et al.,* 1997, Phillips *et al.,* 1991, Phillips *et al.,* 1984a, Silver and Morley, 1992, Stachenfeld *et al.,* 1997, Mack *et al.,* 1994), which is exacerbated by the reduced concentrating ability of the kidney. In a double-blinded crossover study investigating the thirst response in older men, healthy men aged 65-78 and 25-32 years were infused with isotonic, 0.154 M (0.9%) saline or hypertonic, 0.855 M (5% saline) two weeks apart (Phillips *et al.,* 1991). The authors reported less volume expansion in older adult subjects following hypertonic saline than in the younger subjects. Moreover, older adults felt less thirsty and consumed less water than the younger subjects during the hypertonic state, thus demonstrating the increased thirst threshold in older adults (Phillips *et al.,* 1991). Another study showed that older men had a blunted thirst response following 24 hours without fluids compared with younger men (Phillips *et al.,* 1993). The mechanism responsible for this is yet to be defined, but may be a result of blunted osmotic and baroreceptor sensitivity, particularly in the left atrium (Kenney and Chiu, 2001, Stachenfeld *et al.,* 1997) or possibly inhibition of the RAAS as a result of the raised concentrations of ANP (Burrell *et al.,* 1991). It is important to note however, that the amount of fluid consumed on a daily basis is not entirely physiologically driven, but is dependent on consumption that is driven by social factors, habit and other influences, such as the fluid intake with meals (Kenney and Chiu, 2001, Phillips *et al.,* 1984b).

Therefore, the healthy independent older person is generally able to maintain adequate fluid balance through spontaneous consumption of fluids but may become vulnerable to dehydration in a state of physiological stress.

1.3.3 Electrolyte abnormalities in older adults

Electrolyte abnormalities, particularly dysnatraemia, should be considered in the context of water balance. Hypertonic dehydration occurs when proportionally more water than sodium is lost from the ECF compartment. This may occur as a result of age-related thirst impairment and would manifest as serum sodium concentration of greater than 145 mmol/l in the context of dehydration. Hypotonic dehydration on the other hand occurs when the portion of sodium lost is greater than water, resulting in a serum sodium concentration of less than 135 mmol/l, and may occur with the use of diuretics. Isotonic dehydration results from proportionate loss of water and sodium and results in normal serum sodium concentrations. This may occur as a result of diarrhoea, where there is salt and water loss in similar proportions.

1.3.3.1 Dysnatraemia in older adults

Dysnatraemia is the most common electrolyte abnormality in older adults, with age being an independent risk factor (Hawkins, 2003). Clinical manifestations of dysnatraemia vary depending on the severity, with fatigue, seizure and coma being recognised complications. Dysnatraemia, particularly hypernatraemia, is

also linked with increased mortality rates of up to 70% in severe cases (Alshayeb *et al.,* 2011, Snyder *et al.,* 1987), associated with a seven-fold increase in mortality compared with that of age-matched hospitalised patients (Snyder *et al.,* 1987).

Hyponatraemia, on the other hand, is more common in older adults than hypernatraemia and is an independent risk factor for bone fractures (Gankam Kengne *et al.,* 2008, Zilberberg *et al.,* 2008, Kinsella *et al.,* 2010). This may be a result of reduced bone mineral density and increased risk of osteoporosis (Barsony *et al.,* 2009). Moreover, hyponatraemia is associated with a 2.1-fold increase in mortality in mild cases and 4.6-fold increase in severe cases in patients admitted for orthopaedic surgery (Waikar *et al.,* 2009, Zilberberg *et al.,* 2008).

It is important to note that a significant proportion of dysnatraemia in older adults occurs as a result of concurrent disease such as the syndrome of inappropriate ADH secretion (SIADH) and hyperglycaemia (Anderson *et al.,* 1985). Older adults require longer to excrete salt loads due to the age-related reduction in eGFR and they are more likely to become overloaded when challenged with a sodium load. The kidney is also unable to cope with the excess chloride load even in physiologically normal subjects (Chowdhury *et al.,* 2012). Therefore, diuretic use as well as excessive administration of intravenous hypotonic fluids can result in hyponatraemia.

1.3.3.2 Hyperkalaemia in older adults

Age-related renal changes make older adults vulnerable to other electrolyte abnormalities, in particular hyperkalaemia, resulting from impaired ability to secrete potassium and excrete acid, a consequence of age-related decline in distal renal tubular function (Musso *et al.,* 2006, Frassetto and Sebastian, 1996, Berkemeyer *et al.,* 2008, Biswas and Mulkerrin, 1997). Reduced aldosterone response to a potassium infusion was also demonstrated in healthy older adult volunteers when compared with younger controls (Mulkerrin *et al.,* 1995). Furthermore, the age-related blunting of the renin-aldosterone response to an acute rise in serum potassium further increases the susceptibility to hyperkalaemia (Clark *et al.,* 1992). Other mechanisms have also been suggested to contribute to hyperkalaemia. Transtubular potassium concentration gradient, an index of potassium secretory activity in the distal tubule, was shown to be lower in healthy older adult subjects than in the young (Musso *et al.,* 2006).

1.3.4 The impact of prescribing on fluid and electrolyte regulation in older adults

The predisposition of older adults to electrolyte abnormalities is further increased by the underlying co-morbidities that often coexist and can often be precipitated by polypharmacy. Some drugs also interfere with thermoregulation and predispose to dehydration, (Table 1) (Cuddy, 2004). Widespread

unmonitored use of medications such as angiotensin-converting enzyme inhibitors (ACE-I), diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) are significant risk factors for dehydration and electrolyte abnormalities. ACE-I prevent the conversion of angiotensin I to angiotensin II, thereby reduce aldosterone secretion. NSAIDs inhibit prostaglandin synthesis, associated with reduced renin and aldosterone, thus predisposing to hyperkalaemia (Biswas and Mulkerrin, 1997, Nadler *et al.,* 1986).

Table 1: Commonly prescribed drugs that affect thermoregulation.

• Levothyroxine • Selective serotonin reuptake inhibitors • Atypical antipsychotics e.g. olanzapine • Tricyclic antidepressants • Carbamazepine • Anticholinergics • Antihistamines

1.3.5 Hydration and cellular function

The maintenance of adequate cell hydration is essential to cell function and survival because it has profound effects on cell volume. Loss or gain of even a small percentage of cellular water interferes with key metabolic processes and affects the integrity of the cellular architecture as well as membrane integrity mediated by changes in cell volume (Baskett, 1990, Raj, 2006, Razminia *et al.,* 2004). Cell swelling is a necessity for stimulation of key cellular functions such as

proliferation (Convertino *et al.,* 2006), whilst cell shrinkage is key to apoptotic cell death (Jacob *et al.,* 1997).

Cell swelling stimulates protein and glycogen synthesis, and cell shrinkage stimulates proteolysis and glycogen breakdown, with both pathways leading to the production of osmotically more active substances (Haussinger *et al.,* 1993). There is also evidence supporting the effects of cell volume on gene and protein expression, such as the heat shock protein expression and ADH stimulated by cell shrinkage (Baskett, 1990). Maintenance of fluid and electrolyte balance is, therefore, essential to healthy living, no more so than in periods of ill-health. Dehydration, overhydration and salt and water overload have been associated with morbidity and mortality, with older adults at increased risk (Warren *et al.,* 1994, Wilkinson K, 2010, El-Sharkawy *et al.,* 2014).

1.3.6 Acute and chronic effects of hydration status on health

There is a growing body of evidence supporting the link between the state of fluid imbalance and disease including urological, gastrointestinal, circulatory and neurological disorders. However, the evidence is largely associative and lacks consistency with limited number of randomised trials.

1.3.6.1 Dehydration

A state of dehydration occurs with excess loss of total body water and is often associated with electrolyte abnormalities, particularly dysnatremias. Hypertonic dehydration occurs when proportionally more water than sodium is lost from the extracellular fluid compartment. This may occur as a result of age-related thirst impairment, which is seen in older adults. Hypotonic dehydration, on the other hand, occurs when the proportion of sodium lost is greater than the proportion of water lost. This may occur with the use of diuretics or in patients with burns. Isotonic dehydration results from proportionate loss of water and sodium, and results in normal serum sodium concentrations. This may occur as a result of diarrhea, where there is salt and water loss in equivalent proportions. Common causes of isotonic, hypotonic, and hypertonic dehydration are listed in Table 2. The evidence linking dehydration and health disorders are summarised in Table 3a, 3b and 3c.

Table 2: Summary of the conditions linked with hypotonic, isotonic and hypertonic dehydration and associated level of evidence.

Dehydration		
Isotonic	**Hypotonic**	**Hypertonic**
Burns	Vomiting*	Inadequate water intake
Vomiting*	Diarrhoea*	Sweating
Diarrhoea*	Enterocutaneous fistula*	Diabetes insipidus
Ascites	Adrenocortical deficiency	Polyuric phase post-acute tubular necrosis
	Renal failure	Osmotic diuretics
	Cerebral salt wasting	Mannitol*
	Hyperglycaemia	Loop diuretics
	Osmotic diuretics	Enterocutaneous fistula*
	Mannitol*	Osmotic laxatives

* *Depending on electrolytes lost.*

Table 3a: Summary of the evidence linking dehydration to health disorders.

Conditions	Summary of findings	Level of evidence
Urological		
Urinary tract infections (UTI)	Inconsistent findings, however, evidence largely favours the positive effects of 'adequate' fluid intake on UTIs.	IIb
Urolithiasis	Evidence largely from epidemiological studies and RCTs reporting beneficial effects of increased fluid consumption in preventing urolithiasis recurrence.	Ib
Acute kidney injury	Limited evidence, one observational study. However, many experts believe severe dehydration can cause acute kidney injury.	IV
Chronic kidney disease	One population based cross-sectional study showing reduced risk of developing chronic kidney diseases associated with increased fluid consumption.	IV
Bladder cancer	Conflicting evidence on the link between chronic dehydration and bladder cancer.	III
Gastrointestinal		
Functional constipation	Some evidence linking dehydration as a cause of functional constipation. The strongest evidence favours increased fluid consumption to treat constipation during a state of dehydration and as an adjunct to high fibre diet.	III
Colorectal cancer	Evidence largely from retrospective case control studies showing an inverse relationship between increased water consumption and colorectal cancer. The beneficial effects are greater for distal tumours.	III

Level of evidence (based on the Oxford Centre for Evidence Based Medicine Level of evidence guide (Phillips et al., 2009) - Ia – systematic reviews (SR) of RCTs with homogeneity. Ib- Individual RCT with narrow confidence interval and >80% follow up. IIa- systematic reviews of cohort studies with homogeneity. IIb- low quality RCTs and large cohort studies. III- SR of case control studies with homogeneity or individual case control studies. IV- case series and poor cohort and case control studies. V- Expert opinion.

Table 3b: Summary of the evidence linking dehydration to health disorders.

Conditions	Summary of findings	Level of evidence
Circulatory		
Deep vein thrombosis (DVT)	Limited number of studies. Serum hyperosmolality associated with increased risk of DVT in hospitalised patients with stroke.	III
Cerebral infarct	Limited evidence directly linking dehydration as a cause of cerebral infarct. However, some evidence linking serum hyperosmolality to poor outcome following stroke.	III
Coronary heart disease (CHD)	Strongest evidence from a large prospective cohort study which reported that increased water consumption was inversely associated with reduced risk of fatal CHD events.	IIb
Orthostatic hypotension	Good evidence linking dehydration and orthostatic hypotension particular in severe cases that result in significant hypovolaemia.	IIb
Mitral valve prolapse (MVP)	Limited evidence showing that acute mild dehydration induced MVP in healthy subjects and resolved with rehydration.	III
Neurological		
Delirium	Evidence linking dehydration to cognitive impairment is inconsistent. An inverse relationship has been reported between increased water consumption and delirium in long term care residence.	III
Headache	No direct link between dehydration as a cause of headache. Evidence supports increased water consumption helps limit the intensity of migraine.	IIb

Level of evidence (based on the Oxford Centre for Evidence Based Medicine Level of evidence guide (Phillips et al., 2009) - Ia – systematic reviews (SR) of RCTs with homogeneity. Ib- Individual RCT with narrow confidence interval and >80% follow up. IIa- systematic reviews of cohort studies with homogeneity. IIb- low quality RCTs and large cohort studies. III- SR of case control studies with homogeneity or individual case control studies. IV- case series and poor cohort and case control studies. V- Expert opinion.

Table 3c: Summary of the evidence linking dehydration to health disorders.

Conditions	Summary of findings	Level of evidence
Metabolic		
Diabetes mellitus	Evidence from a cohort study suggests an inverse relationship between increased water consumption and type II diabetes. Strongest evidence supports the link between dehydration and poor outcome with diabetic ketoacidosis.	III
Obesity	Inconsistent evidence linking increased water consumption in relation to meals to treat obesity. Some evidence supports the effects of cold water consumption on increased basal metabolic rate.	III
Pregnancy and labour		
Oligohydramnios	Good evidence from multiple RCTs and systematic reviews concluding that dehydration results in a reduced amniotic fluid index which increases with rehydration.	Ib
Labour	Good evidence from multiple RCTs and systematic reviews concluding that 250ml/hr of intravenous fluid results in reduced frequency of prolonged labour in fasted women. However, when patients eat and drink liberally no clear differences were observed.	IIb
Other conditions		
Respiratory disorders	Dehydration in the airways may result in bronchoconstriction and inspiration of humidified air is beneficial in obstructive airway disease. However, no link between total body fluid balance and bronchoconstriction.	III
Dental disorders, hypertension, gallstones and breast cancer	Limited evidence concluding that dehydration may be associated with: dental disorders, hypertension, gallstones and breast cancer	IV

Level of evidence (based on the Oxford Centre for Evidence Based Medicine Level of evidence guide (Phillips et al., 2009) - Ia – systematic reviews (SR) of RCTs with homogeneity. Ib- Individual RCT with narrow confidence interval and >80% follow up. IIa- systematic reviews of cohort studies with homogeneity. IIb- low quality RCTs and large cohort studies. III- SR of case control studies with homogeneity or individual case control studies. IV- case series and poor cohort and case control studies. V- Expert opinion.

1.4 Dehydration and kidney function

Adequate kidney function and filtration are maintained through tightly controlled homeostatic mechanisms. Dehydration when severe can result in hypovolaemia and therefore, hypoperfusion, which can result in renal cell injury and death. This results in decreased urine output and the accumulation of urea and creatinine, the syndrome of AKI. Many definitions and classifications of AKI exist, the most popular of which were the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) and Acute Kidney Injury Network (AKIN) classifications (Table 4) (Lopes, 2013). More recently the Kidney Disease Improving Global Outcomes (KDIGO) guidelines have been adopted as the international standard by which AKI is defined and managed (Khawaja, 2012).

Table 4: Acute kidney injury (AKI) stage and severity definitions according to Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) classifications.

	Stage/Severity	Serum creatinine criteria	Urine output
RIFLE classification	Risk	Increase in SCr by 1.5-fold or decrease in GFR >25%	<0.5 ml/kg/hour for 6 hours
	Injury	Increase in SCr by 2-fold or decrease in GFR >50%	<0.5 ml/kg/hour for 12 hours
	Failure	Increase in SCr by 3-fold or decrease in GFR >75% or if baseline SCr ≥353.6 µmol/l, increase >44.2 µmol/l	<0.3 ml/kg/hour for 24 h or anuria for 12 hours
	Loss of kidney function	Complete loss of kidney function for >4 weeks	-
	End-stage kidney disease	End stage kidney disease for >3 months	-
AKIN classification	1	Increase in SCr ≥26.4 µmol/l or Increase in SCr ≥150% to 200% (1.5- to 2-fold)	<0.5 ml/kg/hour for > 6 hours
	2	Increase in SCr >200% to 300% (>2- to 3-fold)	<0.5 ml/kg/hour for >12 hours
	3*	Increase in SCr >300% (>3-fold) or if baseline SCr ≥353.6 µmol/l, increase ≥44.2 µmol/l	<0.3 ml/kg/hour for ≥24 hours or anuria for ≥12 hours
KDIGO classification	1	Increase in SCr ≥26.5 µmol/l or Increase in SCr by 1.5 to 1.9-fold	<0.5 ml/kg/hour for > 6 hours
	2	Increase in SCr 2- to 2.9-fold	<0.5 ml/kg/hour for >12 hours
	3	Increase in SCr 3-fold or increase in SCr to ≥353.6 µmol/l or initiation of renal replacement therapy	<0.3 ml/kg/hour for ≥24 hours or anuria for ≥12 hours

*GFR, glomerular filtration rate; SCr, serum creatinine. *Stage 3 also includes patients that are requiring renal replacement therapy, independent of the stage of kidney injury. AKIN and guidelines require abrupt change within 48 hours and should be considered after adequate resuscitation and excluding easily reversible causes of reduced urine output, such as obstruction (AKIN). Whilst RIFLE guidelines require changes in serum creatinine from baseline over 1 to 7 days (Bellomo, 2004). KIDGO guidelines require increase in SCr ≥26.5 µmol/l within 48 hours of baseline or by 1.5-fold within 7 days of baseline (KDIGO, 2012)*

Whilst most agree that severe dehydration that results in hypovolaemia is a significant risk factor for AKI, there is disagreement as to the effect of less severe dehydration on kidney function. However, there is evidence linking mild dehydration to kidney impairment. Dehydration resulting in increased serum osmolality by as little as 1% stimulates the release of ADH, increasing water reabsorption in the kidney. ADH also results in peripheral vasoconstriction and renal blood flow redistribution which may lead to progression of existing chronic kidney disease (CKD), a progressive condition that leads to fibrosis and scarring of the kidney (Bolignano *et al*., 2010). It is also proposed that maintaining a state of euhydration reduces plasma ADH and therefore protects against renal damage.

Studies looking into the role of increased fluid intake and CKD are inconsistent. Some researchers have also reported a protective role of increased urine output on the rate of decline in estimated glomerular filtration rate (Clark *et al*., 2011). Strippoli *et al*., 2011 also demonstrated an inverse relationship between water intake and the risk of developing CKD, with those consuming 3.2 l of fluid a day being at lower risk than those who consumed 1.8 l/day (odds ratio [OR], 0.5; 95% confidence interval [CI], 0.32–0.77). However, other researchers have reported increased renal function loss with increased urine volume production in individuals with established CKD (Herber *et al*., 2003, Torres *et al*., 2009).

In the case of AKI, there are no studies that have investigated the effects of dehydration that is not associated with hypovolaemia, on kidney function in the acute phase.

1.5 Dehydration and cognitive function

Studies investigating the effects of hydration on mood have reported adverse effects associated with dehydration. Mild dehydration of as little as 1.4% of body weight can result in degraded mood, increased perception of task difficulty, and reduced ability to concentrate (Armstrong *et al.,* 2012, Wilson and Morley, 2003, Shirreffs *et al.,* 2004). Increased subjective feelings of fatigue, headache, tension, anxiety and deterioration in cognitive performance, including short-term memory impairment, have also been associated with modest restriction of fluid intake (Cian *et al.,* 2000, Shirreffs *et al.,* 2004). Dehydration may also result in increased errors of visual vigilance as well as reduced latency of visual working memory response (Ganio *et al.,* 2011). Dehydration when severe can lead to hypovolaemia and in extreme cases, cerebral hypo-perfusion. Parallels can be drawn with the clinical features associated with haemorrhagic hypovolemic shock, where intravascular volume loss of 800 to 1500 ml can result in anxiety or aggression, and >2000 ml intravascular volume loss can result in confusion and loss of consciousness (Baskett, 1990). However, dehydration of this severity and magnitude is uncommon and the link between more mild dehydration and cognitive impairment is far from conclusive (Beecher and Simeone, 1947).

Hyperosmolality associated with dehydration has also been shown to result in morphological changes within the brain as a result of water movement out of cells down an osmotic gradient (Clark *et al.,* 2012, Lane *et al.,* 2002). Studies have reported increased ventricular volume, inversely proportional to changes in body weight associated with acute dehydration (Kempton *et al.,* 2009, Dickson *et al.,* 2005), which were reversible with rehydration (Laederach-Hofmann *et al.,* 1999). These changes did not impact on cognition using the Tower of London task, although, functional brain changes were demonstrated in subjects dehydrated by 2% of body weight (Kempton *et al.,* 2009). These changes were comparable to morphological brain changes reported in patients with early Alzheimer's disease associated with mild cognitive impairment (Hocking *et al.,* 2001).

Several studies have investigated the effect of rehydration on cognitive function, demonstrating improvement in subjective alertness following rehydration of dehydrated subjects (Neave *et al.,* 2001), with the degree of improvement related to the severity of the thirst perception (Rogers *et al.,* 2001). Studies in children have also supported these findings, showing significant differences in cognitive performance in well-hydrated children that drink supplementary water, in particular short-term memory and visual attention showed significant improvements (Edmonds and Burford, 2009).

In older adults, cognitive impairment is a risk factor for dehydration (Mentes, 2006, El-Sharkawy *et al.,* 2014, El-Sharkawy *et al.,* 2015a). People with dementia

can forget to drink which may lead to dehydration and further cognitive decline. However, there are few clinical studies that investigate the impact of dehydration in this group despite the potential for increased risk. Dehydration has been reported to cause delirium, a state of acute confusion (Seymour *et al.,* 1980, Voyer *et al.,* 2009) which is reversed by water consumption in long-term care residents (Voyer *et al.,* 2009). However, this association between dehydration and delirium reversibility was not shown in cancer patients (Lawlor *et al.,* 2000). In keeping with some of the evidence, national guidelines recommend adequate hydration in patients with delirium.

1.6 Diagnosing dehydration

Clinical detection of electrolyte abnormalities and dehydration is challenging, particularly in older adults, partly due to difficulties in recognising the clinical signs and symptoms of dehydration. This, coupled with limited knowledge by frontline staff and the difficulty in monitoring and managing fluid balance are also contributing factors (Woodrow, 2002), which can result in morbidity and even mortality.

1.6.1 Clinical and bedside tools

Clinical skills, the ability to elicit clinically relevant information from talking to and examining patients is arguably one of the most important and valued bedside tools available. These tools have been utilised for centuries as an effective way to

diagnose and monitor patients and disease. However, inter-observer variations are inevitable as many clinical signs are poorly defined and a number of variations exist in the methods of assessment and quantification. In addition, inadequate techniques and clinician bias, where a clinician may interpret the presence of a sign to fit clinical suspicion based on expectation rather than fact, are not uncommon.

1.6.1.1 Clinical history

The clinical history is of particular relevance when considering acute changes in fluid status, allowing the clinician to stratify some of the risk factors that may affect fluid status, for example, a patient prescribed diuretics is at increased risk of dehydration if they develop diarrhoea and vomiting.

The accuracy of the medical history however, can be limited by various factors including patient understanding of the question as well as clinician interpretation of the answer. Some patients are not always aware of their medical history or medication intake whilst others may not be able to understand or communicate answers to key questions. Furthermore, the medical history even if comprehensive and accurate does not easily allow the quantification of the fluid status beyond the state of dehydration or fluid overload. Other limitations include lack of specificity for example, the sensation of thirst may be a feature of dehydration, however, the ageing process is associated with a blunted thirst

response and hence thirst may be a late feature of dehydration in older adults (Phillips *et al.,* 1984a, Phillips *et al.,* 1984b).

1.6.1.2 Clinical examination

Clinical examination complements the clinical history and provides non-invasive, reproducible and sometimes quantifiable parameters that can allow effective assessment as well as monitoring of hydration status and fluid balance. Moreover, it provides the tools which can be used to assess the impact of fluid status on various organs. However, changes in fluid balance that result in clinically detectable signs often suggest significant changes in volume status.

1.6.1.2.1 Pulse rate

Increased pulse rate (PR), tachycardia [PR >100 beats per minute (bpm)] can occur as a result of hypovolaemia. In isolation tachycardia is a non-specific measurement that can occur physiologically such as with exercise. However, in the context of volume loss/dehydration tachycardia may indicate hypovolaemia, equivalent to 15% blood loss (Baskett, 1990). Postural tachycardia, an increase in PR from supine to a standing state may be an earlier manifestation of hypovolaemia (Raj, 2006). In healthy individuals, there is a physiological response that results in increased cardiac output, heart rate and vascular resistance that compensates for a shift of up to 600 ml of blood to the lower limbs on standing (Smit *et al.,* 1999). These compensatory mechanisms maintain the systolic BP; although, an increase in PR by >30 bpm is thought to be pathological (Raj, 2006).

However, postural tachycardia may be a manifestation of autonomic dysregulation, common in the older adult population as well as those with diabetes, and may give a false change in PR despite normal volume status (Laederach-Hofmann *et al.,* 1999).

Using PR to assess and monitor hydration status is limited because most of the current evidence is derived from studies investigating acute haemorrhage. Therefore, it may not accurately translate to dehydration-induced volume loss. Moreover, it is a late feature of dehydration as significant volume loss is required before a change is detected. Furthermore, it may be blunted or inhibited by drugs such as beta blockers. It is important to note that tachycardia is not specific to hypovolaemia as it often occurs as a result of physiological stress, a manifestation of many disease processes. Cardiogenic shock following fluid overload can also cause tachycardia and hypotension. If this is treated as hypovolaemic shock, it may be detrimental and in severe cases can be fatal.

1.6.1.2.2 Blood pressure

As with PR, BP measurements also form part of clinical guidelines that are used to diagnose, quantify and monitor hypovolaemia. However, this clinical measurement needs to be considered in the clinical context (Baskett, 1990).

BP can be used to calculate the pulse pressure, a measure of the pressure difference between the systolic and diastolic pressure (Convertino *et al.,* 2006), a more sensitive marker of hypovolaemia than systolic or diastolic BP alone. The

mean arterial pressure (MAP), considered to be a measure of the organ perfusion pressure, can also be estimated from systolic and diastolic pressure measures $\frac{2\times(diastolic + systolic\ pressure)}{3}$ (Razminia *et al.,* 2004). However, a 15% drop in circulatory volume is required before any clinically meaningful differences are detected (Baskett, 1990).

Orthostatic hypotension (OH) is a measure of supine and standing BP, and is arguably the most sensitive BP measure of changes in volume status. However, orthostatic changes in BP occur with autonomic dysfunction, and it is not always possible to measure OH as some patients are not able to stand. Significant drops in systolic BP have also been reported in healthy young volunteers (McGee *et al.,* 1999).

Limitations affecting the accuracy of BP to assess hydration status are similar to those reported with PR. In addition, the accuracy of BP readings may be affected by diseased arteries and is also operator dependent (Lane *et al.,* 2002, Clark *et al.,* 2012). Measurements done by different people using opposite arms may report significant discrepancies in readings, reported to be up to 10 mmHg between both arms in normal healthy subjects (Lane *et al.,* 2002). Furthermore, commonly used ambulatory BP monitors report inaccurate BP readings in the context of pulse abnormalities such as atrial fibrillation (Stergiou *et al.,* 2013, Stergiou *et al.,* 2012, Cheng *et al.,* 2013).

1.6.1.2.3 Capillary refill time

Capillary refill time (CRT) is a measure of the time taken for the colour of the skin to return to normal after pressure is applied for five seconds to cause blanching. This is often performed on the patient's finger (peripheral CRT) or chest (central CRT) at heart level and at room temperature. CRT depends on the assumption that perfusion in the distal capillary bed will be impaired with hypovolaemia and therefore result in prolonged CRT (Anderson *et al.,* 2008). Although initially CRT was classified as normal, slowing and very sluggish (Beecher and Simeone, 1947), modern interpretations of this clinical examination tool advise that two seconds is the upper limit of normal for CRT. There is some evidence supporting the accuracy of CRT to assess for hypovolaemia (Saavedra *et al.,* 1991), however, the clinical evidence supporting this cut off for CRT is debated in the literature. Furthermore, CRT is affected by many environmental and patient factors including; low room temperature and lighting (Gorelick *et al.,* 1993) and increased age results in increased CRT with wide variations reported including an increase of 3.3% in CRT per decade (Frank, 2006, Schriger and Baraff, 1988, Anderson *et al.,* 2008). However, in recent years the development of electronic probes to digitally measure CRT using photoplethysmographic (PPG) sensors have demonstrated promising results, although such devices are not yet fully clinically integrated (Shavit *et al.,* 2006, Lima and Bakker, 2005).

1.6.1.3 Changes in body mass

Acute changes in body mass over a short period of time are thought to represent changes in fluid balance given that one millilitre of water equates to one gram in weight, and that acute changes in TBM usually represent changes in fluid status as no other body constituent is lost at such a rate. Serial body mass measurements can be an easy, safe and clinically effective way of measuring changes in fluid balance and as such is often used as a gold standard in many studies investigating hydration. A randomised double-blinded trial investigated two different commonly used intravenous fluids in healthy male volunteers (Chowdhury *et al.,* 2012). Weight measurements and serum biochemistry were measured at regular intervals over a period of four hours after they were infused with 1.5 l of the fluids over one hour period. The authors reported a clear increase in weight by approximately 1.5 kg just after the infusion with an associated increase in blood volume and extracellular fluid (Chowdhury *et al.,* 2012). Furthermore, they demonstrated a reduction in weight over the observation period which corresponded with reduction in blood volume and extracellular fluid (Chowdhury *et al.,* 2012).

However, the use of changes in body mass to assess and monitor hydration status are limited by the fact that it only measures overall balance and not inter-compartmental shifts and large volumes of ECF may be pooled in the gut and therefore be functionally inert. Moreover, when measuring changes in body mass over days one must account for the daily fluctuations of approximately 0.5 kg

(Cheuvront *et al.,* 2004). Nonetheless, when assessing the clinical effectiveness of a treatment for fluid overload, a general trend showing reduction in weight that correlates with improving symptoms is sufficient. Serial measures of body weight and changes in body mass requires identical conditions each time a patient is weighed and may be affected by the clothes a patient is wearing, time in relation to meals as well as bowel and bladder functions. Therefore, it can be difficult to accurately measure in a busy and stressful clinical environment. Other factors that impact on the feasibility and accuracy of using changes in body mass to assess fluid balance include lack of infrastructure and tools to weigh immobile and critically ill patients.

1.6.1.3.1 Other clinical manifestations of hydration status

Dry mucous membranes, sunken eyes, and reduced skin turgor are widely reported in association with dehydration (McGee *et al.,* 1999). Skin turgor is often used as a useful clinical aid to help diagnose dehydration. It involves grasping the skin for approximately three seconds, usually on the back of the hand or forearm and assessing the elasticity of the skin by measuring how quickly it returns to normal (Chassagne *et al.,* 2006). However, this has proven to be an inaccurate measure particularly in the elderly due to age-related changes in skin structure such as loss of elastin (Shuster *et al.,* 1975). Similarly, other age-related changes such as loss of fat (Larrabee Jr and Caro, 1984) and mouth breathing make sunken eyes and dry mucous membranes an unreliable measure of hydration in the elderly.

Axillary sweat measurements have also been used to assess hydration status with varying success in clinical studies. Dry axilla was reported to be 50% sensitive and 82% specific with a diagnostic likelihood ratio of 2.8 at diagnosing dehydration (Eaton *et al.,* 1994). However, this is a very difficult measure to do accurately in routine clinical practice.

Passive leg raise is another method that can be used to assess for volume depletion. This method involves raising the legs of a supine patient to 45° with some evidence to suggest that starting the procedure from a semi-recumbent position before laying the patient supine, then raising the legs is more sensitive at detecting hypovolaemia. This increases the volume of blood return to the heart, effectively resulting in transient increase in the preload whilst the legs are elevated and has been reported to be equivalent to 300 ml intravenous fluid challenge with colloids (Rutlen *et al.,* 1981, Wong *et al.,* 1988, Boulain *et al.,* 2002). Cardiac output or stroke volume is measured usually using an oesophageal Doppler probe just before and then just after the manoeuvre with an increase in more than 10-15% thought to be significant (De Backer, 2006). A hypovolaemic patient would be positioned on the steep part of Starling's curve and the passive leg raise would result in increased preload which results in increased cardiac output as has been described by Frank Starling. However, in a euvolemic patient or indeed one that is fluid overloaded the patient would be positioned on the flat part of Starling's curve and therefore further increase in preload is not associated with an increase in cardiac output. Knowing this is of clinical importance in order

to avoid administering fluids to patients who are already overloaded, particularly those with pre-existing cardiac or respiratory impairment. However, this test is not readily available as it requires access to expensive devices to measure cardiac output. Furthermore, it is contraindicated in patients with head injury as it may raise the intracranial pressure and can also be difficult to perform in the perioperative period. Other similar methods that monitor changes in stroke volume with respiration operate using the same underlying principle. However, they cannot be used in patients who are spontaneously breathing (not mechanically ventilated) and those with arrhythmias (Monnet and Teboul, 2008, Monnet *et al.,* 2005).

1.6.2 Urine measures of hydration

1.6.2.1 Urine output

Urine output is considered by many to be one of the most accurate measures of fluid balance particularly over a 24-hour period, dependent on normal renal function. Low urine output can be an early sign of dehydration, however, in severe cases may result in oliguria (hourly urine output <0.5 ml/kg/hr), a recognised feature of AKI (Bellomo *et al.,* 2012, Cuhaci, 2009). The most common cause of oliguria is renal hypo-perfusion that results from a pre-renal pathology as a consequence of hypovolaemia (Cerda, 2011). However, urine output does not always reflect hydration status as physiological oliguria may occur in the immediate postoperative stage in normovolaemic patients and polyuria may

occur post AKI (Short and Cumming, 1999). The sensitivity and specificity or urine output may be affected by diuretic use. Moreover, the absorption of water following the rapid ingestion of large volumes stimulates the production of large quantities of dilute urine even before equilibrium between the intra and extracellular compartments has occurred (Maresh, 1998). This occurs as a result of protective mechanisms against fluid overload, even in a state of dehydration. This mechanism means that urine volume and other urine markers of hydration might not always be representative of the hydration status (Maresh, 1998, Kovacs *et al.,* 1999, Popowski *et al.,* 2001). Furthermore, the accuracy and reproducibility of urine output as a measure of hydration status is challenging in the clinical setting due to difficulties collecting and measuring urine output in patients who are not catheterised and those that suffer from incontinence or cognitive impairment. In addition, inherent errors in recording and calculating urine output in a busy clinical environment are not uncommon.

Other urinary parameters such as urine colour have been used with varying degrees of accuracy, where light coloured urine indicates a hydrated state and dark coloured urine represents a dehydrated state, owing to the differences in water excreted relative to solutes (Kovacs *et al.,* 1999, Armstrong *et al.,* 1994). However, urine colour may be influenced by the volume of fluid consumed rather than the state of hydration. Additionally, some drugs such as rifampicin cause urine discolouration (orange-coloured urine) and may falsely suggest dehydration.

1.6.2.2 Urinary osmolality

Urine osmolality reflects the solute to water concentration in the urine and is measured using a freezing point depression. Osmometers measure the amount of osmoles of solute particles per kilogram of solution, where a solution with more solute has a lower freezing point than a less concentrated solution (Sweeney and Beuchat, 1993). Dehydration results in water reabsorption from the collecting tubules through aquaporin channels and hence, increased urine osmolality. However, urine osmolality is dependent on normal kidney function and is affected by factors that influence renal solute excretion or water reabsorption, such as in the case of SIADH which results in increased aquaporin channels and water reabsorption thus resulting in concentrated urine. Conversely, low urine osmolality may result as a consequence of low urinary sodium excretion due to renal hypo-perfusion and activation of the RAAS, serum hyponatraemia or injury (Goh, 2004).

It is also important to consider that urine osmolality often represents the osmolality of all urine stored in the bladder between the last void and when the sample was taken and thus may not be an accurate measure of the hydration status at the time of measurement. Urine osmolality may also be influenced by large variations in dietary salt and water consumption (Armstrong *et al*., 2007, Manz *et al*., 2003)

1.6.2.3 Urinary specific gravity

Urine specific gravity (SG) is a measure of urine density relative to pure water and increases urine solute concentration, similar to urine osmolality. Urine SG can be easily measured at the bedside using a hand held refractometer or urine dipstick testing, although studies have reported varying degrees of correlation with urine osmolality (Voinescu *et al.,* 2002). The accuracy of urine SG is affected by factors that affect urine osmolality, but also depends on the method used to measure it. Measurements with a refractometer have proven to be more accurate than dipstick testing which can be more subjective (Kovacs *et al.,* 1999, Stuempfle and Drury, 2003).

1.6.3 Serum biomarkers

Serum biomarkers and in particular osmolality are considered amongst the most reliable methods of assessing hydration status (Cheuvront and Sawka, 2005, Sawka *et al.,* 2005, Bhalla *et al.,* 2000, Sollanek *et al.,* 2011, Cheuvront *et al.,* 2013, Cheuvront *et al.,* 2010, Stookey *et al.,* 2005). Furthermore, they also provide a reliable measure of changes in kidney function which can occur in the context of severe dehydration that results in hypovolaemia and renal hypoperfusion. However, it is important to note that there are many other causes of AKI (Table 5).

Table 5: Common causes of acute kidney injury

Prerenal causes (Hypoperfusion)

- Volume loss e.g. dehydration, haemorrhage
- Drugs e.g. diuretics, angiotensin-converting enzyme inhibitors
- Circulatory failure e.g. shock, cardiac arrhythmia, arterial stenosis/occlusion
- Sepsis

Intrinsic causes (tissue injury)

- Infection
- Drugs e.g. non-steroidal anti-inflammatory drugs
- Autoimmune disease e.g. vasculitis
- Ischaemia e.g. acute tubular necrosis post hypoperfusion
- Prolonged prerenal cause

Post renal (obstruction)

- Renal tract calculus
- Malignancy e.g. renal tract, pelvic (extrinsic compression)
- Fibrosis e.g. post radiotherapy
- Stricture e.g. urethral stricture post infection or surgery

Currently, many clinicians rely on changes in serum urea and creatinine independently and in combination (urea:creatinine ratio) to aid the assessment of hydration status and fluid balance. However, changes in creatinine and urea are not sensitive to small changes in hydration status, and are features of AKI (Sandhofer *et al.,* 2002, Khwaja, 2012). Moreover, there is evidence suggesting that changes in creatinine may lag several days behind actual changes in GFR (Moran and Myers, 1985, Star, 1998). In addition, creatinine production and excretion is affected by various factors such as age, muscle mass and medication, resulting in under or over estimation of kidney function. Raised creatinine

following trauma or rhabdomyolysis does not necessarily indicate renal impairment and CKD can result in overestimation of kidney function due increased tubular secretion of creatinine (Lopes *et al.,* 2012). Conversely, a small, underweight older patient may have a creatinine value within normal laboratory range but this does not rule out dehydration and associated kidney impairment, as an increase in serum creatinine by more than 26 µmol/l within 48 hours may be suggestive of AKI even if the creatinine value is within normal laboratory limits (Cuhaci, 2009).

Serum urea concentrations can also be affected by many factors such as a high protein meals, GI bleed or even sepsis.

Serum osmolality is the measure of osmolality in the ECF measured by freezing point depression and is the key regulated variable in fluid balance (Fitzsimons, 1963, Thrasher *et al.,* 1982, Stocker *et al.,* 2006, Benarroch, 2005, Robertson *et al.,* 1976, Mckinley *et al.,* 1992). For a given solution such as plasma or other body fluids, osmolality (mOsmol/kg), is the number of osmotically active solutes per kilogram contributing to the solution's osmotic pressure.

An increase of as little as 1% in serum osmolality triggers physiological changes that result in the release of ADH and activation of the thirst centre (Fitzsimons, 1963). Osmolarity, a calculated estimate of osmolality (mmol/l or mOsmol/l), is less than osmolality (mOsmol/kg), because the total solvent mass used in the expression of osmolarity excludes the mass of any solutes present.

Osmolality is considered by many to be the gold standard measure of hydration where serum osmolality of 297 mOsmol/kg was shown to be 90% sensitive and 100% specific in young adults dehydrated in a hot environment to between 2% and 7% of body weight (Cheuvront *et al.,* 2010). It can be used to assess hydration status at a set point as well as monitor hydration over time at any given time interval. Although, some argue that serum osmolality does not always accurately reflect TBW due to its tight regulation. This is because most of the supporting evidence is derived from controlled laboratory conditions and therefore may not be accurate in the clinical setting (Armstrong, 2007). Furthermore, in healthy young adults, serum osmolality may not correlate to their hydration status due to tightly regulated internal mechanisms (Armstrong, 2007, Shirreffs, 2003). However, age-related pathophysiological changes in older adults impair their ability to maintain normal osmolality when dehydrated (El-Sharkawy *et al.*, 2014)

Despite the widespread use of serum osmolality to assess hydration status in a variety of human physiological research settings, it has not been fully adopted in the clinical setting. This is likely due to a combination of limited awareness, financial constraints as well as the lack of evidence demonstrating its effectiveness in the clinical setting.

Haematological markers such as haemoglobin, haematocrit and plasma viscosity are used in clinical practice as a guide when assessing fluid status. However,

these can be affected by many disease processes such as anaemia, polycythaemia or inflammation and are notoriously unreliable.

1.6.4 Dilutional methods

Dilutional techniques have traditionally been viewed as the 'gold standard' method of measuring extracellular and TBW. These techniques are based on the assumption that stable isotopes such as deuterium oxide are distributed equally across all fluid compartments. Dilutional methods usually involve intravenous administration or oral ingestion of a tracer substance after collection of baseline serum or urine samples. Repeated sampling of the serum and urine is then performed after the administrated substance has distributed throughout the fluid compartment which usually occurs within four hours. Knowing the quantity of the administered substance, the baseline measurements and repeated measurements allow the calculation of dilution and therefore the distribution, which directly relates to the size of the fluid compartment. Deuterium and deuterium oxide are amongst the most commonly used stable isotopes of hydrogen used to measure TBW. Bromide ingested orally or administered intravenously, is the most commonly used method of measuring the volume of the ECF compartment. ICF volume can then be calculated by subtracting the ECF volume from the TBW. However, this technique is based on the assumption that deuterium distributes equally throughout all the compartments. This has not been verified, as direct sampling of all the fluid compartments is not possible.

Although these methods have proved to be accurate and reproducible, their use is currently limited to laboratory settings. Key to the accuracy of these methods is the timing, for example deuterium requires sufficient time to distribute and reach equilibrium across all the fluid compartments. Changes in fluid status in clinical practice can sometimes be rapid and at times require an immediate intervention. This limits the use of these dilutional techniques in a significant proportion of clinical scenarios, arguably in situations where accurate assessment of fluid status is most needed. Moreover, these techniques are also costly, invasive and time consuming and cannot be repeated in patients to monitor treatment progress.

1.6.5 Bioelectrical impedance

Multi frequency bioelectrical impedance (BIA) technology utilises a range of frequencies from 5 to 500 kHz in order to measure resistance and conductivity of the tissue planes. It assumes that the resistivity is constant in the human body and that the volume of fluid is homogeneously distributed across uniform cross sections like a cylinder (Vaisman *et al.,* 1987, Frank, 2006).

BIA measurements involve the placement of two electrodes, on the right hand and foot while the subject is in a supine position. The electrodes are then connected to a small handheld device that transmits a small electrical current at various frequencies and measures the resistance and reactance of the current. The body composition is then calculated using validated algorithms that have been developed using regression equations and measurements from large study

populations (Kyle *et al.,* 2004a). Low-frequency currents cannot penetrate the cell membrane and therefore are used as a proxy measure of ECF volume. High-frequency currents on the other hand, cross all compartments including the cell membrane and therefore give an estimation of the TBW (Figure 6) (Kyle *et al.,* 2004a). ICF volume is then calculated based on simple subtraction of ECF volume from TBW volume. TBW measured by BIA has been validated using 'gold standard' dilutional techniques such deuterium and show good correlation. Furthermore reference values have been developed for healthy male and female volunteers as well as the elderly (Kyle *et al.,* 2004b, Armstrong, 2005).

Bioelectrical impedance has proven a popular research tool because it is a non-invasive, safe, quick and relatively inexpensive method of measuring body composition. It is also used in clinical practice to measure and monitor fluid status in dialysis patients. However, the accuracy and reproducibility is affected by several environmental and host factors including ambient temperature, electrode placement and the fluid consumed (Table 6).

A study investigating the physiological effects of saline and dextrose in healthy volunteers, demonstrated that despite giving equal volumes of fluid intravenously, BIA reported a drop in ECF volume and TBW with intravenous 5% dextrose, and an increase in TBW and ECF volume with 0.9% saline infusion (Dileep *et al.,* 2001). This is because BIA measurements are independently affected by water and electrolytes and therefore may not be a reliable measure

(Roos *et al.,* 1992). Furthermore, the arms and legs account for the majority of the impedance generated, the trunk only accounts for up to 12% of the impedance despite accounting for approximately 50% of the body mass (Kushner, 1992). Therefore, large changes in water content of the trunk such in the case of ascites will not represent a significant change in impedance whereas small changes in limb fluid content such as in peripheral oedema, exerts much more significant changes.

These factors individually and in combination limit the clinical application of BIA as a reliable tool, given the difficulties in guaranteeing standardised and reproducible conditions in routine clinical practice.

Table 6: Factors that influence bioelectrical impedance accuracy and reproducibility

• Ambient temperature • Electrode placement • Electrical current flow through the body • Resistance by tissue and water • Utilised to provide estimates of body water and body composition • Electrode site placement • Skin temperature and blood flow • Peripheral oedema • Posture and movement • Composition and tonicity of recently ingested fluids • Changes in plasma sodium concentration and plasma osmolality

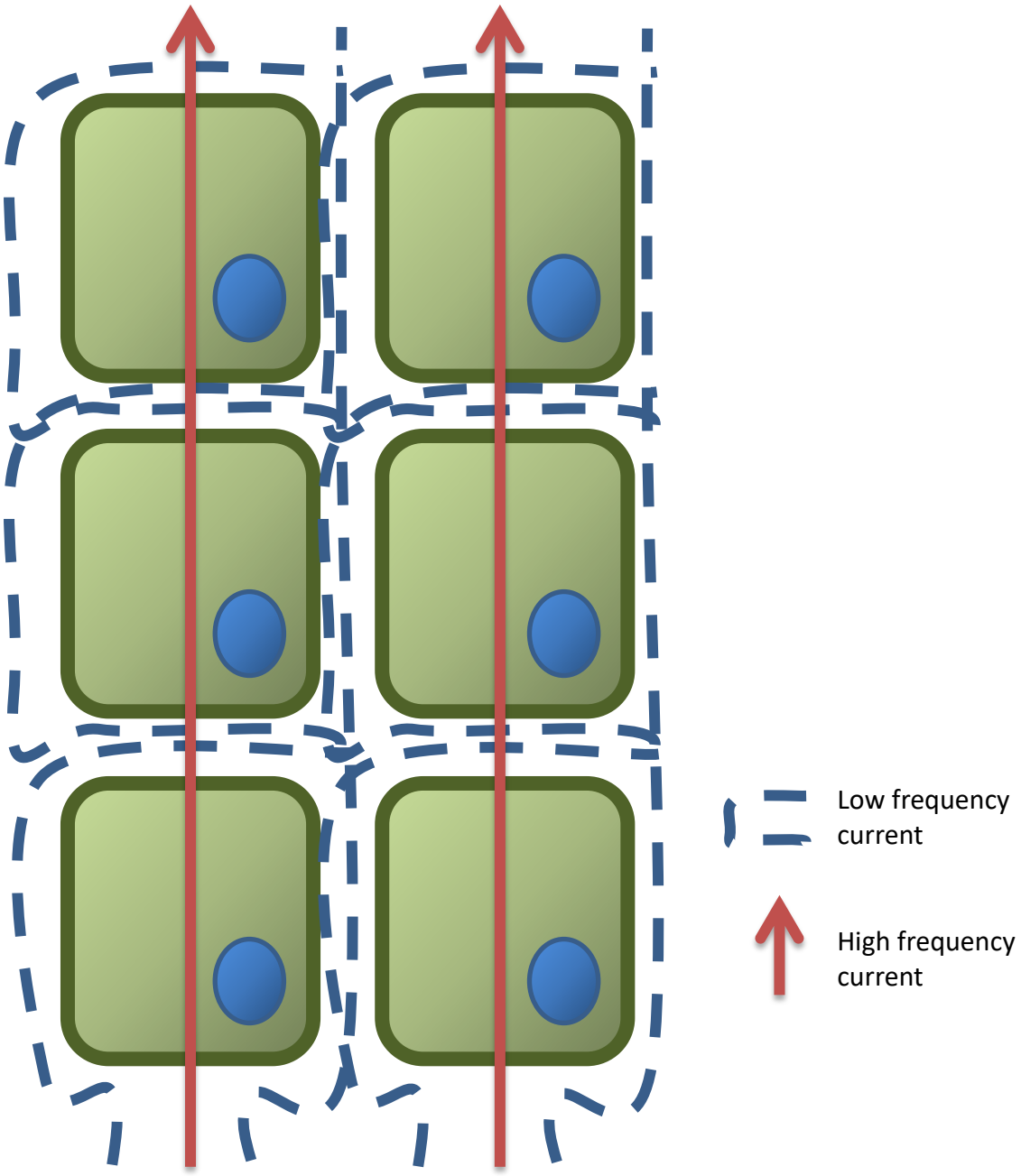


Figure 6: Schematic representation of mechanism underlying BIA. High-frequency currents pass through all the fluid compartments and give an estimation of the TBW. Low-frequency currents cannot penetrate the cell membrane and is used as a proxy measure of extracellular water. Intercellular fluid volume is then calculated by subtraction of extracellular fluid volume from total body water volume.

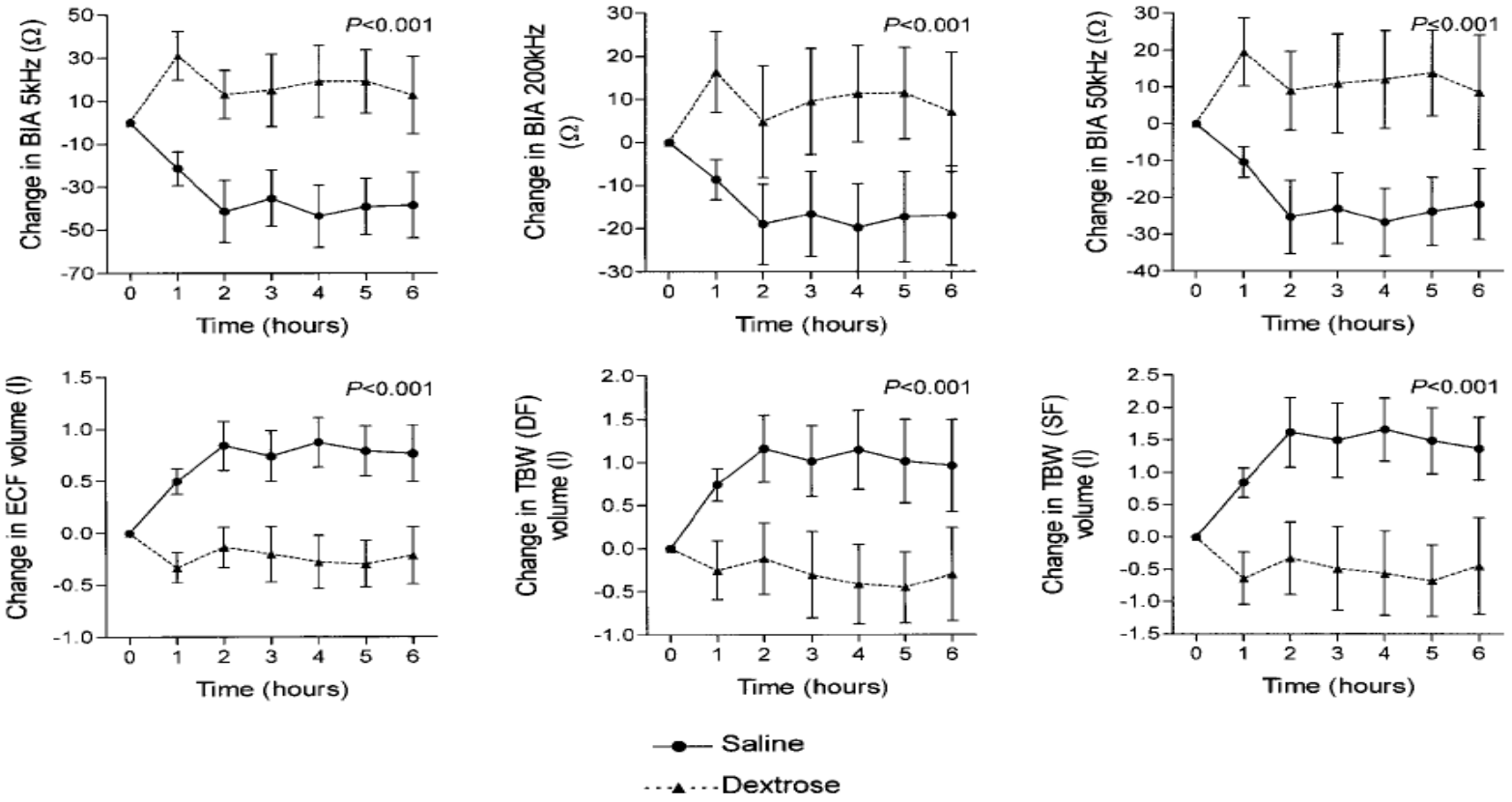


Figure 7: Figure from Lobo *et al.,* 2001 demonstrating that despite giving equal volumes of saline and dextrose infusions, impedance measures implied significant differences in the body fluid volume. Bioelectrical impedance measures demonstrated increase in body fluid with saline and reduction with dextrose compared with time 0. Figure reproduced with permission from publishers.

1.6.6 Invasive monitoring

Central venous pressure (CVP) monitoring is considered to be a direct measure of the BP in the right atrium and vena cava. A probe at the tip of a catheter is threaded through to sit in the lower two-thirds of the superior vena cava. CVP can be helpful for goal directed fluid therapy where low CVP usually indicates hypovolaemia and the response to fluid can be assessed. It is particularly useful in patients who are peripherally oedematous and those with heart failure to allow better assessment and management of fluid balance. This advanced technique requires specialist equipment and experienced clinicians to place and interpret the results (Magder, 2006).

Oesophageal Doppler monitoring uses the technique of goal directed fluid therapy and measures the impact of fluid bolus on stroke volume. It is frequently used in the intraoperative period to help manage fluid balance by infusion of 250 to 300 ml of fluid and measuring the impact on stroke volume by measuring blood flow in the descending aorta. These waveforms generated are then displayed on the monitor which provides measurements for cardiac parameters such as flow time, stroke volume, and cardiac index. If this increases by >10% the bolus is repeated until there is little change in the stroke volume. Although this technique has helped revolutionise intraoperative fluid management, it requires expensive technology and a degree of sophisticated technical ability to place the

probe and interpret the results (Conway *et al.,* 2002, Abbas and Hill, 2008). Moreover, it would be poorly tolerated by patients who are not anaesthetised.

1.7 Hospital care and hydration

Physiological stress associated with hospitalisation can result in deterioration in fluid imbalance, particularly in vulnerable groups including older adults. Older adults are particularly vulnerable to dehydration often due to HCPs experiencing difficulty in assessing and recognising dehydration despite numerous available tools.

A report by the Royal College of Nursing in 2007 suggested that 46% of nurses say there are not enough staff to ensure patients get the help they need to eat and drink (Nursing, 2007). Studies have shown that HCPs, especially nurses and healthcare assistants do not have sufficient knowledge surrounding hydration; this can be a particular problem when identifying patients at risk (Leach *et al.,* 2013).

Patients may also be at higher risk of dehydration due to accessibility of fluids. Those with limited to no mobility cannot reach to pour themselves a drink regardless of whether there is fresh water on their table. Due to pressure area care and the implementation of turn charts, patients are often positioned where they may be unable to reach the fluid (Kayser-Jones *et al.,* 1999).

1.8 Hydration in health care workers

Working as frontline medical and nursing staff is highly demading and requires optimum physical and mental function in order to perform at the highest standards expected of these professionals. Solomon *et al.,* 2010 first investigated dehydration in UK doctors and suggested that a significant proportion may be dehydrated based on urine output. However, it is important to note that this study, published in the Christmas BMJ was aimed at criticising poor research design and therefore had significant limitations.

The effect of dehydration on cognitive function highlights the importance of maintaining optimal hydration status as this may affect clinical decision making and potentially influence patient outcome. This is of particular relevance in HCPs working night shifts which are independently associated with cognitive impairment (Dula *et al.,* 2001). The cognitive performance of 16 emergency physicians following five, eight- hour night shifts was investigated in a cross-over study (Dula *et al.,* 2001). Using the Fluid Scale of the Kaufman Adolescent and Adult Intelligence Test, the authors reported a substantial decline in cognitive performance. Others have reported similar findings in 13 emergency physicians using Southern California Repeatable Episodic Memory Test (REMT), showing that significantly fewer words were recalled by the emergency physicians on the REMT after both day and night shifts (Machi *et al.,* 2012). Such effects could be worsened by dehydration-induced cognitive impairment, a likely risk during busy

night shifts which could have serious consequences for both staff and patient safety.

This supports the need to identify and highlight dehydration in medical staff, which could allow the development of intervention strategies that may help improve working conditions and more importantly enhance patient safety.

2. Hypothesis

I hypothesised that a significant proportion of healthcare professionals would be dehydrated at the end of their shift and this would impair subjective feelings and cognitive function.

I hypothesised that the prevalence of hyperosmolar dehydration in hospitalised older adults would be significantly greater than clinically reported rates and would be associated with increased risk of acute kidney injury and poor clinical outcome.

Equations based on biochemistry performed routinely are likely to provide an accurate and suitable alternative to measured serum osmolality at predicting hyperosmolar dehydration and would be useful as an early predictor of acute kidney injury and clinical outcome.

3. Methodology

3.1 Approvals from regulatory bodies

Approvals were obtained for all studies in line with regional and national guidelines. Chapter 4 was approved by the Nottingham 1 NHS Research Ethics committee, reference 12/EM/0454 and Chapter 5 was approved by the Northampton NHS Research Ethics committee, reference 12/EM/0152. Both studies were also registered on http://clinicaltrials.gov; reference NCT02230774 & NCT01703715, respectively.

Chapters 6-8 comprised of an analysis of a link-anonymised database, therefore the need for ethics permission was waived. However, the protocol was registered with and approved by the hospital audit office (Registration No. 13-099C).

3.2 Ethics and Consent

Informed written consent was obtained prior to recruitment of participants/patients to the study in Chapter 4 and 5. Proxy consent was sought for patients who lacked capacity in Chapter 4, in line with ethical recommendations. Chapters 6-8 comprised of an analysis of a link-anonymised retrospective database and the need for patient consent was waived.

3.3 Eligibility and exclusion criteria

Eligibility and exclusion criteria are detailed in each chapter.

3.4 Collection of blood samples

Blood was sampled by venepuncture or using a venous cannula (Venflon®, Ohmeda, Sweden) into the appropriate Vacutainer® blood collection tube (Becton Dickinson & Co, UK).

Blood sampled (Chapters 4 and 5) was sent and analysed by laboratory technicians at Nottingham University Hospital (NUH) NHS Trust clinical pathology laboratory accredited by Clinical Pathology Accreditation UK Ltd (reference number 2914). Analysis was performed for serum osmolality (by freezing point depression), serum concentrations of sodium, potassium, urea and creatinine (U&Es), estimated glomerular filtration rate (eGFR), and full blood count (FBC). Biochemical and haematological analyses were performed using validated methods previously reported, with an inter-assay coefficient variance of 0.6-4% (Reid *et al.,* 2003).

Hyperosmolar dehydration was defined as serum osmolality >300 mOsmol/kg and impending dehydration as 295-300 mOsmol/kg (Thomas *et al.,* 2008). AKI was defined in accordance with RIFLE and AKIN guidelines widely accepted as the diagnostic benchmark at the time of the data collection (Cuhaci, 2009). Diagnosis and stage of AKI were retrieved from the hospitals AKI electronic-alert database and linked using the patients' unique hospital number and date of admission (Porter *et al.,* 2014). Details of the algorithm used for the alert have been published previously (Porter *et al.,* 2014) (Table 7).

Table 7: Details of the algorithm used for the acute kidney injury alert.

	Stage	Change in serum creatinine (SCr) from baseline*
RIFLE classification	Risk/stage 1	Increase in SCr by 1.5-fold or decrease in GFR >25%
	Injury/stage 2	Increase in SCr by 2-fold or decrease in GFR >50%
	Failure/stage 3	Increase in SCr by 3-fold or decrease in GFR >75% or if baseline SCr ≥353.6 µmol/l, increase >44.2 µmol/l
	Loss of kidney function/stage 3	Complete loss of kidney function for >4 weeks
	End-stage kidney disease/stage 3	End stage kidney disease for >3 months
AKIN classification	Stage 1	Increase in SCr ≥26.4 µmol/l or Increase in SCr ≥150% to 200% (1.5- to 2-fold)
	Stage 2	Increase in SCr >200% to 300% (>2- to 3-fold)
	Stage 3+	Increase in SCr >300% (>3-fold) or if baseline SCr ≥353.6 µmol/l, increase ≥44.2 µmol/l

GFR, glomerular filtration rate; SCr, serum creatinine. [*] *Baseline Scr = The lowest serum creatinine between 7 to 365 days prior to admission. If unavailable, an estimated baseline using the modification of diet in renal disease equation based on-* Estimated GFR (ml/min/1.73m^2) = 186 x (SCr / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black). [+] *Stage 3 also includes patients that are requiring renal replacement therapy, independent of the stage of kidney injury.*

3.5 Collection of urine samples

Urine was sampled (Chapters 4 and 5) and was analysed for osmolality by freezing point depression. Osmolality analysis for Chapter 4 was performed at the NUH NHS Trust clinical pathology laboratory by a technician. Osmolality analysis

for Chapter 5 was performed at the University of Loughborough Sports Science laboratory by a technician.

3.6 Database data collection

Prospective data was collected in line with the study protocol for Chapter 4 and 5. Chapters 6- 8 used a retrospective database collated and populated by NUH staff and computer systems. The database was searched by a specialist data analyst who retrieved data that related to patients aged ≥65 admitted to medical specialties as an emergency between the 1 April 2011 and 31 October 2013.

The trust changed the way dehydration was coded in March 2011 to comply with national guidelines defining dehydration coding and the study start date was chosen to ensure consistency.

Each record represented an individual admission and contained patient identifiers and demographic information including: patient age and gender, the route and dates of admission. The database also contained up to 25 diagnoses related to the admission and comorbidity classified according to the International Classification of Disease (ICD-10) (World Health Organization, 2010). In addition, it also contained details of the dates of death for patients regardless of whether they had died in hospital or in the community up to 29th December 2014. Using these data, length of stay (LOS), in-hospital, 30, 90 and 365-day (one-year) post-admission mortality were calculated. Date of death was retrieved from the hospital database and this was used to identify patients who had died as well as

time to death. LOS was calculated using date of hospital admission and discharge. Patients who died in hospital were excluded from the LOS analysis.

The hospital's database is updated and crosschecked with the National Summary Care Record system by the Data Quality team on a daily basis to ensure accuracy. Primary and secondary diagnoses relating to each admission are coded in accordance with the ICD-10 classification and uploaded onto the hospital database once patients are discharged from hospital or deceased. Regular internal audits are undertaken by a Health and Social Care Information Centre (HSCIC) accredited auditor to ensure quality control and external audits were undertaken by Caspe Healthcare Knowledge Systems (CHKS) (http://www.chks.co.uk) and overseen by Monitor (https://www.gov.uk/government/organisations/monitor). Both audits reported that the coding for the primary and secondary diagnoses were 96% and 93%-95% accurate, respectively.

3.6.1 Validation of database

The study team independently audited the accuracy and appropriateness of the clinical diagnosis of dehydration in Chapters 6 to 8 by reviewing a sample of 200 written and electronic notes selected randomly. Further validation of a larger cohort was carried out using the serum biochemistry measured during the admission. Further biochemical validation was performed using osmolarity calculated using the equation developed by (Krahn and Khajuria, 2006), [1.86 x

(Na + K) + 1.15 x glucose + urea + 14], which has been shown to be up to 97% sensitive and 76% specific at diagnosing dehydration in older adults (Siervo *et al.,* 2014).

3.6.2 Covariates

Covariates including age, gender, comorbidities and illness severity were measured and used in statistical models to help account for potential confounders that can affect outcome.

Gender was obtained from the hospitals database, other variables were calculated using the information retrieved. Age was calculated by subtracting the participant's date of birth from the date they entered the study for Chapter 4 and 5, or date of admission to hospital for the retrospective database studies, Chapters 6-8. Age was then categorised into four time periods each, 65 to 75, 76 to 85, 86 to 95 and >95 years.

To account for comorbidities the Charlson Comorbidity Index (CCI) score was calculated for all records utilising the scoring protocol developed by Charlson *et al.,* 1987 and adapted to the ICD-10 coding system (Quan *et al.,* 2005). CCI was calculated to include all the recorded diagnoses including the primary cause of admission which were coded after patients are discharged or deceased. This information was collected prospectively in Chapter 5 and was calculated in Chapter 6 and 8 using the retrospective database.

National Early Warning Score (NEWS) was calculated in accordance with published guidelines to account for the severity of illness using observations collected at admission (Chapter 5) and for a subset of patients who had electronically reported clinical observations at admission (Chapter 8) (Smith *et al.,* 2013).

3.7 Statistical analysis

Data analysis was performed using IBM® SPSS® Statistics version 22 (IBM® Corporation, Armonk, NY, USA) in Chapters 4 and 5 and Stata Statistical Software, StataCorp. 2013. Release 13. College Station, TX: StataCorp LP for Chapters 6 to 8. Continuous data was assessed for normality visually by viewing distribution plots and by using the Shapiro-Wilkes test. Normally distributed data was presented with means and standard deviations (SD) and Independent Samples *t*-test was used to assess for statistically significant differences. Non parametric data was presented as medians and interquartile ranges (Q1, Q3) and the Mann Whitney *U* or the Kruskal Wallis test when used to assess for statistically significant differences. Chi squared analysis was used to assess for statistically significant differences between categorical variables. *P* value <0.05 was considered statistically significant.

Mortality analysis was performed for Chapters 5, 6 and 8. Risk estimates for mortality were assessed for in-hospital stay, and at 30, 90 days and one year after admission. Kaplan-Meier survival plots were generated to schematically

represent one-year survival stratified by hydration status. Cox regression modelling was used to provide unadjusted and adjusted hazard ratios (HR) as an approximation of risk of AKI in Chapter 8. Cox regression modelling was also used to assess unadjusted and adjusted hazard ratios (HR) as an approximation of risk of mortality in the presence of dehydration, adjustments were made for potential confounding factors. Explanatory variables (potential confounders) considered were age, gender and comorbidities (CCI) were considered in Chapters 5, 6 and 8. Illness severity (NEWS) was considered in Chapters 5 and 8, and frailty (CHSA) score and nutritional status (NRS 2002) in Chapter 5. In this analysis age-unadjusted CCI scores were used in the cox analysis, with age categories investigated separately in keeping with previously validated methods (Charlson *et al.,* 1987, Murray *et al.,* 2006).

3.8 Funding

These studies were supported by funding from the European Hydration Institute, who had no role in the design or execution of the studies.

4. Hydration Amongst Nurses and Doctors On-call: The HANDS On Prospective Cohort Study

4.1 Introduction

The demands of the medical and nursing professions require staff to work long and unsociable hours during both day and night shifts. Frontline staff working on medical and surgical admissions wards face daily challenges and require optimum physical and mental function in order to perform at the highest standards. Staff working in these often hot environments are also amongst the busiest and frequently deal with complex, unwell patients making it difficult to take regular breaks which may predispose to dehydration (Solomon *et al.,* 2010, Alomar *et al.,* 2013).

The available research suggests that physical and mental performance can be adversely affected by dehydration. Moreover, there is increasing evidence linking dehydration to cardiovascular, respiratory, gastrointestinal and urinary conditions (Manz, 2007, El-Sharkawy *et al.,* 2015a). Dehydration of as little as 2% of total body weight may be detrimental to physical, visuomotor, psychomotor and cognitive performance (Adan, 2012, Grandjean and Grandjean, 2007). However, the link between dehydration and cognitive impairment is inconsistent, and some studies have failed to report significant impairment in cognition associated with dehydration (Lieberman, 2007, Lieberman, 2010).

There is also evidence highlighting the importance of HCPs wellness to clinical care, with clinicians reporting that stress, tiredness and burnout may have contributed to the provision of suboptimal care (Firth-Cozens and Greenhalgh,

1997, Shanafelt *et al.,* 2002). Others have gone further to suggest that the health and fitness of employees should be considered as important as patient care, highlighting it as a marker of organisational success and well-being (Alomar *et al.,* 2013, Wallace *et al.,* 2009, Arnetz, 2005, Linzer *et al.,* 2001). This is supported by the link between ill health and sickness absence which is estimated to cost the UK economy over £12 billion in 2004 and 168 million lost working days (National Patient Saftey Agencey, 2007).

Previous studies have shown that dehydration is common amongst doctors working in intensive care (Solomon *et al.,* 2010) and in emergency department staff (Alomar *et al.,* 2013). However, to our knowledge, there are no previous studies investigating the prevalence of dehydration nor its link with cognitive imparment in nurses and doctors on-call working on acute medical and surgical wards.

The primary aim of this study was to assess the prevalence of dehydration in HCPs working on-call on acute medical and surgical wards using objective markers of hydration. The secondary aims were to assess the association between hydration status and changes in cognitive function and subjective feelings.

4.2 Hypothesis

We hypothesised that dehydration would be prevalent amongst HCPs, particularly at the end of their working shift. Junior staff may be at increased risk

due to inexperience in managing time and stress whilst maintaining adequate hydration needs. Moreover, we hypothesised that dehydration may adversely affect subjective feelings of headache, stress and concentration and may also be associated with impaired cognitive function.

4.3 Methodology

This prospective cohort study was conducted between March 2013 and April 2014 at a large university teaching hospital in the UK. All HCPs working on acute medical and emergency surgical wards were eligible for inclusion, but were excluded if; they were pregnant, unwell in the 6 weeks preceding the study, had pre-existing renal disease or taking diuretics or antihypertensive medications.

Participants arrived on the ward where they were due to work approximately 20 minutes before commencing their shift and demographics were recorded. Following this, they were asked to empty their bladder and provide a 5 ml urine sample. Height and weight were then measured and recorded using Seca scales 959 to the nearest 0.05 kg. A 10 ml blood sample was collected and sent for analysis of full blood count, serum osmolality, urea and electrolytes, and blood glucose.

Participants then completed a visual analogue subjective feelings questionnaire using an eight-question 100 mm visual analogue scale previously used to assess the impact of fluid restriction on subjective feelings (Shirreffs *et al.,* 2004). They then undertook a series of computer-based cognitive function tests for 15

minutes, as described in Table 8 (Ashbridge *et al.,* 1997, Müller and Krummenacher, 2006, Trick *et al.,* 2005, Sternber.S, 1966, Sternberg, 1969, Corsi, 1972, Kessels *et al.,* 2000, Stroop, 1935, MacLeod, 1991).

Table 8: Cognitive tests and functions measured

Cognitive test	Cognitive functions measured
Visual search threshold test[1]	Visual cognition and selective attention
Stroop colour naming interference test[2]	Sensitivity to interference and the ability to suppress an automatic response, and is a classical measure of frontal lobe function
Sternberg memory paradigm[3]	Working memory and basic sensorimotor speed
Corsi-test[4]	Visuo-spatial short term working memory

1. (Ashbridge et al., 1997, Müller and Krummenacher, 2006, Trick et al., 2005), 2. (Stroop, 1935, MacLeod, 1991), 3. (Sternberg, 1966, Sternberg, 1969), 4. (Corsi, 1972, Kessels et al., 2000).

Following the pre-shift assessment, participants worked their normal shift but were asked to keep a food and fluid diary, from which fluid intake was estimated. Participants were also provided with Salter scales 1066 and asked to measure and record the mass of each urine void to the nearest 0.001 kg during the course of the day and hourly urine output was calculated (oliguria defined as urine output <0.5 ml/kg/hour) (Khwaja, 2012). Blood, urine and cognitive function tests were repeated at the end of the shift. Participants who worked both day and night shifts were invited to participate in the study for one day and one night shift to allow for comparison. Dehydration was defined as urine osmolality >800

mOsmol/kg (Popowski *et al.,* 2001, Shirreffs, 2003, Shirreffs and Maughan, 1998, Armstrong *et al.,* 1994).

4.4 Results

Of the 92 participants recruited, four dropped out and 88 participants, representing 130 shifts, completed the study. Of these, 46 (52%) participated in the study for one shift, and 42 (48%) for two shifts. Participant and shift details are summarised in Table 9.

Table 9: Shift and demographic details of the study participants

Category		**All HCP (n=88)**	**Nurse (n= 40)**	**Doctor (n= 48)**
Age: mean (SD)		29 (7)	32 (9)	27 (3)
Gender: n (%)	**Female**	60 (68)	35 (88)	25 (52)
	Male	28 (32)	5 (13)	23 (48)
Job description	**Surgery**	38 (43)	20 (23)	18 (21)
	Medicine	50 (59)	20 (23)	30 (34)
Grade: n (%)	**Junior nurse**	32 (36)	32 (80)	-
	Senior Nurse	8 (9)	8 (20)	-
	Foundation Doctor	28 (32)	-	28 (58)
	Speciality Doctor	18 (21)	-	20 (42)
***Type of shift:** n (%)	**Day**	41 (47)	17 (43)	24 (50)
	Night	47 (53)	23 (59)	24 (50)
	Both	42 (48)	28 (70)	14 (29)
Hours worked: mean (SD)		12.5 (0.5)	12.5 (0.2)	13.2 (0.4)
Shift stress: mean (SD)		67 (18)	68 (19)	67 (19)
Shift intensity: mean (SD)		70 (18)	71 (20)	71 (16)
Length of breaks [minutes]: mean (SD)		43.7 (31)	43.6 (13.4)	40.5 (31.9)

4.4.1 Prevalence of dehydration amongst health care professionals

Of the 87 participants who had urine osmolality measured at the start of the shift, 31 (36%) were dehydrated. Of the 80 who had urine osmolality measured at the end of the shift, 36 (45%) were dehydrated (*P*=0.17). Figure 8 demonstrates the change in hydration status from the start to the end of the shift.

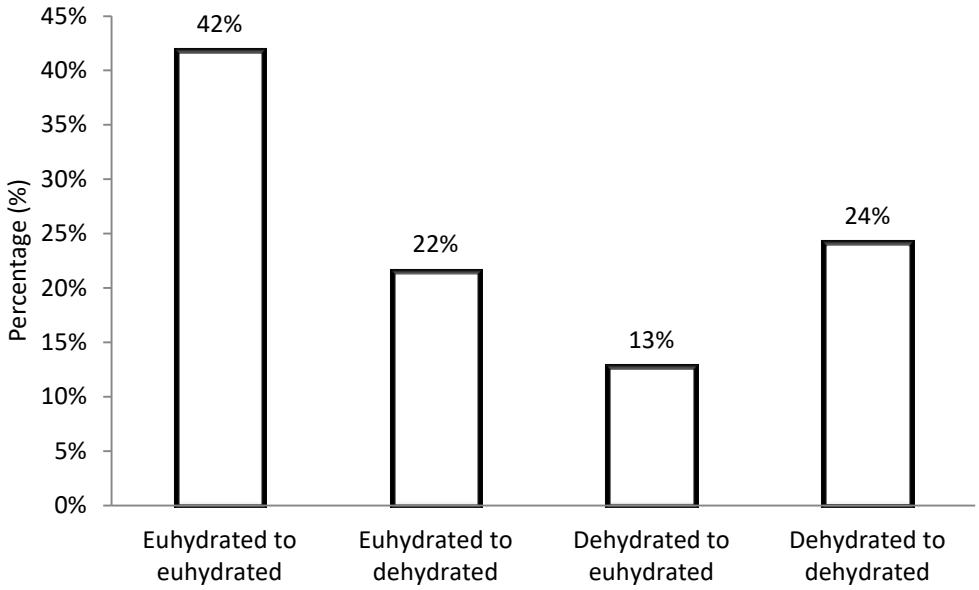


Figure 8: Change in hydration status from the start to the end of the shifts amongst healthcare professionals.

Mean (SD) urinary osmolality was significantly greater at the end of the shift when compared with the start [720 (282) *vs.* 622 (297) mOsmol/kg, *P*=0.031]. Change in body weight mirrored change in hydration status over the course of the shift (Figure 9). Changes in serum biomarkers are listed in Table 10.

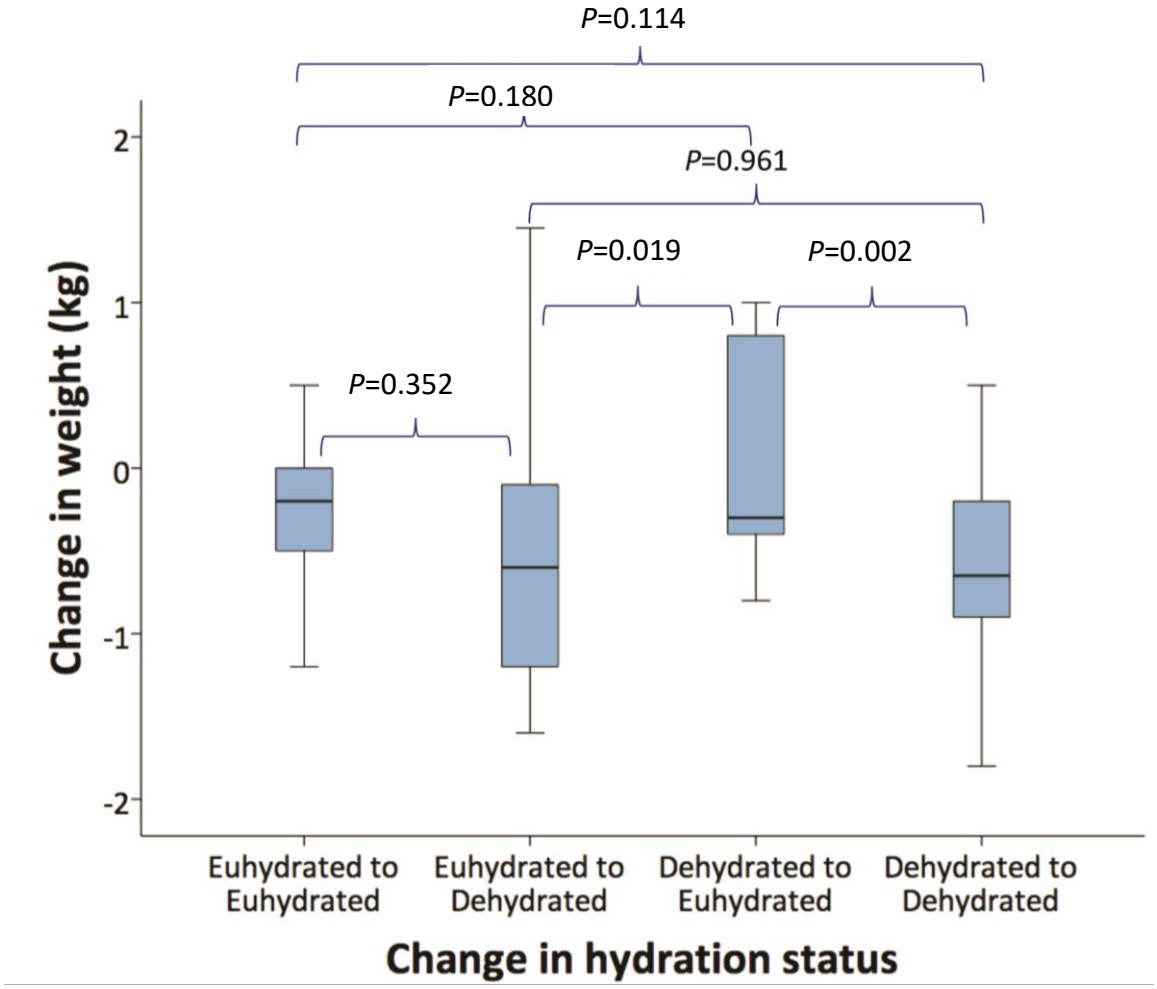


Figure 9: Change in weight with change in hydration status between the start and end of the shifts amongst healthcare professionals.

Table 10: Serum biomarkers before and after the shifts

	Start/End of Shift	Mean (SD)	*P* value
Serum osmolality (mOsmol/kg)	Start (n=82)	294 (5)	**0.006**
	End (n=79)	292 (5)	
Sodium (mmol/l)	Start (n=85)	140 (2)	0.053
	End (n=81)	139 (2)	
Potassium (mmol/l)	Start (n=88)	3.9 (1.2)	0.104
	End (n=88)	3.6 (1.5)	
Urea (mmol/l)	Start (n=85)	4.9 (1.4)	0.820
	End (n=81)	5.0 (1.4)	
Creatinine (mmol/l)	Start (n=85)	76 (15)	0.485
	End (n=81)	75 (15)	
Urea:creatinine ratio	Start (n=85)	66 (17)	0.496
	End (n=81)	68 (17)	
Haemoglobin (g/l)	Start (n=85)	139 (15)	**0.008**
	End (n=80)	133 (14)	
Haematocrit	Start (n=85)	0.418 (0.036)	**0.001**
	End (n=80)	0.400 (0.034)	
Glucose (mmol/l)	Start (n=83)	5.1 (0.8)	**0.006**
	End (n=80)	4.8 (0.6)	
Urine osmolality (mOsmol/kg)	Start (n=87)	622 (297)	**0.031**
	End (n=80)	720 (282)	

Figure 10 compares the differences in fluid consumption with change in hydration status over the course of the shift. It demonstrates that those who became dehydrated at the end of the shift consumed significantly less fluid than those who maintained a euhydrated status at the end of their shifts. Urine output followed similar patterns (Figure 11). Subjective feelings at the start and end of shifts are reported in Table 11.

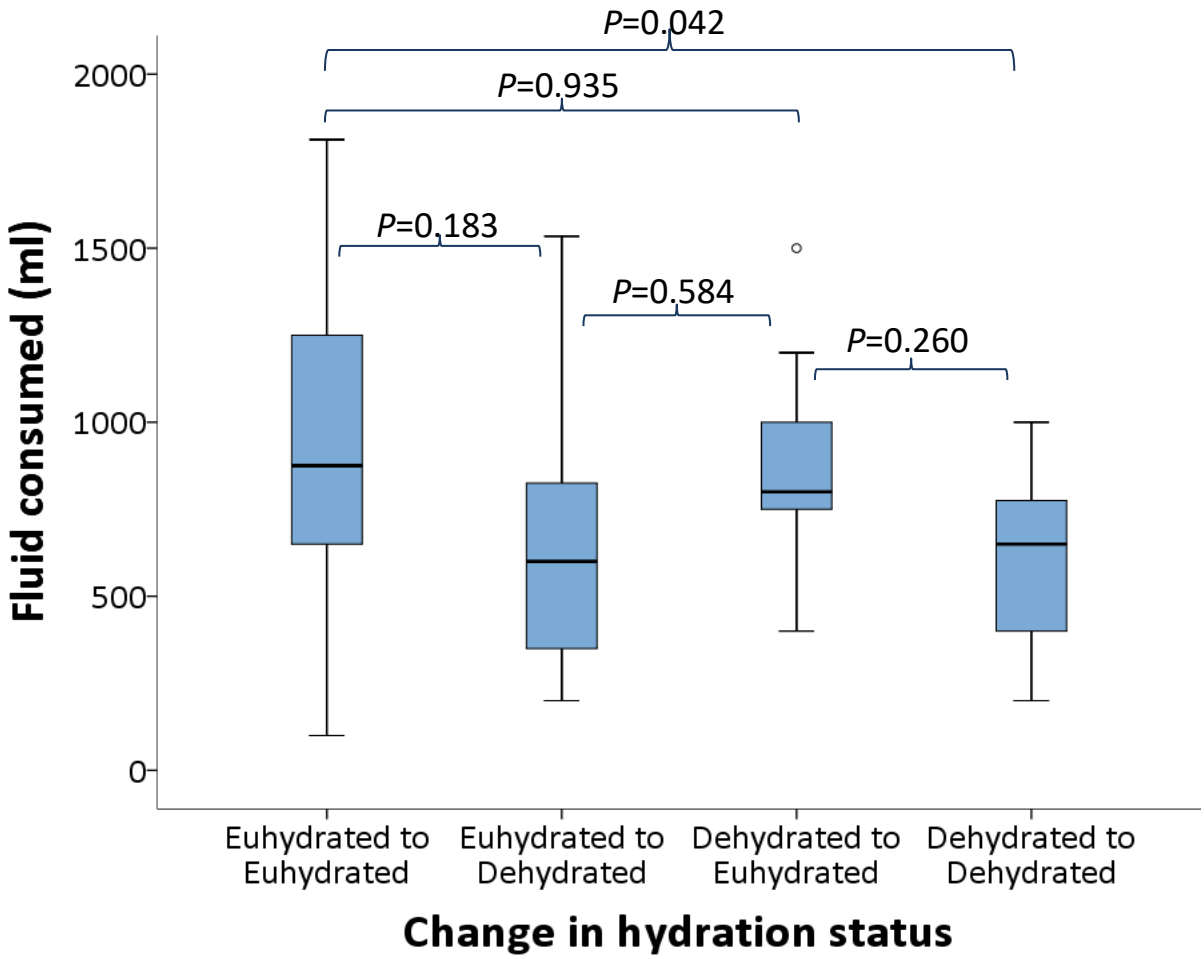


Figure 10: Fluid consumed and change in hydration status between the start and end of the shifts amongst healthcare professionals.

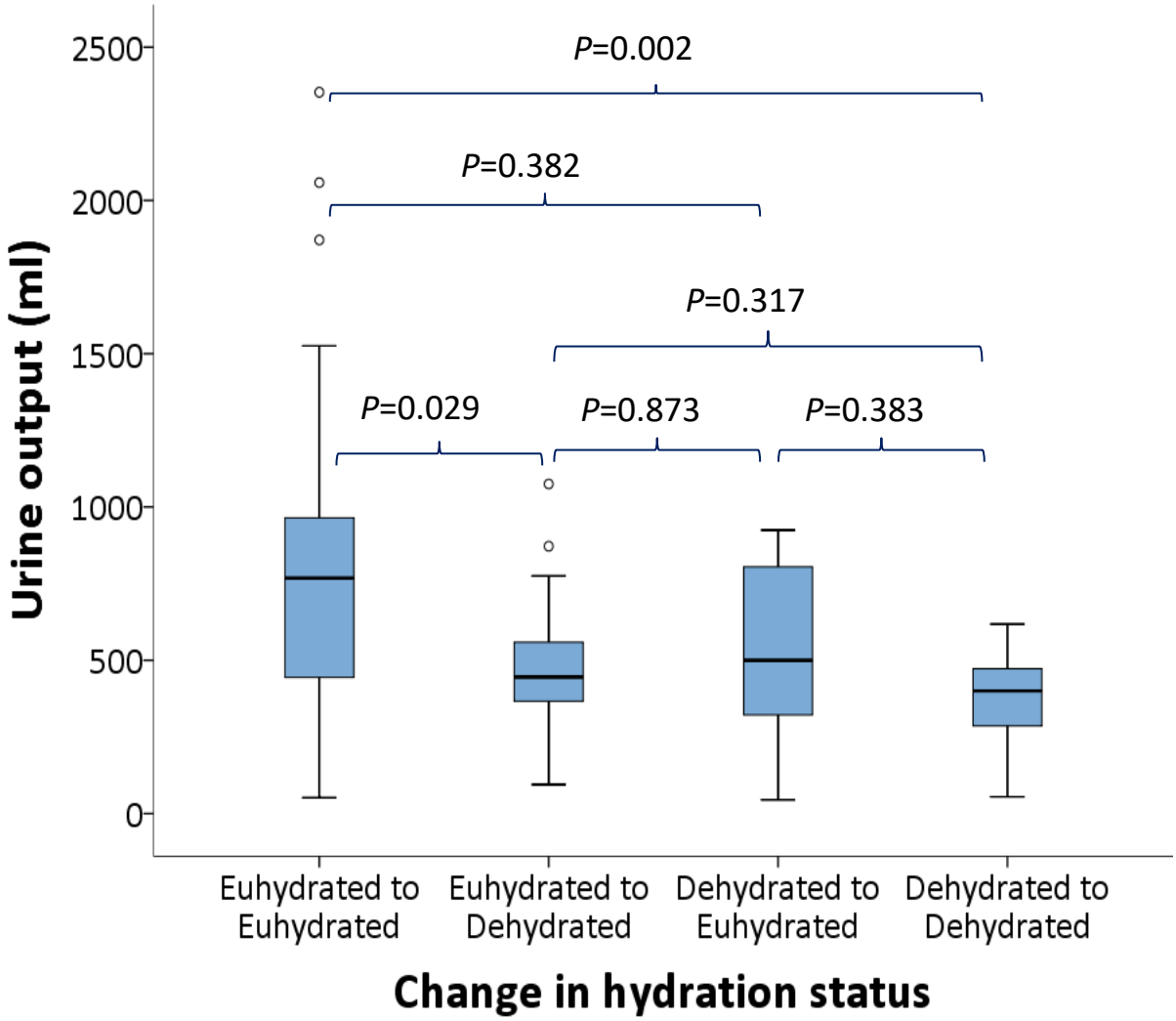


Figure 11: Urine output and change in hydration status between the start and end of the shifts amongst healthcare professionals.

Table 11: Hydration status and subjective feelings at the start and end of the shift, values are in mm on a 0-100 mm scale.

Subjective feelings	Hydration status	Start of shift			End of shift		
		n	Mean (SD)	*P* value	n	Mean (SD)	*P* value
Thirst	Euhydrated	54	35 (25)	**0.030**	39	76 (19)	0.973
	Dehydrated	31	48 (27)		35	76 (21)	
Hunger	Euhydrated	54	15 (19)	0.052	39	53 (28)	0.637
	Dehydrated	31	25 (23)		35	56 (28)	
Tired	Euhydrated	54	36 (19)	**0.036**	39	76 (21)	0.067
	Dehydrated	31	46 (24)		35	84 (16)	
Alert	Euhydrated	54	67 (21)	0.902	39	45 (20)	0.912
	Dehydrated	31	67 (19)		35	45 (23)	
Concentration	Euhydrated	54	70 (21)	0.753	39	43 (18)	0.886
	Dehydrated	31	72 (20)		35	44 (21)	
Stress	Euhydrated	54	22 (20)	0.231	39	40 (26)	0.354
	Dehydrated	31	27 (10)		35	35 (36)	
Headache	Euhydrated	54	11 (20)	0.847	39	37 (33)	0.181
	Dehydrated	31	12 (18)		35	47 (29)	
Refreshed	Euhydrated	53	55 (26)	0.531	39	24 (21)	0.793
	Dehydrated	31	52 (21)		35	23 (18)	

Seventy-nine participants recorded their urine output for the duration of the shift. Thirty-two (41%) produced <0.5 ml/kg/hour of urine and were therefore oliguric (Khwaja, 2012), with significant differences in the total fluid consumed and urine output between the groups (Table 12).

Table 12: Fluid intake, urine output, oliguria, and change in hydration status

	Not-oliguric n (%)	**Oliguric n (%)**	***P* value**
Fluid consumed (n=79): mean (SD)	868 (358)	669 (362)	**0.024**
Urine output (n=79): mean (SD)	815 (428)	316 (142)	**<0.001**
Euhydrated to euhydrated (n=31): n (%)	24 (77%)	7 (23%)	**0.043**
Euhydrated to dehydrated (n=16): n (%)	7 (44%)	9 (56%)	
Dehydrated to euhydrated (n=9): n (%)	5 (56%)	4 (44%)	
Dehydrated to dehydrated (n=19): n (%)	8 (42%)	11 (58%)	

**oliguria, urine output < 0.5mg/kg/hour*

4.4.1.1 Day *vs.* night shifts

Forty-two participants were involved in the study for one day and one night shift. There were no significant differences in the intensity or stress of the shifts (Table 13). Of the day shifts, 40 (95%) had urine osmolality measured at the start and 37 (88%) at the end, 16 (40%) were dehydrated at the start and 19 (51%) at the end of day shift respectively, *P*=0.482. Of the night shifts, 39 (93%) had urine osmolality measured at the start, and 38 (91%) at the end of the shift. Of these, 12 (31%) were dehydrated at the start, and 17 (45%) at the end of the night shift (*P*=0.647) respectively. There were no significant differences in change in hydration status or oliguria between day and night shifts (Table 14).

Table 13: Shift details, fluid consumed and urine output, comparing day and night shifts.

Shift details		Mean (SD)	*P* value
Hours worked: hours	Day (n=42)	12.8 (0.6)	0.484
	Night (n=42)	12.7 (0.4)	
Shift stress*	Day (n=40)	69 (16)	0.126
	Night (n=36)	68 (19)	
Shift busy*	Day (n=40)	73 (16)	0.222
	Night (n=36)	68 (21)	
Overall length of breaks: minutes	Day (n=40)	42 (23)	0.441
	Night (n=36)	48 (38)	
Total fluid consumed: ml	Day (n=40)	836 (402)	0.693
	Night (n=37)	875 (455)	
Urine output: ml	Day (n=40)	635 (510)	0.138
	Night (n=37)	493 (273)	

**100 mm visual analogue scale*

Table 14: Change in hydration status and oliguria - day *vs.* night shifts

		Day shift (n=40)	Night shift (n=37)	*P* value
Change in hydration status	Euhydrated to euhydrated: n (%)	16 (43%)	15 (40%)	0.113
	Euhydrated to dehydrated: n (%)	6 (16%)	11 (29%)	
	Dehydrated to euhydrated: n (%)	3 (8%)	7 (18%)	
	Dehydrated to dehydrated: n (%)	12 (32%)	5 (13%)	
Oliguria	Not-oliguric*: n (%)	22 (55%)	18 (49%)	0.577
	Oliguric*: n (%)	18 (45%)	19 (51%)	

**oliguria, urine output < 0.5 ml/kg/hour*

4.4.1.2 Nurse *vs.* doctor shifts

Forty participants, (46%), were nurses and 48 (55%) were doctors. All of the nurses had urine osmolality measured at the start and 37 (93%) at the end of the shift. Of these, 17 nurses, (43%), were dehydrated at the start of the shift and 16 (43%) at the end. Forty-seven (98%) of the doctors had urine osmolality measured at the start and 43 (90%) at the end. Of these, 14 (30%) were dehydrated at the start and 20 (47%) at the end of the shift. There were no statistically significant differences between the hydration status of nurses and doctors at the start and end of the shift, *P*=0.770 and *P*=0.284 respectively.

Thirty-five (88%) nurses and 44 (92%) doctors measured their fluid intake and urine output over the course of the shift. The mean (SD) volume of fluids consumed by nurses was 911.3 ml (395.6) *vs*. 688.4 ml (353.1) for doctors, *P*=0.010. However, there were no differences in the urine output between nurses and doctors, 611mls (438.1) *vs.* 614.6mls (411.2) respectively, *P*=0.864. Furthermore, 17 (48.6%) nurses and 15 (34%) doctors were oliguric, *P*=0.193.

There were no significant differences between the hydration status of junior and senior nurses at the start or end of the shift, 13 (41%) *vs.* 3 (38%), *P*=0.872 and 12 (41%) *vs.* 3 (38%), *P*=0.786, respectively. However, a significantly higher proportion of foundation doctors (junior doctors) were dehydrated at the start and end of the shift compared with speciality doctors (more senior doctors), 11 (39%) *vs.* 4 (21%), *P*=0.188 and 17 (63%) *vs.* 4 (25%), *P*=0.011, respectively.

4.4.1.3 Medical *vs.* surgical shifts

There were significant differences in the hydration status between specialities (Table 11). Surgical nurses consumed the greatest volume of fluid during their shifts and produced the most urine, with a mean (SD) of 1083.5 ml (405.9) and 766.1 ml (598.1) respectively. Doctors working in surgical wards, however, consumed the lowest volume of fluid and passed the least urine, mean (SD) of 641.5ml (423.2) and 472.9ml (266.0) respectively. There were no statistically significant differences in the prevalence of oliguria between the groups (Table 15).

Table 15: Change in hydration status and oliguria, comparing surgical and medical shifts.

	Nurse		*P* value	Doctor		*P* value
	Surgery	**Medicine**		**Surgery**	**Medicine**	
Euhydrated to Euhydrated	13 (68%)	3 (17%)	**0.001**	6 (35%)	12 (46%)	0.486
Euhydrated to Dehydrated	4 (21%)	2 (11%)		4 (24%)	7 (27%)	
Dehydrated to Euhydrated	2 (11%)	4 (22%)		1 (6%)	3 (12%)	
Dehydrated to Dehydrated	0 (0%)	9 (50%)		6 (35%)	4 (15%)	
Oliguric*:	7 (44%)	10 (56%)	0.429	6 (35%)	9 (32%)	0.519
Not Oliguric*	9 (56%)	8 (44%)		11 (65%)	19 (68%)	

**oliguria, urine output <0.5 ml/kg/hour*

4.4.2 Dehydration and cognitive function

Cognitive tests revealed trends towards an increase in the number of errors made in dehydrated participants, but this was statistically significant only with the single number and five-letter Sternberg test (Figures 12, 13 & Table 16). There were no significant differences in the time taken to perform the cognitive tests (Table 16).

There were also no significant differences in cognitive scores and hydration status during night shifts. However, during day shifts, dehydration was associated with increased error at the start and end of the shifts in the three letters Sternberg test (Table 17).

Table 16: Time to perform cognitive tests and results comparing euhydrated and dehydrated states from start and end of shifts

	Cognitive test	Hydration status	Start of the shift*		End of the shift+	
			Mean (SD)	*P* value	Mean (SD)	*P* value
Time to perform test: minutes: mean (SD)	**Visual Search Baseline**	Euhydrated	989 (135)	0.938	1010 (153)	0.995
		Dehydrated	992 (136)		1010 (150)	
	Visual Search Interference	Euhydrated	2624 (818)	0.787	2694 (897)	0.744
		Dehydrated	2674 (827)		2634 (650)	
	Stroop Simple	Euhydrated	777 (208)	0.985	758 (214)	0.627
		Dehydrated	776 (243)		735 (200)	
	Stroop Complex	Euhydrated	1098 (283)	0.252	1135 (342)	0.844
		Dehydrated	1182 (371)		1151 (343)	
	Sternberg one number	Euhydrated	525 (80)	0.171	547 (110)	0.788
		Dehydrated	557 (128)		540 (119)	
	Sternberg three letter	Euhydrated	595 (98)	0.771	616 (148)	0.758
		Dehydrated	602 (122)		605 (136)	
	Sternberg five letter	Euhydrated	692 (182)	0.913	706 (168)	0.467
		Dehydrated	688 (132)		680 (136)	
Number of errors: median (Q1, Q3)	**Stroop simple [no. errors]:** median (Q1,Q3)	Euhydrated	0 (0,1)	0.696	0 (0,0)	0.841
		Dehydrated	0 (0,1)		0 (0,0)	
	Corsi [no. error]: median (Q1,Q3)	Euhydrated	4 (4,5)	0.639	5 (4,6)	0.391
		Dehydrated	4 (4,5)		4 (4,5)	
Max. Sequence: median (Q1, Q3)	**Corsi [max. sequence]:** median (Q1,Q3)	Euhydrated	7 (6,7)	0.167	7 (6,7)	0.867
		Dehydrated	6 (6,7)		7 (5,7)	

**Start of shift: Euhydrated (n=51), dehydrated (n=31).*

+ End of shift:-Euhydrated (n=40), dehydrated (n=36).

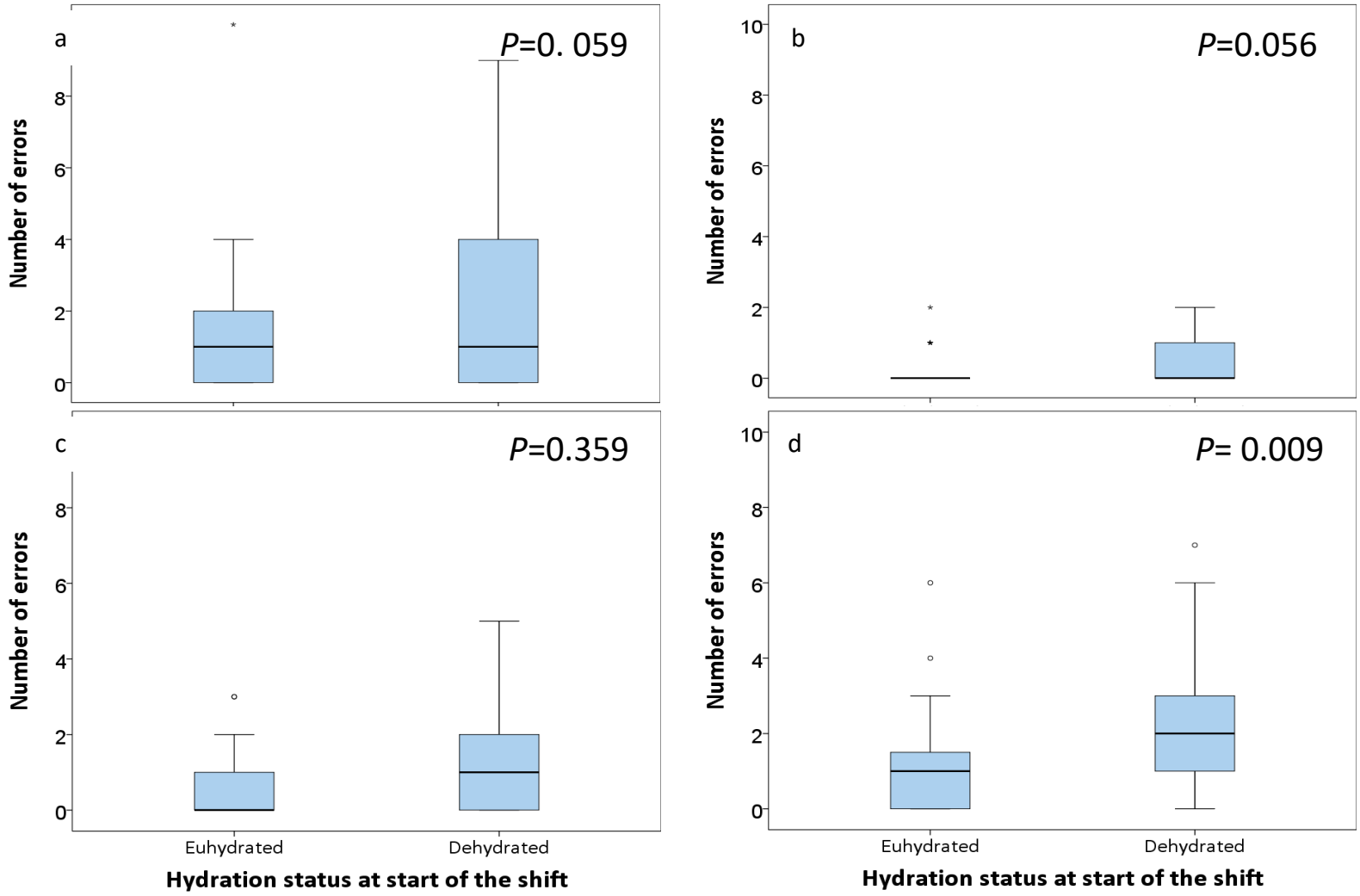


Figure 12: Hydration status and cognitive function at the start of shifts amongst healthcare professionals. (a) Complex Stroop, (b) Single letter Sternberg, (c) Three letter Sternberg, (d) Five letter Sternberg.

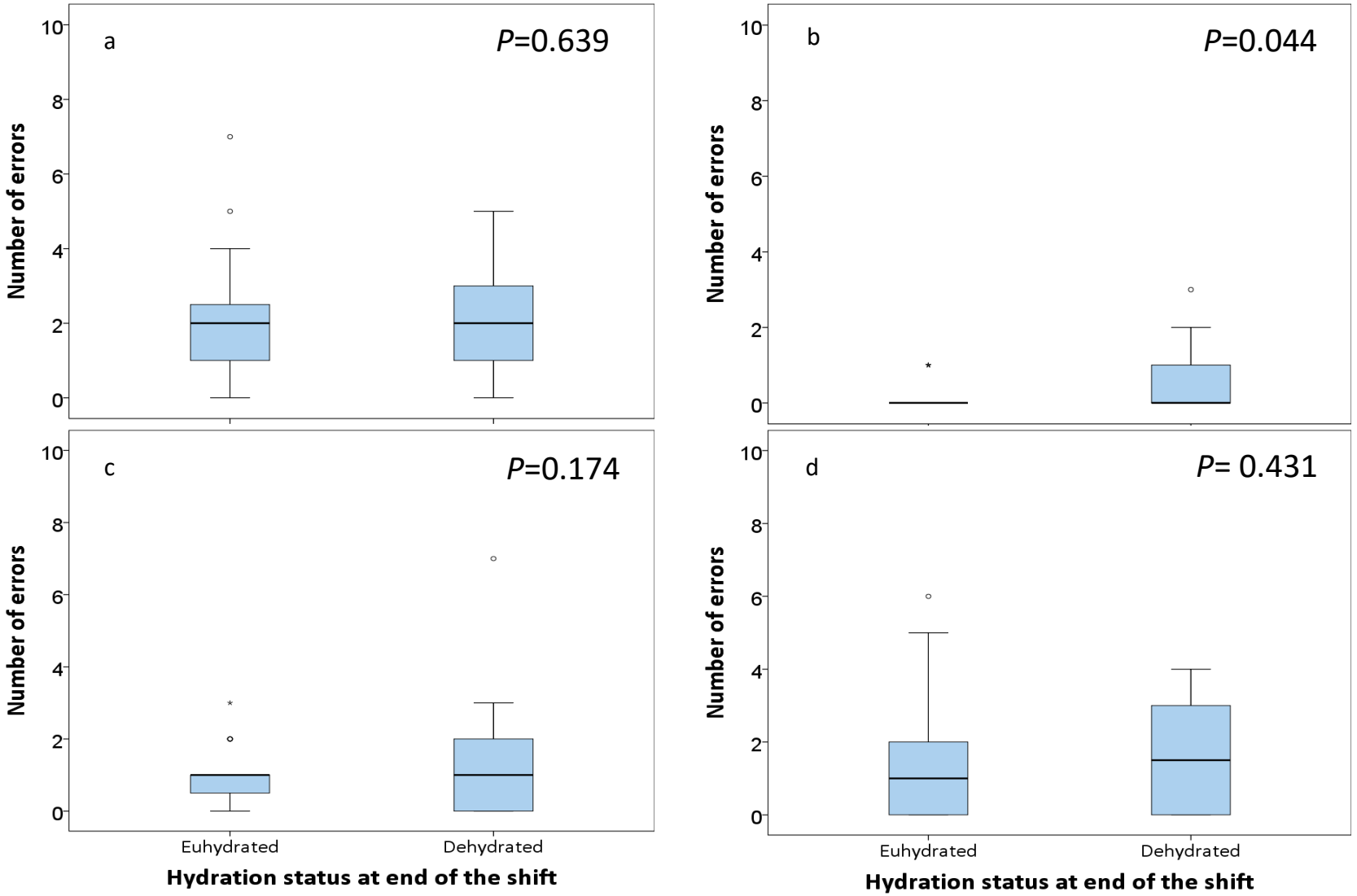


Figure 13: Hydration status and cognitive function at the end of the shift amongst healthcare professionals. (a) Complex Stroop, (b) Single letter Sternberg, (c) Three letter Sternberg, (d) Five letter Sternberg.

Table 17: Cognitive function and hydration status before and after day and night shifts.

Cognitive test	Day shifts			Night shifts		
	Euhydrated	**Dehydrated**	***P* value**	**Euhydrated**	**Dehydrated**	***P* value**
Stroop simple start [no. errors]: median (Q1,Q3)	0 (0, 0)	1 (0, 1)	0.095	0 (0, 0)	0 (0, 0)	0.575
Stroop simple end [no. errors]: median (Q1,Q3)	0 (0, 1)	0 (0, 1)	0.298	0 (0, 0)	0 (0, 0)	0.908
Stroop complex start [no. errors]: median (Q1,Q3)	1 (0, 2)	2 (1, 2)	0.095	1 (0, 2)	2 (0, 4)	0.312
Stroop complex end [no. errors]: median (Q1,Q3)	2 (1, 3)	1 (1, 3)	0.988	2 (0, 2)	2 (1, 3)	0.706
Sternberg single no. start [no. errors]: median (Q1,Q3)	0 (0, 0)	0 (0, 1)	0.503	0 (0, 1)	0 (0, 0)	0.256
Sternberg single no. end [no. errors]: median (Q1,Q3)	0 (0, 0)	0 (0, 0)	0.169	0 (0, 0)	0 (0, 0)	0.685
Sternberg three letter. start [no. errors]: median (Q1,Q3)	0 (0, 1)	1 (1, 2)	**0.021**	0 (0, 2)	1 (0, 2)	0.816
Sternberg three letter. end [no. errors]: median (Q1,Q3)	1 (0, 1)	2 (1, 2)	**0.003**	1 (1, 1)	1 (0, 2)	0.908
Sternberg five letter. start [no. errors]: median (Q1,Q3)	1 (0, 1)	2 (0, 3)	0.359	1 (0, 2)	1 (1, 3)	0.699
Sternberg five letter. end [no. errors]: median (Q1,Q3)	1 (0, 2)	2 (1, 2.5)	0.134	1 (1, 3)	1 (1, 3)	1.000
Corsi [max. sequence] start: median (Q1,Q3)	7 (6, 7)	7 (6, 7)	0.633	6 (5, 7)	7 (6, 8)	0.142
Corsi [max. sequence] end: median (Q1,Q3)	6 (6, 8)	7 (7, 8)	0.408	6 (6, 7)	7 (6, 8)	0.199
Corsi [no. errors] start: median (Q1,Q3)	5 (4, 5)	4 (4, 5)	0.594	5 (4, 5)	4 (4, 5)	0.168
Corsi [no. errors] end: median (Q1,Q3)	5 (4, 5)	4 (4, 5)	0.599	5 (4, 5)	5 (4, 5)	0.931

4.5 Discussion

The prevalence of dehydration amongst HCPs whilst at work was examined and found that over a third studied were dehydrated at the start of their shift, and close to half at the end of the shift. Moreover, a significant proportion of staff were oliguric and produced less than 0.5 ml/kg/hour of urine. Subgroup analysis revealed that close to one-third of doctors studied were dehydrated at the start of their shift and nearly half at the end. In nurses, a different pattern emerged with a greater proportion of nurses than doctors dehydrated at the start of their shift. However, a similar proportion were dehydrated at the end.

Moreover, a comparison of hydration status during day and night shifts in those that participated in the study for two shifts, demonstrated that there were greater rates of dehydration at the start of the day shifts compared with night shifts. Again, a significantly greater proportion of nurses, who start work up to two hours before doctors, were dehydrated at the start of their day shift. This study also demonstrated interesting patterns when comparing the hydration status of HCP's working on medical and surgical wards. On surgical wards, nurses consumed the greatest volume of fluid and had the lowest prevalence of dehydration at the start and end of their shift, and none were dehydrated both at the start and end of their shift. Conversely, on medical wards, nurses consumed significantly less fluid than their surgical counterparts and had the highest prevalence of dehydration.

Nurses often have protected break times; however, the ability to have an undisturbed break may be influenced by the location of the staff room. Interestingly in this study, the staff room where medical nurses often took their break was located on the ward whereas for surgical nurses, this was off the ward. This set up may have supported surgical nurses in maintaining undisturbed breaks and therefore allowing adequate fluid consumption during break times.

A different pattern emerged in doctors. Although the vast majority of the doctors were euhydrated at the start of their shifts, the prevalence of dehydration amongst foundation grade doctors was nearly double that of more senior speciality doctors. Moreover, at the end of the shift, three-quarters of the speciality doctors were euhydrated, however, most of the foundation doctors were dehydrated. These patterns may be related to knowledge and awareness of the importance of hydration as previously discussed. However, another contributing factor is that senior doctors are more likely to have developed the ability to prioritise work and breaks. In this study, despite longer breaks, less busy and stressful shifts, a significant proportion of junior doctors were dehydrated at the end of their shift, likely a consequence of difficulty taking quality breaks and prioritising fluid consumption. Unlike nurses, in this study doctors did not have structured protected break times or access to on/close ward staff/break rooms. Doctors are also often contacted during break periods, particularly during busy on calls. This coupled with limited/no access to convenient break areas makes it

difficult to prioritise hydration. Moreover, foundation doctors are usually more ward-based and are the first point of call for nursing staff so are more likely to be disturbed than senior colleagues.

A key reason for the high prevalence of dehydration is related to inadequate fluid consumption, with the mean volume of fluid consumed being approximately 30% less in participants who were dehydrated at the end of the shift than in those who were euhydrated at the end of the shift when comparing all HCPs. Inadequate access to drinking water, the common practice of missing or limiting breaks, and restricted access to staff-rooms, are therefore likely contributing factors. This, together with the widespread practice of dissuading HCPs to consume food or fluids on-wards in order to maintain a professional image, are likely to add to this problem. Such practices make it difficult for staff to achieve or maintain an optimal, or even adequate, hydration status, particularly during busy and stressful shifts, which are the norm in most emergency admission's wards. However, a communication (Wade, 2010) in response to a study investigating hydration status in ICU staff (Solomon *et al.,* 2010) highlighted that this practice was not in keeping with the views of patients and visitors. In this communication patients' visitors and staff from medical and surgical wards were invited to answer questions related to the practice of food and fluid consumption in view of patients and relatives. Sixty-seven (94%) of the 71 patients and all 18 of the visitors who responded, did not mind whether HCPs drank in view of

patients who could eat and drink, with similar responses from patients who were 'nil by mouth'.

Another contributing factor to the high prevalence of dehydration amongst HCPs is increased fluid loss through excessive sweating. Current UK health and safety legislation dictates that the minimum working temperature is 16^{o}C, but there is no legislation for maximum working temperatures (Executive, 1992). Hospitals are often hot and humid environments, with evidence suggesting ambient temperatures reaching up to 30^{o}C and that approximately 90% of UK hospital wards are of a design type that makes them susceptible to overheating (Change, 2014). Moreover, where air-conditioning is used without humidification, the relative humidity of the environment will fall which can greatly increase respiratory water loss. Maintenance of optimal working environmental temperatures and humidity is therefore likely to help reduce fluid loss through sweating given that some HCPs have been reported to walk up to five miles during a day shift (Hendrich *et al.,* 2008).

The high prevalence of dehydration amongst HCPs at the start of the shift in this study may be related to early starts as previously reported with other shift workers (Brake and Bates, 2003), and may be counteracted by pre-shift bolus oral fluid loading.

Lack of awareness has also been identified as a cause of dehydration in other shift workers, and this has been shown to improve with education (Rogers *et al.,* 2001). This may also be reflected in the HCPs' approach to personal fluid

management, particularly when faced with a busy and challenging working environment.

The present study demonstrated a small but significant increase in errors made during short-term working memory tasks, which was most evident in short term functional working memory (Sternberg memory test). Moreover, a small but consistent pattern of increased errors associated with other cognitive tests were seen, although this was not statistically significant. It is important to highlight that although these cognitive changes were small, they may be of relevance to clinical practice given the number and complexity of tasks performed by HCPs. This may also be of relevance in the context of complex surgical procedures, which at times can be lengthy, and performed under conditions that predispose to dehydration, whilst requiring a multitude of cognitive and psychomotor skills to complete in a safe and efficient manner (Kahol *et al.,* 2008).

Changes related to dehydration draw parallels with the adverse effects of sleep deprivation, where psychomotor performance in surgeons performing laparoscopy has been shown to be impaired with fatigue (Gaba and Howard, 2002). Interestingly, the present study revealed that when comparing day and night shifts in those who have participated in this study over two shifts, no significant differences were demonstrated in the prevalence of dehydration. Furthermore, contrary to previous reports of increased cognitive impairment associated with night shifts (Dula *et al.,* 2001, Machi *et al.,* 2012(Dula *et al.,* 2001, Machi *et al.,* 2012), there were no significant differences in cognitive

function associated with dehydration during night shifts. However, dehydration was associated with a small but significant increase in the number of errors made with the Sternberg three-letter short term memory tests before and after day shifts.

This study suggests a link between dehydration and increased subjective feelings of thirst and tiredness. Others have also linked mild dehydration with headache, anxiety, reduced alertness, fatigue, increased perception of task difficulty and reduced ability to concentrate (Ganio *et al.,* 2011, Shirreffs *et al.,* 2004, Cian *et al.,* 2000, Armstrong *et al.,* 2012, Wilson and Morley, 2003), and have shown improvement with rehydration (Neave *et al.,* 2001).

Given the link between dehydration and ill health and reports linking stress, tiredness and burnout in HCPs to suboptimal patient care (Firth-Cozens and Greenhalgh, 1997, Shanafelt *et al.,* 2002), it is therefore prudent to encourage and facilitate HCP wellness to help facilitate high standards of clinical care.

4.6 Limitations

The present study reports significant findings with potential clinical implications, but there are limitations which should be considered when interpreting the results. This is a single centre study, although the NHS trust is one of the largest in the UK with a work force which is likely to be representative of other centres across the UK with similar working conditions. HCPs involved in the study were aware of the study aims and objectives and this may have influenced their behaviours. However, there was no clear

incentive to act differently and the researchers stressed the importance of maintaining normal behaviour whilst involved in the study.

The use of urine osmolality as a measure of hydration status in this study is consistent with the opinions of many scientists and clinicians that support urine osmolality as one of the most accurate objective measures of hydration status (Sawka *et al.,* 1996, Armstrong *et al.,* 2013b, Armstrong *et al.,* 2013a, Popowski *et al.,* 2001, Shirreffs, 2003, Shirreffs and Maughan, 1998, Armstrong *et al.,* 1994). However, it is important to note that urine osmolality is a measure of the osmolality of the pooled urine in the bladder produced since the time of the last micturition, which may vary between participants. Therefore, hydration status reported in this study is likely to represent the hydration over the period of time from the last micturition rather than at a specific time point when the urine was collected. Furthermore, it can be influenced by recent fluid consumption which may induce diuresis and hypo-osmolar urine production, which may result in artificial dilution of the urine osmolality (Popowski *et al.,* 2001, Shirreffs, 2003, Shirreffs and Maughan, 1998, Armstrong *et al.,* 1994). However, in the present study, urine osmolality is likely to be an accurate representative of hydration status as clear and significant relationships between urine osmolality and other markers of hydration, including change in weight and urine output, were observed.

4.7 Conclusion

This study highlights for the first time that a significant proportion of HCPs were dehydrated at the start and end of medical and surgical shifts, many of whom were oliguric. The effects of dehydration on cognitive function were inconsistent, and mostly not statistically significant. However, trends were observed showing increased error with dehydration. Although widely debated, cognitive impairment associated with dehydration is important to highlight as it may affect decision making and potentially influence patient outcome. There is little disagreement regarding the challenges and difficulties frontline HCP's face, and thus knowing the prevalence of dehydration may allow for low-cost intervention strategies which could help improve working conditions and may enhance patient safety.

5. Hydration and Outcome in Older Patients admitted to hospital: The HOOP prospective cohort study

5.1 Introduction

Older adults are susceptible to dehydration due to age related pathophysiological changes (El-Sharkawy *et al.,* 2014). These changes often result in a hyperosmolar state, which can lead to alterations in cell metabolism and function, mediated by changes in cell volume (Lang, 2007, Haussinger *et al.,* 1993, Manz and Wentz, 2005).

Hyperosmolar dehydration (HD) is a state of water depletion and occurs when water loss is greater than salt loss. It is considered the most common form of dehydration in older adults and has been linked with increased morbidity and mortality (Stookey *et al.,* 2005, Gorelick *et al.,* 1993, Warren *et al.,* 1994). Studies have demonstrated associations between serum hyperosmolarity and poor outcome in patients admitted to hospital with stroke and critical illness, as well as those with acute coronary syndrome receiving percutaneous coronary intervention (Rohla *et al.,* 2014, Holtfreter *et al.,* 2006, Manz and Wentz, 2005, Bhalla *et al.,* 2000). However, few studies have adequately assessed the prevalence of dehydration in hospitalised older adults and the impact on outcome, with many failing to adjust for key confounding factors associated with mortality such as comorbidities.

This study aimed to investigate the prevalence of HD in hospitalised adults aged ≥65 years, admitted as emergencies to a large UK teaching hospital and to assess its impact on short and long-term outcomes.

5.2 Hypothesis

We hypothesised that HD would be prevalent in hospitalised older adults and would be associated with poor outcome. The prevalence of HD may be significantly greater than clinically reported dehydration due to limitations of clinical features of dehydration in older adults.

5.3 Methodology

This prospective cohort study, conducted between 31st August 2012 and 30th April 2014, was designed to include patients aged ≥65 years admitted as an emergency to hospital. Patients who were moribund, with terminal illness and a predicted life expectancy of < 3 months as well as those on end of life pathways were excluded, in line with the research ethics committee approval (Figure 14).

Data collected from the participants, medical notes and/or relatives included demographics and cause of hospital admission as well as comorbidities. These were used to calculate the Charlson Comorbidity Index (CCI) (Charlson *et al.,* 1994, Charlson *et al.,* 1987). Bedside observations were used to calculate the National Early Warning Score (NEWS), a validated measure of illness severity (Smith *et al.,* 2013). The participant's ability to perform daily activities necessary to independent living was assessed using the Barthel Activity of Daily Living index (ADL) score, with a potential score of 0-20 with higher scores indicating a better ability to perform the ADL (Wade and Collin, 1988). Cognitive function was assessed using the Mini Mental State Examination

(MMSE), with a potential score between 0 and 30, where lower scores suggest cognitive impairment (Folstein *et al.,* 1975). The Confusion Assessment Method (CAM) was also used to assess for evidence of delirium (Ely *et al.,* 2001). Frailty was assessed using the seven point Canadian Study of Health and Ageing clinical frailty scale (CSHA), with higher scores indicating increased frailty (Rockwood *et al.,* 2005). Participants were also screened for malnutrition using the Nutrition Risk Screening tool (NRS) 2002 (Kyle *et al.,* 2006, Kondrup *et al.,* 2003). Data were also collected on typical fluid consumption habits by asking participants to estimate the average number of cups of beverages consumed on a typical day. If participants were unable to recall this, efforts were made to obtain the information from relatives or carers. Study participants also marked a 100 mm visual analogue scale to indicate subjective feelings of symptoms associated with dehydration: this questionnaire was previously used to assess the relationship between dehydration and subjective feelings (Shirreffs *et al.,* 2004). The tools used for data collection are presented in the appendix section.

Most patients admitted acutely to hospital undergo routine venous blood sampling. Where possible, this sample was used to measure serum osmolality (by freezing point depression) as well as serum concentrations of sodium, potassium, urea and creatinine, eGFR and a full blood count. In addition, a 5 ml urine sample was collected where possible. HD was defined as serum osmolality >300 mOsmol/kg and impending HD as 295-300 mOsmol/kg (Thomas *et al.,* 2008, Armstrong, 2007, Armstrong, 2005).

Pulse rate, blood pressure, respiratory rate, temperature and body weight were also measured. Participants who were still in hospital 48 hours after admission were reviewed and the same measurements were repeated. Participants who had been discharged were not reviewed at this point. Following discharge, length of hospital stay excluding mortality (LOS), discharge destination and mortality were recorded. All the study participants were followed up using the hospital's electronic records which were reviewed at 30 and 90 days as well as 12 months post admission.

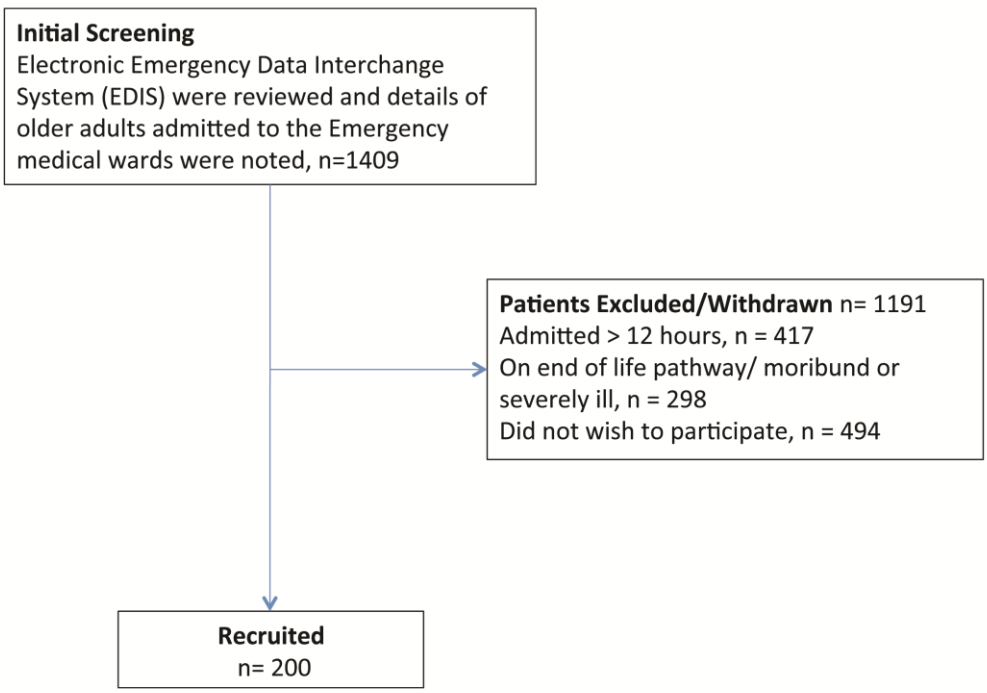


Figure 14: Screening and recruitment of participants for the hydration and outcome in older adults study.

5.4 Result

Two-hundred participants were recruited to the study (Figure 14). Blood samples were obtained from all 200 participants, of whom 187 had serum osmolality measured. One hundred and sixteen of the participants were reviewed at 48 hours after admission: 110 of these underwent venous blood sampling, and 95 had serum osmolality measured. Admission and 48 hour serum osmolality measures were available for 92 participants. Table 18a and 18b summarises participant characteristics at admission and at 48 hours after admission.

Table 18a: Descriptive statistics of participants recruited to the study at admission and those still in hospital 48 hours after admission.

		All at admission (n=200)	**At 48 hours after admission (n=116)**
Age (years): mean (SD)		81 (8)	83 (7)
Gender	**Male:** n (%)	107 (53.5)	62 (53.4)
	Female: n (%)	93 (46.5)	54 (45.6)
Canadian study of health and aging (CSHA) scale: median (Q1,Q3)		4 (3,5)	4 (3,6)
Charlson Comorbidity Index : median (Q1, Q3)		4 (3, 5)	4 (3,5)
Barthel activities of daily living index: median (Q1, Q3)		17 (11, 20)	16 (10, 20)
Cognitive assessment (MMSE)[a]: mean (SD)		24.6 (6.0)	22.2 (10.0)
Confusion Assessment Method (CAM) score % with delirium: n (%)		70 (35.0)	31 (26.7)

a) *MMSE – Mini Mental State Examination. Results available in 159 study participants at admission and 59 at 48 hours after admission.*

Serum osmolality was measured in 187 (94%) patients. One hundred and sixteen (58%) participants were reviewed at 48 hours after admission: 110 (95%) of these underwent venous blood sampling and 95 (86%) had serum osmolality measured. Admission and 48 hour serum osmolality measures were available for 92 (46%) participants.

Table 18b: Descriptive statistics of participants recruited to the study at admission and those still in hospital 48 hours after admission.

		All at admission (n=200)	At 48 hours after admission (n=116)
Nutritional assessments (NRS 2002)[a] : median (Q1,Q3)		1 (1, 4)	1 (1, 4)
Nutritional assessments (NRS 2002)[a] - % at risk of malnutrition: n (%)		70 (38.0)	40 (36.4)
Weight (kg)[b]: mean (SD)		71.0 (17.4)	72.6 (18.5)
Height (cm)[b]: mean (SD)		165.2 (12.6)	166.5 (12.7)
Body mass index (BMI)[b] – mean (SD)		26.8 (6.6)	26.4 (7.1)
Approximate average daily fluid consumption (ml)[c]: mean (SD)		1379 (544)	1343 (547)
Fluid consumption in past 48 hours[c]	**Unchanged: n (%)**	106 (60.2)	25 (29.1)
	Increased: n (%)	8 (4.5)	25 (29.1)
	Decreased: n (%)	62 (35.2)	36 (41.9)
Source of admission	**Emergency department: n (%)**	173 (86.5)	100 (86.2)
	General practitioner referral: n (%)	27 (13.5)	16 (13.7)
Residence prior to admission	**Home: n (%)**	173 (86.5)	99 (85.3)
	Community care: n (%)	27 (13.5)	17 (14.7)

a) *NRS 2002 – Nutrition Risk Screening tool 2002. Results available in 184 study participants at admission and 110 at 48 hours after admission.*
b) *Weight, height and BMI measurements available in 161 study participants at admission and 93 at 48 hours after admission.*
c) *Average fluid consumption based on assumption that each cup of fluid consumed amounts to approximately 200 ml of fluid. Data available in 176 study participants at admission and 86 at 48 hours after admission.*

Serum osmolality was measured in 187 (94%) patients. One hundred and sixteen (58%) participants were reviewed at 48 hours after admission: 110 (95%) of these underwent venous blood sampling and 95 (86%) had serum osmolality measured. Admission and 48 hour serum osmolality measures were available for 92 (46%) participants.

5.4.1 Prevalence of dehydration

Sixty-nine (37%) participants were found to have a serum osmolality >300 mOsmol/kg and were classified as having HD at admission to hospital. A further 40 (21%) participants had impending dehydration (serum osmolality 295-300 mOsmol/kg). Of those with HD at admission, 44 (64%) were reviewed again at 48 hours and 36 (82%) had a repeat serum osmolality measure. Twenty-two of these 36 (61%) also had HD at 48 hours after admission. Of the 92 participants in whom serum osmolality was measured at admission and 48 hours later, 14 (15%) had HD at 48 hours but were euhydrated at admission and 22 (20%) had HD on both occasions. However, on review of the medical notes, dehydration was clinically reported by the medical team in only 15 (8%) and acute kidney injury (AKI) in 24 (12%) of all the cases.

The prevalence of HD increased with age and comorbidity. Sixteen (23%) participants aged 65-74 years had HD whereas 27 (36%) of those >84 years had HD at admission. Similarly, 17% of participants with mild comorbidities (CCI 1-2) had HD at admission *vs.* 43% of those with severe comorbidities (CCI ≥5). However, there were no significant differences in the age, gender, comorbidities, nutritional status or MMSE scores between those euhydrated and those with HD at admission to hospital (Table 19a and 19b). There were also no statistically significant differences in pulse rate, blood pressure, temperature or subjective feelings (data not shown). However, biochemical differences were demonstrated (Table 20) between those euhydrated and those dehydrated at admission to hospital.

Table 19a: Descriptive statistics of patients recruited to the study at admission comparing euhydrated (serum osmolality ≤300 mOsmol/kg) and dehydrated patients (serum osmolality >300 mOsmol/kg)

		Euhydrated (n = 118)	Dehydrated (n=69)	*P* value
Age: mean (SD)		82 (7)	81 (8)	0.86
Gender	**Male:** n (%)	66 (55.9)	34 (49.3)	0.38
	Female: n (%)	52 (44.1)	35 (50.7)	
Canadian study of health and aging (CSHA) scale: median (Q1,Q3)		4 (3,5)	4 (3,6)	0.29
Charlson Comorbidity Index: median (Q1, Q3)		4 (2,5)	4 (3,5)	0.22
National Early Warning Score (NEWS): median (Q1, Q3)		1 (0, 2)	1 (1, 2)	0.658
Barthel activities of daily living index: mean (SD)		15.2 (5.2)	14.7 (5.7)	0.63
Cognitive assessment (MMSE)[a]: mean (SD)		24.5 (5.9)	24.4 (6.6)	0.93
Cognitive assessment (MMSE)[a]: % with delirium: n (%)		29 (29.3)	14 (28.0)	0.87
Confusion Assessment Method (CAM) score % with delirium: n (%)		38 (32.2)	27 (39.1)	0.34
Nutritional assessments (NRS 2002)[b], median (Q1,Q3)		1 (1, 4)	1 (1, 4)	0.578
Nutritional assessments (NRS 2002)[b], % at risk of malnutrition: n (%)		38 (35.8)	27 (41.5)	0.457
Weight (kg)[c]: mean (SD)		68.4 (17.3)	75.3 (15.6)	0.02
Height (cm) [c]: mean (SD)		165 (12.6)	165 (13.9)	0.76
Body mass index (BMI): [c] mean (SD)		25.4 (6.1)	27.1 (7.3)	0.06

Dehydrated refers to hyperosmolar dehydration (serum osmolality >300 mOsmol/kg), 187 (94%) had serum osmolality measured. One hundred and sixteen (58%) participants were reviewed at 48 hours after admission: 110 (95%) of these underwent venous blood sampling and 95 (86%) had serum osmolality measured. Admission and 48 hour serum osmolality measures were available for 92 (46%) participants. Acute kidney injury includes all stages

a. *MMSE – Mini Mental State Examination. Results available in 159 study participants at admission 99 euhydrated and 50 dehydrated*
b. *NRS 2002 – Nutrition Risk Screening tool 2002. Results available in 184 study participants at admission 110 euhydrated and 62 dehydrated*
c. *Weight, height and BMI measurements available in 161 study participants at admission 100 euhydrated and 51 dehydrated*

Table 19b: Descriptive statistics of patients recruited to the study at admission comparing euhydrated (serum osmolality ≤300 mOsmol/kg) and dehydrated patients (serum osmolality >300 mOsmol/kg).

		Euhydrated (n = 118)	Dehydrated (n=69)	*P* value
Approximate average daily fluid consumption (ml)[a]: mean (SD)		1406 (558)	1326 (540)	0.40
Fluid consumption in past 48 hours [b]	**Unchanged: n (%)**	59 (55.7)	39 (67.2)	0.22
	Increased: n (%)	7 (6.6)	1 (1.7)	
	Decreased: n (%)	40 (37.7)	18 (31.0)	
Source of admission	**Emergency department: n (%)**	102 (86.4)	61 (88.4)	0.70
	General practitioner referral: n (%)	16 (13.6)	8 (11.6)	
Residence prior to admission	**Home: n (%)**	103 (87.3)	59 (85.5)	0.73
	Community care: n (%)	15 (12.7)	10 (14.5)	
Clinical diagnosis	**Dehydration: n (%)**	9 (7.6)	6 (8.9)	0.33
	Acute kidney injury[c]: n (%)	6 (5.1)	15 (21.7)	**<0.001**

Dehydrated refers to hyperosmolar dehydration (serum osmolality >300 mOsmol/kg), 187 (94%) had serum osmolality measured. One hundred and sixteen (58%) participants were reviewed at 48 hours after admission: 110 (95%) of these underwent venous blood sampling and 95 (86%) had serum osmolality measured. Admission and 48 hour serum osmolality measures were available for 92 (46%) participants. Acute kidney injury includes all stages

a) *Weight, height and BMI measurements available in 161 study participants at admission 100 euhydrated and 51 dehydrated*
b) *Average fluid consumption based on assumption that each cup of fluid consumed amounts to approximately 200 ml of fluid. Data available in 176 study participants at admission 106 euhydrated and 58 dehydrated.*
c) *Acute kidney injury includes all stages of the condition*

Table 190: Blood and urine results at admission and 48 hours after admission comparing those dehydrated to euhydrated.

	Admission			48 hours after admission		
	Euhydrated (n = 118)	**Dehydrated (n = 69)**	***P* value**	**Euhydrated (n = 59)**	**Dehydrated (n = 33)**	***P* value**
Haemoglobin (g/l): mean (SD)	12.7 (2.1)	12.5 (2.3)	0.48	13.0 (10.5)	11.6 (2.4)	0.45
Platelets ($X10^9$/l): mean (SD)	267.9 (120.3)	234.1 (88.7)	0.05	248.3 (84.6)	212.1 (88.1)	0.05
White cell count ($X10^9$/l): mean (SD)	11.0 (6.7)	11.0 (5.5)	0.95	8.2 (3.3)	8.4 (3.6)	0.74
Haematocrit (L/l): mean (SD)	0.38 (0.06)	0.39 (0.07)	0.95	0.36 (0.58)	0.36 (0.67)	0.7
Sodium (mmol/l): mean (SD)	136.2 (5.9)	141.3 (6.5)	**<0.001**	136.6 (4.1)	142.4 (4.9)	**<0.001**
Potassium (mmol/l): mean (SD)	4.3 (0.5)	4.4 (0.6)	0.14	4.2 (0.5)	4.6 (0.3)	0.28
Urea (mmol/l): mean (SD)	7.6 (3.2)	8.1 (1.8)	**<0.001**	7.1 (2.6)	11.3 (6.0)	**<0.001**
Creatinine (mmol/l): mean (SD)	85.1 (31.4)	133.5 (62.2)	**<0.001**	96.1 (27.8)	120.2 (51.7)	**0.02**
eGFR (ml/min): mean (SD)	62.8 (18.8)	46.1 (19.5)	**<0.001**	59.7 (16.7)	51.6 (18.0)	**0.03**
Serum Osmolality mOmsol/kg: mean (SD)	288.6 (12.4)	312.4 (16.5)	**<0.001**	291.0 (8.3)	309.4 (7.9)	**<0.001**
Urine Osmolality* mOmsol/kg: mean (SD)	523.1 (214.2)	505.1 (166.3)	0.76	5401.1 (168.0)	551.3 (162.7)	0.89

**Results available in 42 study participants at admission 26 euhydrated and 16 dehydrated at admission and 23 cases at 48 hours, 15 euhydrated and 8 dehydrated.*

5.4.2 Hydration status and outcome

Overall, 14 (7%) participants died in-hospital, 11 (79%) of whom were dehydrated at admission (*P*=0.001). The 30-day mortality was greater in those dehydrated at admission than in those who were euhydrated [11 (16%) *vs*. 5 (4%) respectively (*P*=0.01)]. Numerically higher mortality rates were also seen with HD at 90 days and one year after admission but these were not statistically significant (Table 21). Comparable patterns were demonstrated when comparing changes in hydration status over 48 hours, (Table 17). Cox regression survival analysis adjusted for age, gender, comorbidity, NEWS, frailty and nutritional status demonstrated that participants dehydrated at admission to hospital were at greater risk of mortality in-hospital than those euhydrated at admission (Table 21).

The median (Q1, Q3) length of hospital stay between those euhydrated and those dehydrated at admission was 4 (1, 11) vs. 5 (1, 11) days, *P*=0.73.

Table 201: Hydration status and mortality in hospitalised older adults.

Mortality [a]	**Euhydrated (n=118)**	**Dehydrated (n=69)**	***P* value**	**Unadjusted HR (95%CI)**	***P* value**[+]	**Adjusted HR (95%CI)** [b]	***P* value**[+]	**Euhydrated to euhydrated (n=46)**	**Euhydrated to Dehydrated (n=14)**	**Dehydrated to euhydrated (n=12)**	**Dehydrated to dehydrated (n=20)**	***P* value**
In-hospital: n (%)	3 (3)	11 (16)	**0.001**	6.76 (1.89 to 24.23)	**0.003**	6.04(1.64 to 22.25)	**0.007**	2 (4)	1 (7)	0 (0)	5 (25)	**0.03**
30 day: n (%)	5 (4)	11 (16)	**0.01**	4.07 (1.41 to 11.41)	**0.009**	3.52 (1.19 to 10.41)	**0.024**	3 (7)	1 (7)	0 (0)	5 (25)	0.07
90 day: n (%)	16 (14)	16 (23)	0.09	1.91 (0.95 to 3.82)	0.068	1.82 (0.90 to 3.65)	0.095	7 (15)	3 (21)	2 (17)	8 (40)	0.15
One year: n (%)	28 (24)	19 (28)	0.57	1.20 (0.67 to 2.13)	0.542	1.14 (0.64 to 2.03)	0.655	13 (28)	4 (29)	3 (25)	9 (45)	0.53

[a] Mortality rate after admission to hospital. [b] Model adjusted for age, gender, illness severity- National Early Warning Score (NEWS), Comorbidities-Charlson Comorbidity Index (CCI), Frailty- Canadian Study of Health and Aging (CSHA) and nutrition- Nutrition Risk Screening (NRS) 2002.[+]Comparing with those euhydrated at admission. Dehydrated refers to hyperosmolar dehydration (serum osmolality >300 mOsmol/kg).

5.5 Discussion

This study has demonstrated that when using serum osmolality as a marker of hydration, HD appeared to be present in over a third of older adults admitted to hospital as medical emergencies. This may be a result of late presentation resulting from delayed recognition/detection of HD in the community setting by the participants, carers or HCPs. This study also reports for the first time, the prevalence of HD at 48 hours after admission, which was similar to that at admission.

The prevalence of HD increased with age suggesting that older adults are more vulnerable to dehydration during their hospital admission. This may be a consequence of age-related pathophysiological changes that render older adults susceptible to salt and water imbalance or a result of increased comorbidities and associated polypharmacy which further impairs homeostatic mechanisms (El-Sharkawy *et al.,* 2014).

This study also highlights the poor outcome associated with HD in hospitalised older adults. Overall, participants diagnosed with HD at admission were shown to be six times more likely to die in hospital compared with those without HD, independent of key confounders such as age, gender, CCI (includes cause of admission), NEWS and risk of malnutrition. These findings are in keeping with a previously published US study where the authors reported a 17% 30-day mortality and a 48% one-year mortality in participants admitted with dehydration diagnosed clinically, without adjustment for confounders (Warren *et al.,* 1994).

The causes of this are likely to be multifactorial, with undiagnosed HD possibly being a major contributing factor, given that nearly a quarter of those with HD at admission were also diagnosed with AKI by the medical team during the hospital stay. These findings also suggest that AKI may be a strong contributing factor to mortality in the HD group, as was reported by the 2009 UK National Confidential Enquiry into Patient Death which highlighted that as many as 12,000 deaths could be prevented annually within the NHS by treating the 'avoidable' causes of AKI such as dehydration (National Confidential Enquiry into Patient Outcome and Death, 2009, Ftouh and Thomas, 2013).

No significant differences in LOS were observed between the two groups, however, this is probably a consequence of the complex and often lengthy process (including non-medical issues) of discharge of the older adult from hospital.

One of the challenges facing HCP is the difficulty in diagnosing dehydration in older adults given the complex nature of this condition and its associated clinical manifestations. This study demonstrated that in this setting there were significant differences between groups in some of the biomarkers of hydration including, urea, creatinine and sodium. However, there were few differences in some of the clinical features typically associated with dehydration.

5.6 Limitations

Some limitations should be considered when interpreting these results. This was a single centre study, although the hospital is one of the largest in the UK serving a diverse population that represents the wider UK population.

Many scientists and clinicians support serum osmolality as one of the most accurate objective measures of hydration status. Hyperosmolality, however, does not represent all forms of dehydration but rather only that associated with hypertonicity. Dehydration associated with excess salt and water loss may present with hypoosmolality (Sawka *et al.,* 1996, Thomas *et al.,* 2008, Armstrong *et al.,* 2013b). Moreover, salt-free oral fluid consumption or intravenous administration may also result in hypoosmolality, highlighting the need to consider salt and water balance when using serum osmolality to assess hydration status (Lobo *et al.,* 2001b, Kenney *et al.,* 1990).

It is also important to consider that the use of serum osmolality to assess hydration status does not necessarily represent the overall 24-hour fluid balance, but rather the hydration status at the time of blood sampling given that serum osmolality is tightly regulated (Armstrong *et al.,* 2013a). Moreover, using serum osmolality of >300 mOsmol/kg to define HD may denote a state of severe HD of approximately 4-5% of body weight and may therefore have underestimated the prevalence of HD in this study (Armstrong *et al.,* 1997, Cheuvront *et al.,* 2013).

HD may be a manifestation of disease severity, and an increase in mortality would therefore be expected, although attempts were made to account for confounders including age, gender, frailty, nutritional status and cause of admission and comorbidities using the CCI as well as illness severity (NEWS). However, although validated and widely used, the CCI does not account for all comorbidities.

This study included a relatively small sample of patients although likely to be representative of the wider population. However, further work is required to clarify the prevalence of HD and indeed clinically diagnosed dehydration in a larger population and assess the impact on outcome.

5.7 Conclusion

This study highlights a high prevalence of HD in older adults admitted to hospital as a medical emergency, and shows that a significant proportion remained dehydrated 48 hours after admission. Despite accounting for confounding variables, HD was associated with increased risk of death.

6. Clinically diagnosed dehydration and outcome in hospitalised older adults: A cohort study

6.1 Introduction

Maintenance of fluid and electrolyte balance is essential to normal physiological function and older adults are susceptible to fluid and electrolyte imbalance due to numerous factors associated with ageing. (El-Sharkawy *et al.,* 2014) Cognitive impairment can inhibit the recognition of dehydration-related symptoms, physical disability may restrict access to water, (Gaspar, 1999) and embarrassment associated with urinary urgency and incontinence may force older adults to restrict their fluid intake.

Studies have reported an association between acute and chronic dehydration and several other conditions including urinary tract infections, urolithiasis, delirium as well as respiratory, gastrointestinal and cardiovascular disorders. (El-Sharkawy *et al.,* 2015a, Manz and Wentz, 2005)

Dehydration has also been linked with mortality (Warren *et al.,* 1994, El-Sharkawy *et al.,* 2015b). A pilot study was conducted (Chapter 5) to investigate the prevalence of dehydration at admission in 200 older adults and reported that HD (serum osmolality >300 mOsmol/kg) was associated with a six-fold increase in the in-hospital mortality, independent of age, gender, nutritional status, frailty, comorbidities (CCI) and illness severity (NEWS) (El-Sharkawy *et al.,* 2015b). Moreover, it showed that the prevalence of HD was significantly greater than clinically reported dehydration (El-Sharkawy *et al.,* 2015b). Furthermore, a study from the US also reported low prevalence of clinically diagnosed dehydration which was associated with a

17% 30 day mortality (Warren *et al.,* 1994). However, it is unclear whether the findings from the US studies reflect the prevalence of dehydration and impact on outcome in UK centres.

This study aimed to measure the prevalence of dehydration diagnosed clinically during hospital admission in older adults. This study also aimed to assess the effects of dehydration diagnosed clinically on mortality and LOS.

6.2 Hypothesis

We hypothesised that the prevalence of clinically reported dehydration would be low, consistent with previous findings from the US and those reported in Chapter 5. Clinically reported dehydration would be associated with increased mortality independent of confounders as was reported in Chapter 5. Moreover, dehydration would also likely be associated with increased hospital stay given the association with increased age and comorbidity (Warren *et al.,* 1994, El-Sharkawy *et al.,* 2015b)

6.3 Methodology

This retrospective cohort study in older adult patients aged ≥ 65 years was conducted using data from a large UK university teaching hospital NHS Trust. The diagnosis of dehydration (ICD-10 E86.X) was recorded by the hospital's coders where hospital clinicians diagnosed patients to be in a state of severe

dehydration or dehydration treated with IV solutions and excludes other diagnoses of hypovolaemia consistent with national coding protocols.

6.3.1 Sub group analysis

The principal diagnoses corresponding to each admission were grouped into disease categories according to ICD-10 chapters to allow for sub-group analysis of conditions that commonly cause hospital admission in older adults. This included cardiovascular, respiratory and gastrointestinal conditions. Covariates calculated above were used in this analysis. However, the CCI did not include the primary cause of hospital admission for this analysis. Details of the methods used are listed in Chapter 3.

6.4 Results

6.4.1 Prevalence of dehydration

A total of 42,553 unique patient records were identified between 1 April 2011 and 31 October 2013, of which 32,980 (77.5%) patients were admitted to medical specialties. Figure 15 describes cohort selection methods and Table 22 lists the summary of the patient characteristics.

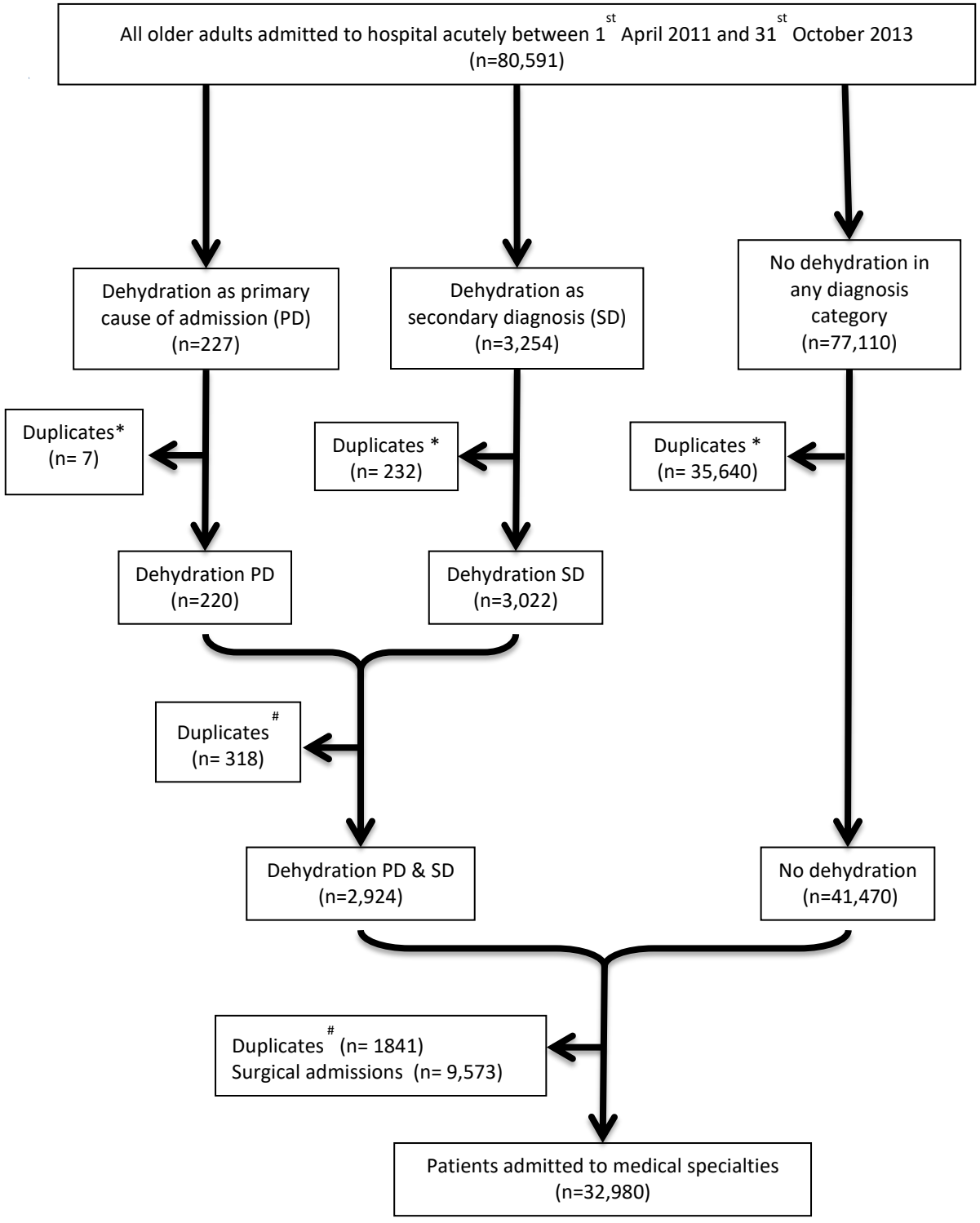


Figure 15: Data selection methods to investigate the prevalence of clinically diagnosed dehydration amongst hospitalised older adults: * First admission episode selected. # Dehydrated patient episodes selected over non-dehydrated episodes.

Table 22: Demographics and characteristics of the study cohort. Comparing those with and without dehydration during hospitalisation.

		All patients (n=32980)	Without dehydration (n=30048)	With dehydration (n=2932)	*P* value*
Age (years): n (%)	**65 - 75**	1386 (4.2)	1338 (4.5)	48 (1.6)	<0.001
	76 - 85	23651 (71.7)	21790 (72.5)	1861 (63.5)	
	86 - 95	7338 (22.3)	6405 (21.3)	933 (31.8)	
	>95	605 (1.8)	515 (1.7)	90 (3.1)	
Gender: n (%)	**Female**	17670 (53.6)	16102 (53.6)	1568 (53.5)	<0.001
	Male	15310 (46.4)	13946 (46.4)	1364 (46.5)	
Charlson Comorbidity Index: n (%)	**None**	8100 (24.6)	7717 (25.7)	383 (13.1)	<0.001
	Mild	15172 (46.1)	14015 (46.6)	1157 (39.5)	
	Moderate	5665 (17.2)	4993 (16.6)	672 (22.9)	
	Severe	4043 (12.3)	3323 (11.1)	720 (24.6)	
Admission Method: n (%)	**ED**	20860 (63.3)	19272 (64.1)	1588 (54.2)	<0.001
	GP	9886 (30.0)	8738 (29.1)	1148 (39.2)	
	other	2234 (6.8)	2038 (6.8)	196 (6.7)	

**P value comparing patients with and without dehydration. ED-Emergency department. GP- General Practice*

Dehydration was noted in 2,932 (8.9%) patients and was the primary cause of admission in 190 (0.6%). Patients with dehydration had greater mean (SD) age, 81.4 *vs*. 78.6 years, and higher median CCI score, 2 (1, 4) *vs*. 1 (0, 3) *P*<0.001. The prevalence of dehydration was also shown to increase with age and comorbidity (Figure 16).

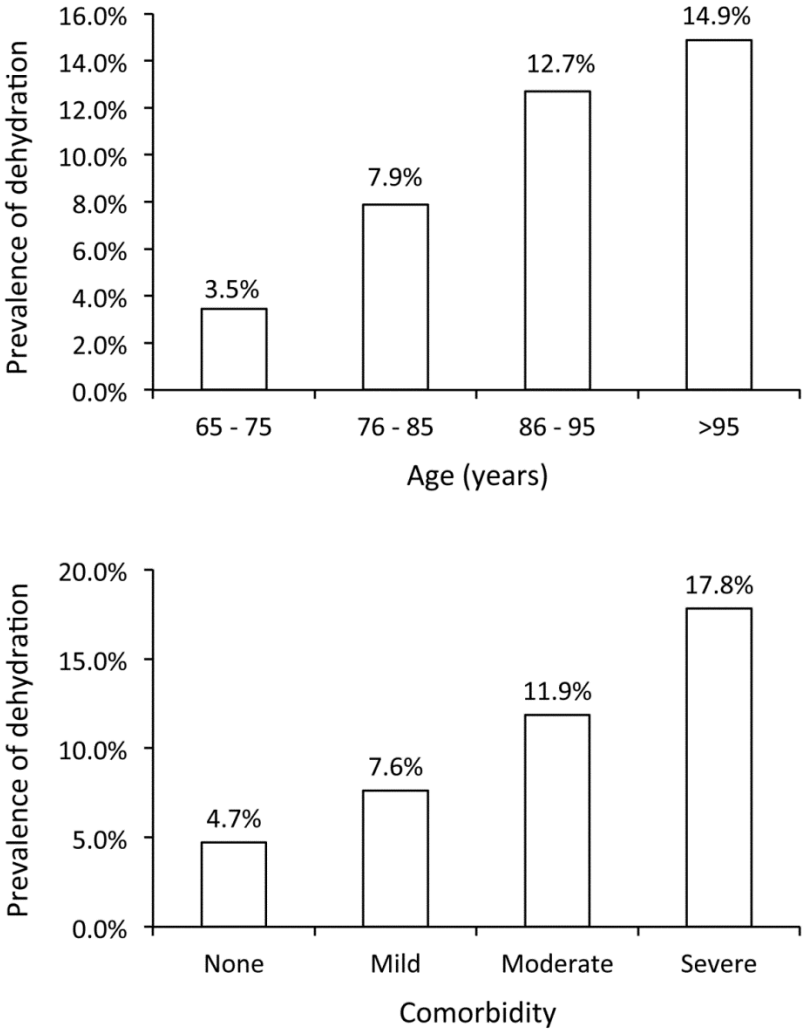


Figure 16: (Top) Prevalence of dehydration with increased age. (Bottom) Prevalence of dehydration with Charlson Comorbidity Index unadjusted for age. 'None' (no comorbidity, 0 points), 'Mild' (mild comorbidity, 1-2 points), 'Moderate' (moderate comorbidity, 3-4 points) and 'Severe' (severe comorbidity, ≥5 points)

6.4.2 Dehydration and acute kidney injury

AKI was reported in 1,399 (47.7%) patients with dehydration, compared with 4,768 (15.9%) patients without dehydration, *P*<0.001. Moreover, a greater proportion of those with dehydration had stage 3 AKI, compared with those without dehydration, 22.2% *vs*. 12.3%, respectively, *P*<0.001. Delirium,

dementia and urinary tract infections (UTI) were also more prevalent in those with dehydration (Table 23).

Table 213: Hydration status and associated conditions.

		Without dehydration (n=30048)	With dehydration (n=2932)	*P* value
Acute kidney injury: n (%)		4768 (15.9)	1399 (47.7)	**<0.001**
Acute kidney injury stage: n (%)	**Stage 1**	3249 (68.1)	713 (51.0)	**<0.001**
	Stage 2	933 (19.6)	375 (26.8)	
	Stage 3	586 (12.3)	311 (22.2)	
Urinary tract infection: n (%)		1026 (3.4)	222 (7.6)	**<0.001**
Dementia: n (%)		2541 (8.5)	581 (19.8)	**<0.001**
Delirium: n (%)		599 (2.0)	187 (6.4)	**<0.001**

6.4.3 Dehydration and mortality

Mortality rates at all time points were consistently higher in patients diagnosed with dehydration (Table 20). Kaplan Meier survival plots demonstrated a significant reduction in survival in those diagnosed with dehydration, and whilst the rate of death in those with dehydration reduced with time, the difference in mortality was maintained one year after admission, *P*<0.001 (Figure 17). Cox regression analysis adjusted for age, gender and comorbidity (CCI) demonstrated that those with primary or secondary diagnoses of dehydration were twice as likely to die in-hospital, HR 2.11 (1.92 to 2.32), *P*<0.001. Table 24 lists the unadjusted and adjusted HR for

the 30- and 90-day mortality as well as one-year post admission mortality. Sub-group analysis revealed similar trends associated with dehydration that were independent of the primary cause of hospital admission for patients admitted with principal diagnoses (ICD-10) of cardiovascular, respiratory or gastrointestinal disease (Table 25a, 25b and Figure 18a and 18b).

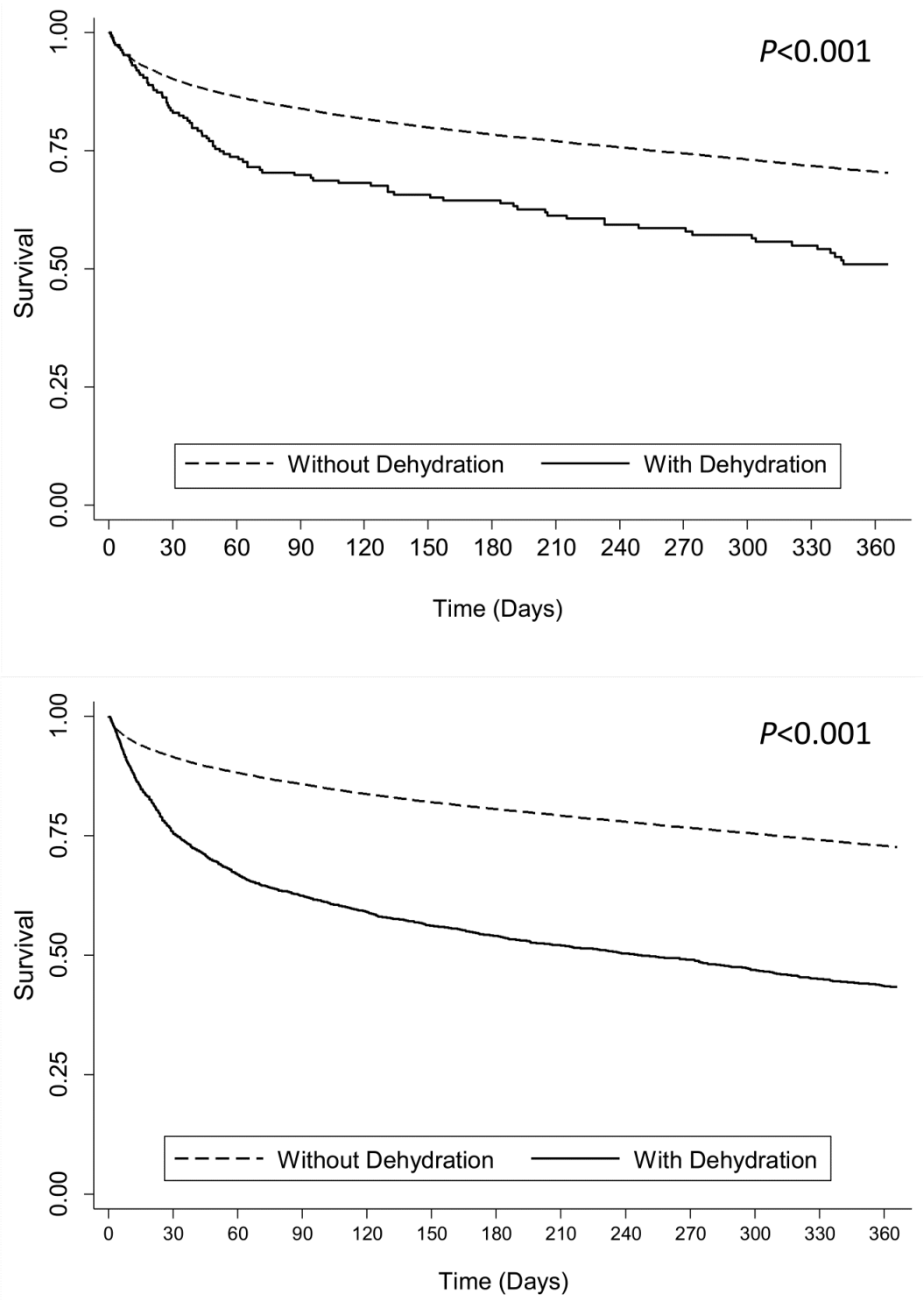


Figure 17: Kaplan Meier survival plot demonstrating differences in mortality for dehydration as a primary diagnosis (top), and as a secondary diagnosis (bottom).

Table 22: Dehydration and outcome in older adults admitted to hospital, comparing those with and without clinically reported dehydration using Cox and linear regression analysis.

		In-hospital mortality	*P* value	30-day mortality	*P* value	90-day mortality	*P* value	one year mortality	*P* value
Without Dehydration (n=30048)	n (%)	2133 (7.1)	-	2526 (8.4)	-	416 (13.8)	-	7422 (24.7)	-
Dehydration recorded in any diagnosis category (n=2932)	n (%)	580 (19.8)	**<0.001**	700 (23.9)	**<0.001**	1076 (36.7)	**<0.001**	1545 (52.7)	**<0.001**
	Unadjusted	2.96 (2.70 to 3.24)	**<0.001**	3.015 (2.77 to 3.278)	**<0.001**	3.02 (2.82 to 3.22)	**<0.001**	2.68 (2.54 to 2.83)	**<0.001**
	Adjusted*	2.12 (1.92 to 2.32)	**<0.001**	2.16 (1.98 to 2.35)	**<0.001**	2.127 (1.984 to 2.280)	**<0.001**	1.91 (1.8 to 2.02)	**<0.001**
Dehydration (PD) (n=190)	n (%)	19 (10.0)	0.37	32 (16.8)	**0.001**	56 (29.5)	**<0.001**	84 (44.2)	**<0.001**
	Unadjusted	1.24 (0.97 to 2.40)	0.348	1.755 (1.239 to 2.487)	**<0.002**	1.982 (1.523 to 2.579)	**<0.001**	1.83 (1.48 to 2.27)	**<0.001**
	Adjusted*	0.92 (0.59 to 1.44)	0.712	1.304 (0.922 to 1.846)	0.133	1.44 (1.10 to 1.89)	**0.003**	1.34 (1.07 to 1.68)	**<0.001**
Dehydration (SD) (n=2744)	n (%)	561 (20.4)	**<0.001**	668 (24.3)	**<0.001**	1020 (37.2)	**<0.001**	1461 (53.2)	**<0.001**
	Unadjusted	3.07 (2.80 to 3.37)	**<0.001**	3.052 (2.845 to 3.268)	**<0.001**	3.05 (2.85 to 3.27)	**<0.001**	2.72 (2.57 to 2.872)	**<0.001**
	Adjusted*	2.19 (2.0 to 2.41)	**<0.001**	2.15 (2.0 to 2.31)	**<0.001**	2.15 (2.01 to 2.310)	**<0.001**	1.934 (1.821 to 2.052)	**<0.001**

**Adjusted for Age, gender and Charlson Comorbidity Index. PD primary cause of admission. SD, secondary diagnosis. The data demonstrates a significant reduction in survival in those diagnosed with dehydration as PD, SD or in any diagnosis category, and whilst the rate of death in those with dehydration reduced with time, the difference in mortality was maintained one year after admission even after adjusting for key confounders P<0.001.*

Table 235a: Dehydration and outcome in older adults admitted to hospital, comparing those with and without clinically reported dehydration using univariate and multivariate Cox regression analysis.

Primary diagnosis[+]		**In-hospital mortality**	***P* value**	**30-day mortality**	***P* value**	**90-day mortality**	***P* value**	**One year mortality**	***P* value**	**Length of hospital stay*:** Median (Q1, Q3)	***P* value**
Cardiovascular disease	Without dehydration: n(%)	535 (8.81)	**<0.001**	587 (9.67)	**<0.001**	809 (13.33)	**<0.001**	6070 (21.6)	**<0.001**	3 (1, 8)	**<0.001**
	With dehydration: n(%)	40 (25.97)		44 (28.57)		69 (44.81)		88 (57.14)		15 (5, 19)	
	Unadjusted HR	3.15 (2.28 to 4.34)	**<0.001**	3.13 (2.31 to 4.25)	**<0.001**	3.817 (2.99 to 4.88)	**<0.001**	3.44 (2.77 to 4.27)	**<0.001**	-	-
	Adjusted HR[#]	2.14 (1.55 to 2.95)	**<0.001**	2.13 (1.56 to 2.90)	**<0.001**	2.53 (1.98 to 3.22)	**<0.001**	2.15 (1.70 to 2.72)	**<0.001**	-	-
Respiratory disease	Without dehydration: n(%)	519 (13.59)	**<0.001**	601 (15.74)	**<0.001**	800 (20.95)	**<0.001**	1226 (32.11)	**<0.001**	4 (1,8)	**<0.001**
	With dehydration: n(%)	110 (30.64)		132 (36.77)		179 (49.86)		233 (64.9)		9 (5, 17)	
	Unadjusted HR	2.41 (1.96 to 2.96)	**<0.001**	2.52 (2.08 to 3.04)	**<0.001**	2.75 (2.34 to 3.24)	**<0.001**	2.71 (2.35 to 3.11)	**<0.001**	-	-
	Adjusted HR[#]	1.77 (1.44 to 2.18)	**<0.001**	1.90 (1.57 to 2.30)	**<0.001**	2.02 (1.71 to 2.38)	**<0.001**	2.01 (1.74 to 2.32)	**<0.001**	-	-

[+]Three most common admission diagnosis categories. [#]Adjusted for Age, gender and Charlson Comorbidity Index. length of hospital stay excluding in-hospital mortality.*

Table 25b: Dehydration and outcome in older adults admitted to hospital, comparing those with and without clinically reported dehydration using univariate and multivariate Cox regression analysis.

Primary diagnosis[+]		**In-hospital mortality**	***P* value**	**30-day mortality**	***P* value**	**90-day mortality**	***P* value**	**One year mortality**	***P* value**	**Length of hospital stay*: Median (Q1, Q3)**	***P* value**
Gastrointestinal disease	Without dehydration: n(%)	113 (7.99)	**<0.001**	124 (8.77)	**<0.001**	188 (13.3)	<0.001	341 (24.12)	**<0.001**	2 (1, 5)	**<0.001**
	With dehydration: n(%)	40 (19.32)		40 (19.32)		69 (33.33)		102 (49.28)		6 (3,15)	
	Unadjusted HR	2.52 (1.76 to 3.62)	**<0.001**	2.28 (1.60 to 3.26)	**<0.001**	2.74 (2.076 to 3.61)	<0.001	2.39 (1.92 to 2.99)	**<0.001**	-	-
	Adjusted HR[#]	1.88 (1.31 to 2.69)	**<0.001**	1.67 (1.16 to 2.40)	**<0.001**	2.03 (1.54 to 2.67)	<0.001	1.83 (1.45 to 2.29)	**<0.001**	-	-

[+]Three most common admission diagnosis categories. [#]Adjusted for Age, gender and Charlson Comorbidity Index. length of hospital stay excluding in-hospital mortality. Sub-group analysis revealed significant reduction in survival in those diagnosed with dehydration as a secondary diagnosis. This increased mortality was independent of the primary cause of hospital admission for patients admitted with principal diagnoses (ICD-10) of cardiovascular, respiratory or gastrointestinal disease as well as key confounders (CCI).*

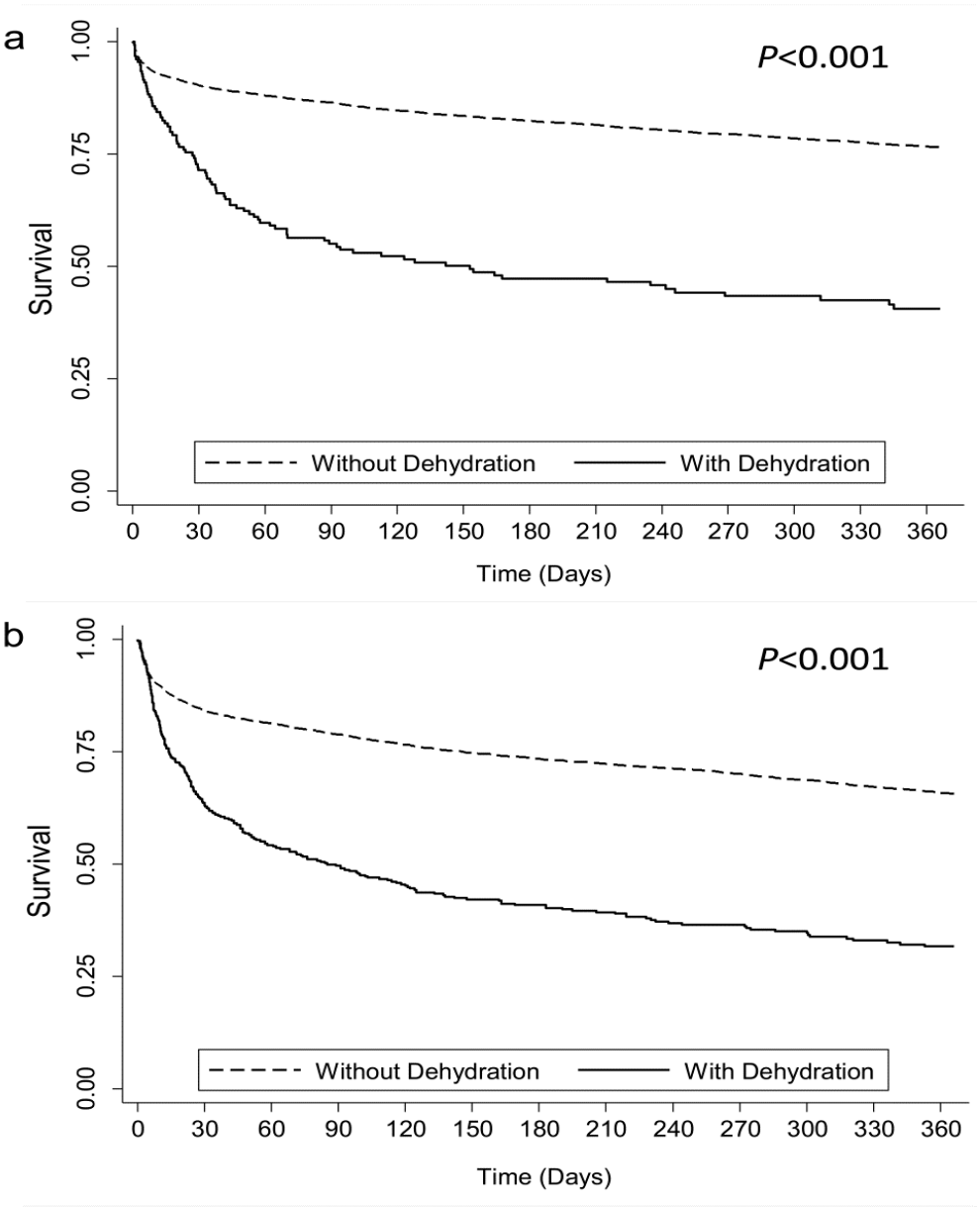


Figure 18a: Kaplan Meier survival plot demonstrating differences in mortality between patients with and without dehydration for patients admitted with a primary diagnosis of (a) cardiovascular and (b) respiratory conditions categorised according to ICD-10.

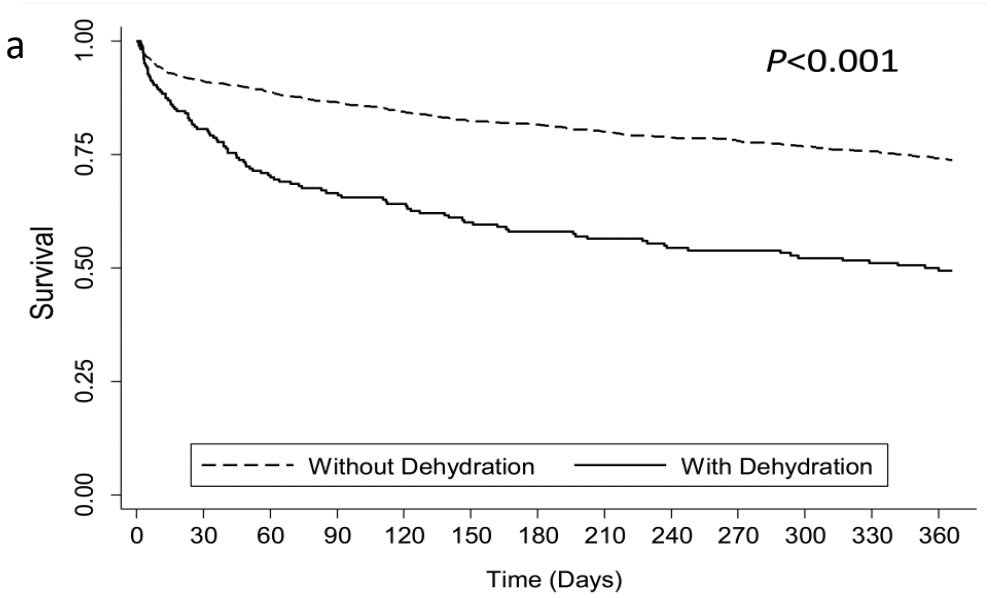


Figure 18b: Kaplan Meier survival plot demonstrating differences in mortality between patients with and without dehydration for patients admitted with a primary diagnosis of (a) gastrointestinal conditions categorised according to ICD-10.

6.4.4 Dehydration and length of hospital stay

The median (Q1, Q3) LOS (excluding in-hospital deaths) in the 190 patients admitted with a primary diagnosis of dehydration was 4 (1, 9) days. Patients diagnosed with dehydration during their hospital admission (n=2,932) had a median (Q1, Q3) LOS of 8 (4, 19) days compared with 3 (1, 8) days for patients without the condition, *P*<0.001. The greatest difference was seen in patients admitted with acute cardiovascular conditions where the median LOS was 13 (5, 19) days for patients diagnosed with dehydration compared with 3 (1, 8) days for patients without the diagnosis, *P*<0.001.

6.4.5 Data validation

Two hundred medical records were identified randomly and audited by the study team: 169 (85%) were diagnosed with dehydration, 73 (43%) of these were diagnosed by an experienced clinician (specialist registrar or consultant). A second investigator also audited 164 of the selected notes independently and both agreed that in 124 (76%) cases that the diagnosis of dehydration was appropriate, with 'substantial agreement', Kappa statistic 0.754, $P<0.001$.

Biochemical validation was conducted for 6,155 patient admissions that had the required serum biochemistry measures for the equation by Krahn and Khajuria, 2006. Patients diagnosed clinically with dehydration had a mean (SD) osmolarity of 301 (22) *vs.*294 (12) for patients without dehydration, $P<0.001$.

6.5 Discussion

The present study highlights that clinically diagnosed dehydration was reported in nearly 10% of hospitalised older adults. Half of these patients were also diagnosed with AKI, using a validated automatic detection algorithm incorporating internationally accepted criteria (based on rise in serum creatinine, SCr). Dehydration was associated with a significant increase in LOS and the risk of death in older adults diagnosed with dehydration was twice that of patients without the diagnosis, independent of age, gender and comorbidities.

The findings of the present UK study are consistent with a previous report from the US which also used clinical coding criteria. (Warren *et al.,* 1994)

Warren *et al.,* 1994 reported that 1.4% of the 10 million older adult admissions reviewed were diagnosed with dehydration as the principal cause of hospitalisation and 6.7% as a secondary diagnosis. However, the prevalence of dehydration reported clinically was significantly lower than estimates based on biochemical measures of dehydration. (Stookey *et al.,* 2005, Bennett *et al.,* 2004, El-Sharkawy *et al.,* 2015b). Stookey *et al,* 2005 used the 1992 Established Populations for Epidemiologic Studies of the Elderly to classify 1,737 older adult participants according to multiple dehydration indices and reported that up to 60% of community-dwelling older adults were dehydrated. Others have demonstrated that up to 48% of older adults were dehydrated at admission to hospital, although significant variations have been reported depending on the method used to assess for the condition. (Stookey *et al.,* 2005, Bennett *et al.,* 2004). The significant disparity in the prevalence of dehydration between biochemical and clinically-diagnosed dehydration is likely to be multifactorial. Firstly, in the present study, only patients with severe dehydration or dehydration requiring IV fluid therapy were captured by the coders. Secondly, there are significant challenges with diagnosing dehydration in older adults due to the lack of specific clinical features which are often erroneously attributed to other causes. This, together with the current absence of validated hydration assessment tools compounds the problem and results in undiagnosed and therefore underreported dehydration in the clinical settings.

The present study highlights several key conditions associated with dehydration including dementia, delirium and UTI, although it is difficult to determine whether these conditions were present as a consequence of dehydration or have resulted in dehydration. However, several healthy volunteer studies have previously linked dehydration with cognitive impairment and morphological brain changes (increased ventricular size proportional to body weight loss). (Kempton *et al.,* 2009, Dickson *et al.,* 2005) Direct inverse associations between dehydration and delirium have also been reported in residents of nursing homes. (Seymour *et al.,* 1980, Voyer *et al.,* 2009) In the case of UTI, animal models have demonstrated that increased urinary volume and flow reduces the antimicrobial load and the associated reduced urine osmolality provides a favourable environment for immune cell activity. (Beetz, 2003) Clinical studies have also shown that increased fluid consumption may prevent UTI recurrence. (Beetz, 2003)

Dehydration as a primary or secondary diagnosis was shown to be associated with poor outcome in hospitalised older adults. Patients admitted to hospital with a primary diagnosis of dehydration had a 16.8%, 30 day and 44.2%, one-year mortality. Moreover, patients diagnosed with dehydration in any diagnosis category during their hospital admission were twice as likely to die in hospital compared with those without the diagnosis, independent of age, gender and comorbidity (CCI).

This relationship continued after stratifying for common causes of hospital admissions categorised in accordance with ICD-10. Patients admitted with

cardiovascular, respiratory or gastrointestinal conditions and diagnosed with dehydration during their hospital episode had a two-fold increase in the risk of in-hospital mortality compared with those admitted with the same diagnosis category but not reported to be dehydrated clinically. This was also independent of age, gender and comorbidities (CCI). These finding are supported by studies linking serum hyperosmolality with poor outcome following acute coronary syndrome and stroke. (Bhalla *et al.,* 2000, Rohla *et al.,* 2014)

One potential explanation for this increased mortality rate associated with dehydration is late clinical detection given that nearly half of those with dehydration had a concomitant diagnosis of AKI, which is associated with high mortality. (Lewington and Kanagasundaram, 2011). The relationship between dehydration and AKI is complicated by the fact that modern definitions of AKI are based on rises in SCr. Some definitions suggest that dehydration should be excluded as a cause of rise in SCr before a diagnosis of AKI is given. In practice this is difficult, particularly with increasing use of AKI e-alerts. (Porter *et al.,* 2014) These findings also highlight the importance of early diagnosis of dehydration.

Significantly greater LOS was demonstrated in patients diagnosed with dehydration compared with those without. The median LOS for patients admitted with a primary diagnosis of dehydration was 4 days. In the case of dehydration as a secondary diagnosis, the LOS was nearly three-times that of those without dehydration (8 days *vs*. 3 days respectively). If this increase in

LOS was a direct consequence of dehydration, it would equate to substantial avoidable costs. It is important to note however, that any cost implications related to dehydration are difficult to fully quantify given that dehydration is underreported using current methods.

6.6 Limitations

This study reports significant findings with potential clinical implications, however, there are some limitations that need to be considered when interpreting the results. Firstly, dehydration may be a manifestation of disease severity and therefore, increased LOS and mortality would be expected. However, the regression modelling demonstrated that dehydration was associated with poor outcome independent of age, gender and comorbidities.

Secondly, this was a single centre study and may not be representative of other UK centres, although numerous publications from hospital and community settings suggest that fluid mismanagement may be more widespread. (Powell and Paterson-Brown, 2011, 2009, Leach *et al.,* 2013)

Finally, this was a retrospective study that was dependent on accuracy of coding for the diagnosis. Diagnosing dehydration is difficult in older adults and therefore the prevalence may have been underestimated. However, the accuracy of entry of data was validated by auditing case notes. Moreover, local and independent audits demonstrated that the diagnosis was both appropriate and accurate in the majority of cases. Furthermore, serum osmolarity was used as an objective measure of dehydration to support the

accuracy of the data. However, further work is required using objective measures to assess the prevalence of dehydration and the relationship with AKI and outcome.

6.7 Conclusions

This study highlights that a small but significant proportion of hospitalised older adults are diagnosed with severe dehydration which is associated with a substantial increase in LOS and mortality, independent of age, gender and comorbidities. Despite the limitations reported, the implications of this study are serious and require further investigation to help prevent avoidable morbidity and mortality as well as reduce costs.

7. An analysis of equations to calculate osmolarity and predict hyperosmolar dehydration in hospitalised older adults

7.2 Introduction

Dehydration indicates a loss of body water resulting in a state of hypohydration, and depending on the corresponding amounts of electrolyte loss in addition to water, may be classified as isotonic, hypotonic or hypertonic. A diagnosis of dehydration should therefore be considered in the context of changes in serum electrolyte concentrations as well as tonicity (serum osmolality). Iso-osmolar dehydration occurs when salt loss is proportional to water loss. Hypoosmolar dehydration occurs in approximately 2.8% of community-dwelling older adults and results from greater salt than water loss (Stookey *et al.,* 2004). Conversely, hyperosmolar dehydration results from greater water than solute loss and is thought to be the most common form of dehydration in older adults, reported in up to 60% of "well" community-dwelling older adults (Stookey *et al.,* 2004, Stookey *et al.,* 2005).

Current clinical methods of assessing and monitoring hydration status are unreliable in older adults Schols *et al.,* 2009, Shimizu *et al.,* 2012b, Shimizu *et al.,* 2012a, Fortes *et al.,* 2014, Eaton *et al.,* 1994, Fletcher *et al.,* 1999, McGee *et al.,* 1999, Weinberg and Minaker, 1995). Serum osmolality (mOsmol/kg) is a measure of solute concentration as measured by freezing point depression. It is widely seen as the most reliable objective measure of hydration status (Bhalla *et al.,* 2000, Sollanek *et al.,* 2011, Cheuvront *et al.,* 2013, Cheuvront *et al.,* 2010, Stookey *et al.,* 2005). Although widely used in human physiological research settings, it has not been fully adopted in clinical practice. This may be due to a combination of limited awareness and financial constraints. There is

also a lack of evidence supporting serum osmolality as an effective clinical tool to aid the assessment of hydration status or as a predictor of kidney injury or outcome in patients.

For a given solution such as plasma or other body fluid, osmolality (mOsmol/kg), is the number of osmotically active solutes per kilogram contributing to the solution's osmotic pressure.

Osmolarity (mOsmol/l or mmol/l) is less than osmolality, because the total solvent mass used in the expression of osmolarity excludes the mass of any solutes present.

At physiological solute concentrations, the mass of the solute is small relative to the mass of the solvent, but the solutes do not behave as perfect osmolytes so the differences between calculated osmolarity and the measured osmolality are likely to be small with little clinical significance. Therefore, in the present clinical study, mOsmol/kg is equivalent to mOsmol/l. Moreover, differences in equations were measured in mmol/l; equivalent to mOsmol/l, given that one mmol/l of osmotically active solute equates to an osmolarity of one mOsmol/l.

Several equations have been published that use routinely measured biochemical parameters to calculate serum osmolarity or to estimate serum osmolality. Osmolarity was originally used in clinical practice to estimate the osmolar gap, the difference between measured serum osmolality and calculated osmolarity used to guide clinical treatment of unmeasured

osmotically active substances such as ethanol and methanol (Glasser *et al.,* 1973, Lynd *et al.,* 2008).

The accuracy of 36 published equations for the estimation of serum osmolarity or osmolality was assessed in a population that included acutely ill hospital patients (n = 195) as well as adults attending outpatient clinics (n = 41) (Fazekas *et al.,* 2013). The authors reported that mean differences upto 35 mmol/l were observed between measured and calculated osmolality using some published formulae, but the mean difference could be as little as 0.5 mmol/l depending on the equation used (Fazekas *et al.,* 2013). Nonetheless, even when there was good agreement between measured and predicted mean values, a large error was observed in individual values: even the "best" equation gave a 95% confidence interval of -6.5 to 7.5 mmol/l. Siervo *et al.,* 2014 investigated the accuracy of osmolarity equations in community-dwelling older adults and demonstrated that some can be 97% sensitive at predicting HD (serum osmolality >300 mOsmol/kg). However, to our knowledge no studies have assessed the accuracy of these equations in hospitalised older adults in diagnosing hyperosmolar dehydration. Such equations are not only useful in research settings but may also allow use in clinical practice to assess and monitor hydration status.

This study aimed to assess the accuracy of 35 published equations (Fazekas *et al.,* 2013, Siervo *et al.,* 2014) in estimating measured serum osmolality and diagnosing hyperosmolar dehydration.

7.3 Methodology

An electronic database from a large UK university teaching hospitals NHS trust was searched by a specialist data analyst who retrieved data relating to patients aged ≥ 65 years admitted to medical specialties as an emergency between the 1 April 2011 and 31 October 2013. The methods used to select the cohort are summarised in Figure 19. HD was defined as measured serum osmolality >300 mOsmol/kg, measured by freezing point depression (Thomas *et al.,* 2008, Armstrong, 2007, Armstrong, 2005).

7.4 Osmolarity estimate

With the widespread use of bedside glucose monitoring, laboratory blood glucose measurements are no longer performed routinely. Therefore, in order to investigate the suitability of the equations to estimate serum osmolality and thus diagnose HD, the two most accurate osmolarity equations were adapted by replacing the blood glucose concentration with a constant value. The constant values were derived from median/mean population values, stratified by diabetes status. The results were compared with 35 equations published previously (Edelman *et al.,* 1958, Holmes, 1962, Jackson and Forman, 1966, Gerich *et al.,* 1971, Jetter, 1969, Mahon *et al.,* 1968, Boyd and Baker, 1971, Dorwart, 1973, Glasser *et al.,* 1973, Ross and Christie, 1969, Stevenson and Bowyer, 1970, Wilson, 1973, Bhagat *et al.,* 1984, Dorwart and Chalmers, 1975, Jenkins and Larmore, 1974, Snyder *et al.,* 1992, Hoffman *et al.,* 1993, Koga *et al.,* 2004, Rasouli and Kalantari, 2005, Wojtysiak *et al.,* 1999,

Khajuria and Krahn, 2005, Bianchi *et al.,* 2009) and complied in two publications (Fazekas *et al.,* 2013), (Siervo *et al.,* 2014).

7.5 Statistical analysis

Statistical analysis was performed as outlined in Chapter 3. In addition, to assess whether estimated osmolality differed systematically from measured osmolality, mean (SD/95% CI) differences between the two values were calculated for each of the equations and differences of <2 mmol/l were considered to be meaningful. The Bland-Altman method (Dewitte *et al.,* 2002, Connelly, 2008) was used to assess whether differences depended on the magnitude of the osmolality values. Regression analysis was performed on the mean and differences between osmolality and osmolarity to investigate further the effects relating to the magnitude of the values. Sensitivity and specificity analyses were performed using area under the curve (AUC) and receiver operating characteristic (ROC) analysis (Zweig and Campbell, 1993). To compare the findings of this study with those of Siervo *et al.,* 2014, their online supplementary table containing mean of the difference and SD was used. SD was converted to 95% CI.

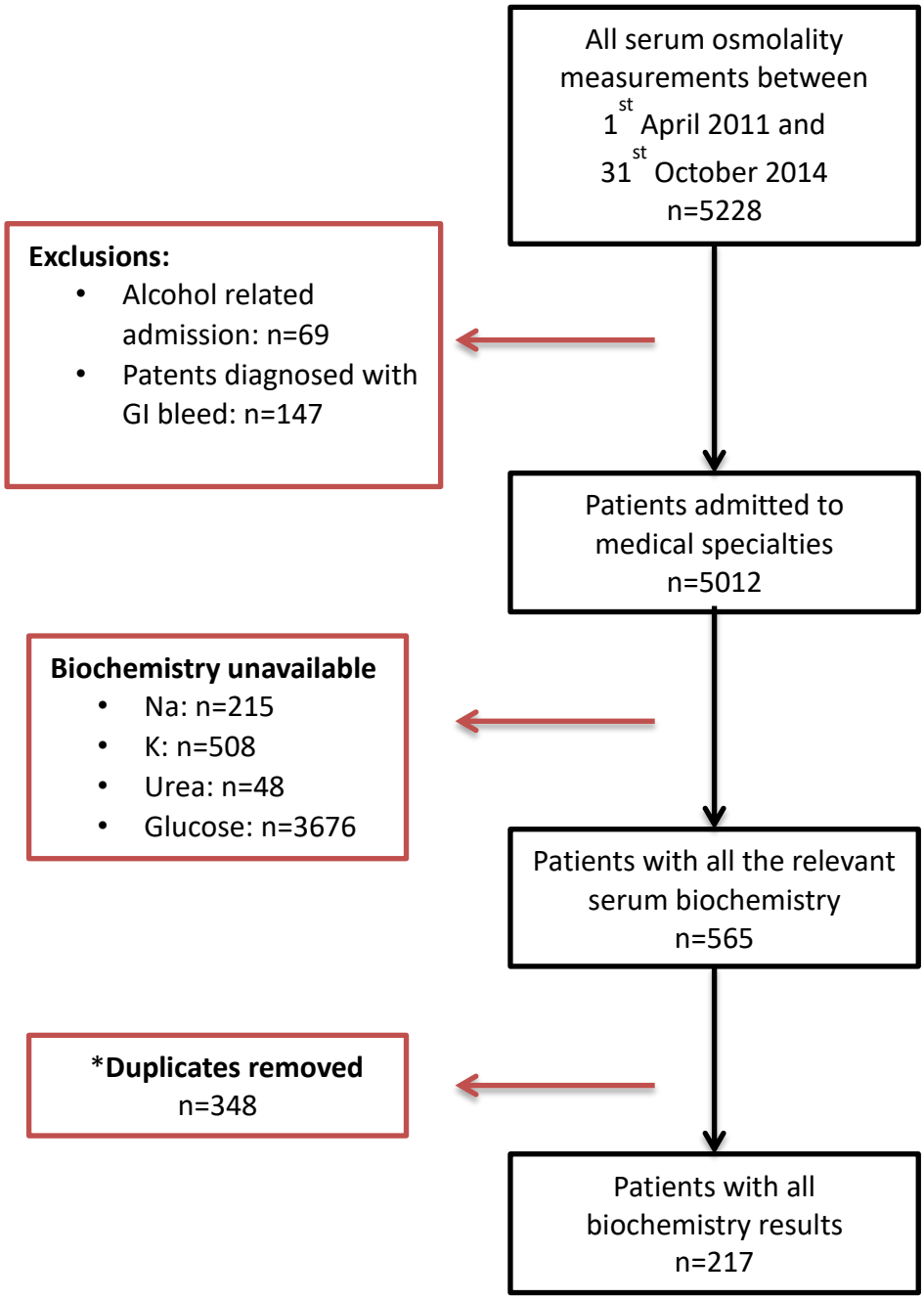


Figure 19: Cohort selection methods. All serum osmolality measurements were identified together with the biochemistry performed on the same sample. Patients who did not have a reported serum sodium, potassium, urea and glucose were excluded. In addition, patients admitted with methanol poisoning or any alcohol related conditions including alcohol intoxication were excluded to reduce the risk of an artificially high osmolar gap. Patients admitted with hypovolaemia resulting from blood loss including those with gastrointestinal bleeding, were also excluded to minimise the effects of non-water loss hypovolaemia. In cases where more than one serum osmolality was measured during the same admission, only the first measurement was selected. *duplicates indicate multiple serum osmolality measurements from the same patient, first value was preferentially selected. K-Potassium, Na-Sodium.

7.6 Results

7.6.1 Cohort description

Of the 5228 measurements of serum osmolality made, 217 unique older adult patient records were identified who had serum osmolality, sodium, potassium, urea and glucose, all measured from the same blood sample (Figure 19). HD was present in 51 (23%) patients, of which, 28 (55%) had diabetes. Table 26 lists the patient demographics and summarises the measured serum biochemistry for the cohort.

Table 246: Cohort demographics and serum biochemistry, comparing patients with and without diabetes.

		All patients (n=217)	**Patients without diabetes (n=155)**	**Patients with diabetes (n=62)**	***P* value**
Age (years): mean (SD)		78.4 (8.2)	77.9 (8.2)	79.2 (7.1)	0.288
Charlson Comorbidity Index : median (Q1,Q3)		1 (1,3)	1 (0, 2)	3 (2, 5)	**<0.001**
Gender: n (%)	**Female**	126 (58)	90 (58.1)	36 (58.1)	0.996
	Male	91 (52)	65 (41.9)	26 (41.9)	
Serum Osmolality (mOsmol/kg): mean (SD)		284.5 (26.22)	278.9 (21.4)	298.5 (31.4)	**<0.001**
Sodium (mmol/l): mean (SD)		131.3 (9.7)	130.8 (8.9)	132.7 (11.5)	0.194
Potassium (mmol/l): mean (SD)		4.2 (0.8)	4.1 (0.7)	4.5 (0.9)	**<0.001**
Glucose (mmol/l): median (Q1,Q3))		6.6 (5.4, 9.7)	5.9 (5.1, 7.3)	14.1 (8.0, 22.2)	**<0.001**
Urea (mmol/l): median (Q1,Q3)		6.5 (4.6, 9.8)	6 (4.3, 8.5)	7.5 (5.2, 12)	**0.003**
eGFR* : median (Q1,Q3)		72 (52, 90)	78 (60, 90)	54 (38, 83)	**0.001**

***Estimated glomerular filtration rate.** Comparison of cohort demographic and serum biochemistry, comparing patients with and without diabetes.*

7.6.2 Mean of the difference between osmolality and osmolarity

The mean (95% CI) of the difference between serum osmolality and the calculated osmolarity using the equations was consistently and significantly greater in equations that did not account for blood glucose concentration (Tables 27a to 27e). All the equations within a clinically acceptable overall deviation from the measured value (<2 mmol/l) included glucose and urea concentrations. The lowest overall mean (95% CI) of the difference was observed with equation 33 (Bianchi *et al.,* 2009), 0.2 (-0.7 to 1.2) mmol/l. When stratified by diabetes status, the mean (95% CI) of the difference was greater in patients with diabetes. However, equation 32 (Khajuria and Krahn, 2005) demonstrated the greatest overall consistency and when stratified by diabetes, with an overall mean (95% CI) of the difference of -1.1 (-2.0 to -0.1) mmol/l, -1.0 (-1.8 to -0.1) mmol/l in patients with diabetes and -1.1 (-2.0 to -0.1) mmol/l in patients without diabetes.

Using the two most accurate equations 32 (Khajuria and Krahn, 2005) and 33 (Bianchi *et al.,* 2009), glucose was replaced with the median population glucose concentration, 8.5 mmol/l for patients with diabetes and 6.4 mmol/l for patients without diabetes (equations 32^{a} and 33^{a} respectively). The lowest mean (95% CI) of the difference was -0.1 (-1.4 to 1.1) mmol/l, seen in patients without diabetes using equation 33^{a} and increased in patients with diabetes to 11.3 (9.3 to 13.3) mmol/l. Equation 32^{a} demonstrated similar results in patients with diabetes -0.8 (-2.8 to -2.0) mmol/l and in patients without diabetes 9.8 (7.8 to 17.6) mmol/l.

Table 257a: Mean (95% CI) of the difference between measured serum osmolality and calculated osmolarity using published equations, mmol/l.

Equation no.	Equation description	All patients (n=217)	Patients without diabetes (n=155)	Patients with diabetes (n=62)
Equation 1	$1.75 \times Na^+ + glucose + 0.5 \times urea + 10.1$	30.7 (29.5 to 31.8)	29.5 (28.3 to 30.6)	33.5 (32.3 to 34.6)
Equation 2	$2.63 \times Na^+ - 65.4$	4.6 (2.5 to 6.7)	0.4 (-1.1 to 1.9)	15.0 (12.2 to 17.7)
Equation 3	$1.86 \times Na^+ + glucose + 0.5 \times urea$	26.3 (25.1 to 27.4)	25.3 (24.1 to 26.4)	29.0 (27.9 to 30.0)
Equation 4	$2 \times (Na^+ + K^+) + glucose + 0.5 \times urea$	-0.5 (-1.5 to 0.6)	-1.2 (-2.2 to -0.1)	1.4 (0.4 to 2.4)
Equation 5	$2 \times Na^+$	21.9 (19.8 to 23.9)	17.3 (15.9 to 18.7)	33.2 (30.5 to 35.8)
Equation 6	$2 \times Na^+ + glucose + 0.5 \times urea$	7.9 (6.8 to 9.0)	7.0 (5.9 to 8.1)	10.4 (9.34 to 11.4)
Equation 7	$2 \times Na^+ + 7$	14.9 (12.8 to 16.9)	10.3 (8.9 to 11.7)	26.2 (23.5 to 28.8)
Equation 8	$2 \times Na^+ + 10$	11.9 (9.8 to 13.9)	7.3 (5.9 to 8.7)	23.2 (20.5 to 25.8)

Table 27b: Mean (95% CI) of the difference between measured serum osmolality and calculated osmolarity using published equations, mmol/l.

Equation no.	Equation description	All patients (n=217)	Patients without diabetes (n=155)	Patients with diabetes (n=62)
Equation 9	$2 \times Na^+ + glucose$	12.1 (10.7 to 13.4)	10.7 (9.4 to 12.0)	15.3 (13.9 to 16.6)
Equation 10	$2.1 \times Na^+$	8.7 (6.63 to 10.7)	4.3 (2.9 to 5.7)	19.9 (17.2 to 22.5)
Equation 11	$2 \times Na^+ + glucose + 0.93 \times 0.5 \times urea$	8.2 (7.1 to 9.3)	7.2 (6.1 to 8.3)	10.8 (9.7 to 11.8)
Equation 12	$(2 \times (Na^+ + K^+) + glucose + 0.5 \times urea) \times 0.985$	3.8 (2.7 to 4.9)	3.0 (1.9 to 4.1)	5.8 (4.8 to 6.8)
Equation 13	$1.86 \times Na^+ + glucose + 0.5 \times urea + 5$	25.8 (24.6 to 26.9)	24.8 (23.6 to 25.9)	28.5 (27.4 to 29.5)
Equation 14	$2 \times Na^+ + 0.9 \times glucose + 0.93 \times urea \times 0.5$	9.2 (8.05 to 10.3)	7.9 (6.8 to 9.0)	12.7 (11.5 to 13.8)
Equation 15	$2 \times Na^+ + 0.5 \times urea$	17.8 (15.9 to 19.6)	13.6 (12.4 to 14.8)	28.3 (25.8 to 30.7)
Equation 16	$(1.86 \times Na^+ + glucose + 0.5 \times urea)/0.93$	6.9 (5.8 to 8.0)	6.2 (5.1 to 7.3)	8.7 (7.7 to 9.7)

Table 27c: Mean (95% CI) of the difference between measured serum osmolality and calculated osmolarity using published equations, mmol/l.

Equation no.	Equation description	All patients (n=217)	Patients without diabetes (n=155)	Patients with diabetes (n=62)
Equation 17	$1.9 \times (Na^+ + K^+) + glucose + 0.5 \times urea$	13.1 (12.0 to 14.1)	12.3 (11.2 to 13.4)	15.1 (14.0 to 16.1)
Equation 18	$1.85 \times Na^+ + glucose + 0.5 \times urea + 8.55$	19.1 (17.9 to 20.2)	18 (16.8 to 19.1)	21.8 (20.7 to 22.8)
Equation 19	$1.86 \times Na^+ + glucose + 0.5 \times urea + 9$	17.3 (16.1 to 18.4)	16.3 (15.1 to 17.4)	20.0 (18.9 to 21.0)
Equation 20	$1.86 \times Na^+ + glucose + urea + 9$	13.2 (12.2 to 14.1)	12.5 (11.5 to 13.5)	15.1 (14.2 to 15.9)
Equation 21	$2 \times (Na^+ + K^+) + glucose + 0.93 \times 0.5 \times urea$	-0.2 (-1.2 to 0.9)	-1.0 (-2.0 to 0.1)	1.7 (0.7 to 2.7)
Equation 22	$1.89 \times Na^+ + 1.38 \times K^+ + 1.08 \times glucose + 1.03 \times urea + 7.47$	4.0 (3.1 to 5.0)	3.7 (2.7 to 4.7)	4.7 (3.9 to 5.5)
Equation 23	$1.86 \times (Na^+ + K^+) + glucose + urea + 10$	4.4 (3.4 to 5.4)	3.9 (2.9 to 4.9)	5.7 (4.8 to 6.6)

Table 27d: Mean (95% CI) of the difference between measured serum osmolality and calculated osmolarity using published equations, mmol/l.

Equation no.	Equation description	All patients (n=217)	Patients without diabetes (n=155)	Patients with diabetes (n=62)
Equation 24	$2 \times Na^+ + 0.9 \times glucose + 0.93 \times 0.5 \times urea + 8$	1.2 (0.1 to 2.3)	-0.1 (-1.2 to 1.0)	4.6 (3.4 to 5.8)
Equation 25	$1.86 \times Na^+ + 1.03 \times glucose + 1.28 \times 0.5 \times urea$	24.9 (23.8 to 25.9)	24.0 (22.9 to 25.1)	27.1 (26.1 to 28.0)
Equation 25a,	$(1.86 \times Na^+ + 1.03 \times glucose + 1.28 \times 0.5 \times urea) \times 0.985$	28.8 (27.7 to 29.8)	27.8 (26.7 to 28.9)	31.2 (30.1 to 32.2)
Equation 26	$1.36 \times Na^+ + 1.6 \times glucose + 0.45 \times urea + 91.75$	-5.3 (-6.7 to -3.8)	-4.7 (-6.0 to -3.3)	-6.6 (-8.0 to -5.1)
Equation 27	$2 \times Na^+ + glucose + urea + 35.2$	-31.4 (-32. to -30.)	-32 (-32. to -31.0)	-29.7 (-30.9 to -28.3)
Equation 27a	$(2 \times Na^+ + glucose + urea + 35.2) \times 0.985$	-26.6 (-27.2 to -25.3)	-27.4 (-28.0 to -26.4)	-24.7 (-25.0 to -23.0)
Equation 28	$1.897 \times Na^+ + glucose + urea \times 0.5 + 13.5$	8.0 (6.9 to 9.1)	6.9 (5.8 to 8.0)	10.6 (9.5 to 11.6)

Table 27e: Mean (95% CI) of the difference between measured serum osmolality and calculated osmolarity using published equations, mmol/l.

Equation no.	Equation description	All patients (n=217)	Patients without diabetes (n=155)	Patients with diabetes (n=62)
Equation 29	$1.9 \times (Na^+ + K^+) + glucose + urea \times 0.5 + 5$	8.1 (7.0 to 9.2)	7.3 (6.2 to 8.4)	10.1 (9.1 to 11.1)
Equation 30	$1.86 \times (Na^+ + K^+) + glucose + urea$	14.4 (13.4 to 15.3)	13.9 (12.9 to 14.9)	15.7 (14.8 to 16.5)
Equation 31	$2 \times Na^+ + 1.15 \times glucose + urea$	2.4 (1.5 to 3.3)	2.2 (1.2 to 3.2)	2.9 (2.1 to 3.7)
Equation 32	$1.86 \times (Na^+ + K^+) + 1.15 \times glucose + urea + 14$	-1.1 (-2.0 to -0.1)	-1.1 (-2.0 to -0.1)	-1.0 (-1.8 to -0.1)
Equation 33	$1.09 \times 1.86 \times Na^+ + glucose + urea$	0.2 (-0.7 to 1.2)	-0.4 (-1.3 to 0.6)	1.9 (1.02 to 2.8)

List and description of equations used in the study, with mean (95% CI) of the difference between measured serum osmolality and calculated osmolarity in all study patients and stratified by diabetes status. This data shows that the mean (95% CI) of the difference between serum osmolality and the calculated osmolarity using the equations was consistently and significantly greater in equations that did not account for blood glucose concentration. Moreover, increase accuracy was seen in patients without diabetes.

7.6.3 Bland-Altman analysis

Equations that demonstrated an overall mean of the difference of <2 mmol/l and maintained this after stratification by diabetes status, were further analysed for agreement using Bland-Altman methods (Dewitte *et al.,* 2002, Connelly, 2008). These were equations 4 (Gerich *et al.,* 1971, Jackson and Forman, 1966), 21 (Jenkins and Larmore, 1974), 32 (Khajuria and Krahn, 2005) and 33 (Bianchi *et al.,* 2009) (Tables 27a to 27e). Equation 32 (Khajuria and Krahn, 2005) and 33 (Bianchi *et al.,* 2009) demonstrated greatest agreement and consistency when stratified by diabetes status (Figure 20). This trend was also seen for equations 32^{a} and 33^{a} but only in the cohort without diabetes (Figure 21).

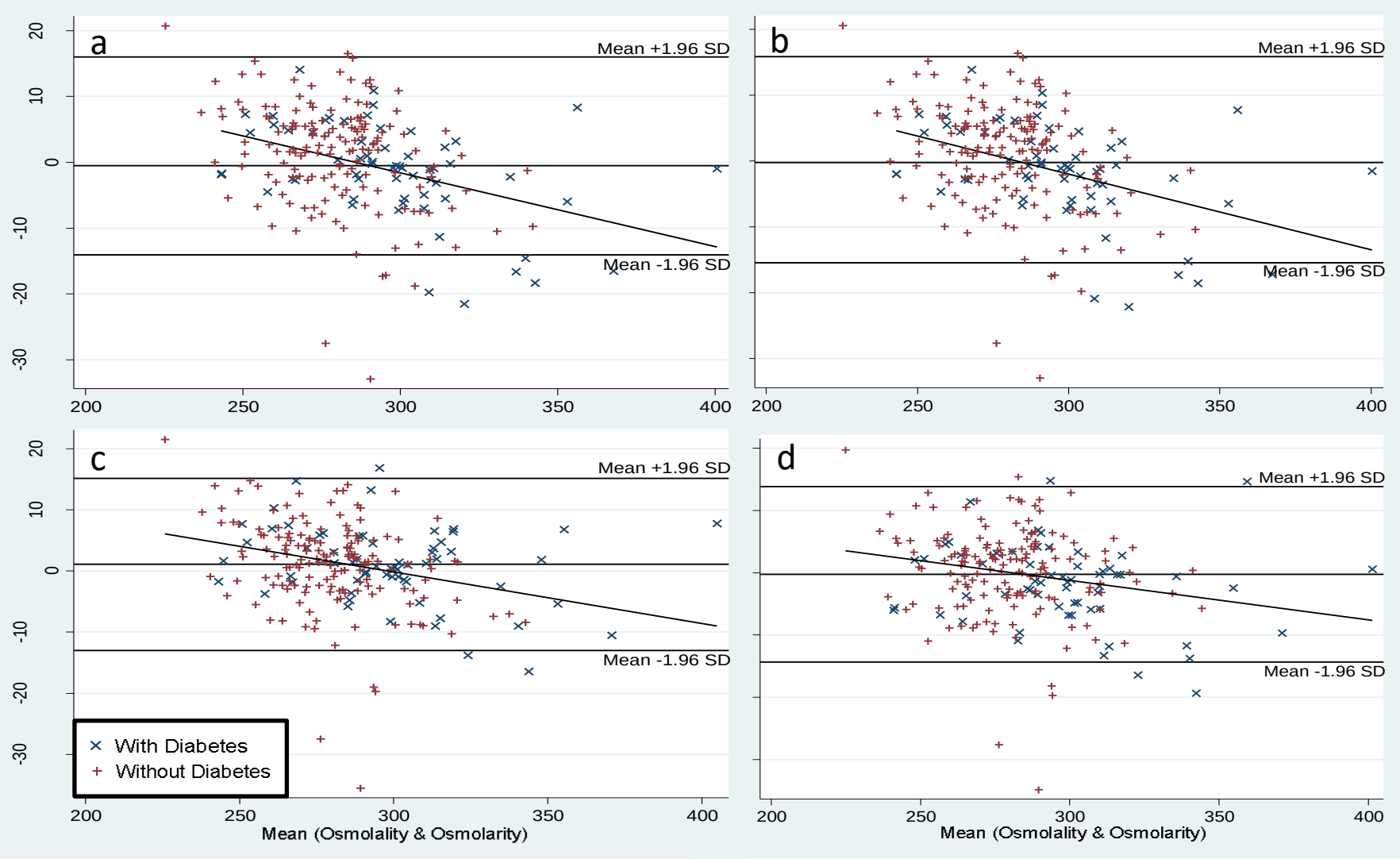

a
b
c
d
Mean +1.96 SD
Mean -1.96 SD
20
10
0
-10
-20
-30
200
250
300
350
400
With Diabetes
Without Diabetes
Mean (Osmolality & Osmolarity)

Figure 20 (above): Bland-Altman plots demonstrating the relationship between measured serum osmolality and calculated osmolarity for equations with the lowest and most consistent mean of difference between osmolality and osmolarity. Regression coefficient and R^2 for these plots are listed below.

	Whole cohort		Without Diabetes		With Diabetes	
	R^2	Regress coefficient (95% CI)	R^2	Regress coefficient (95% CI)	R^2	Regress coefficient (95% CI)
Equation 4 (a)	0.15	-1.20 (-1.58 to -0.82)	0.11	-0.83 (-1.19 to -0.46)	0.19	-1.82 (-2.74 to -0.89)
Equation 21 (b)	0.16	-1.207 (-1.19 to -0.47)	0.20	-0.83 (-1.19 to -0.47)	0.20	-1.81 (-2.72 to -0.90)
Equation 32 (c)	0.08	-1.01 (-1.46 to -0.57)	0.12	-0.913 (-1.31 to -0.52)	0.06	-1.23 (-2.54 to -0.14)
Equation 33 (d)	0.05	-0.775 (-1.23 to -0.32)	0.03	-0.513 (-0.95 to -0.08)	0.03	-0.94 (-2.10 to 0.23)

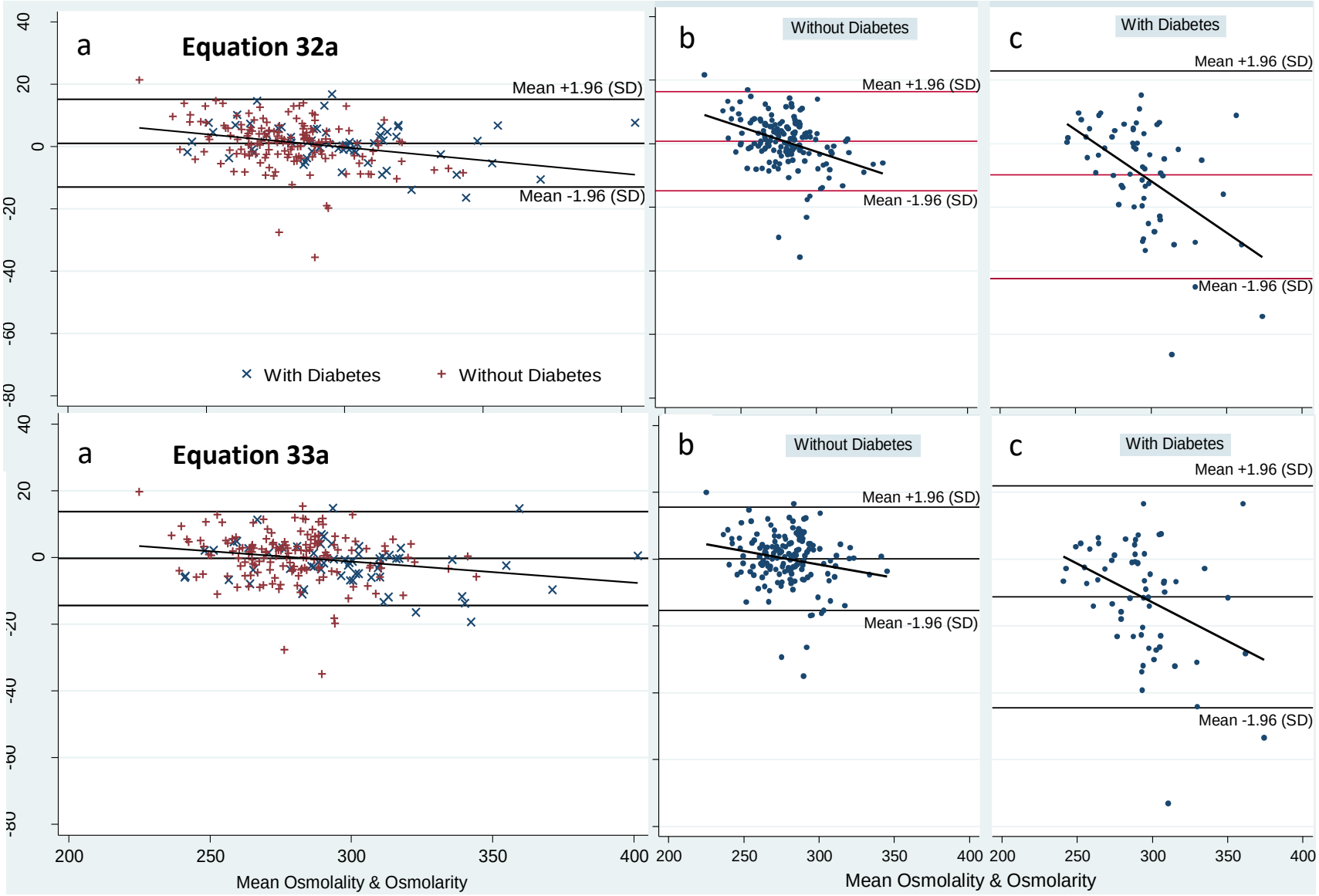

a
Equation 32a
Mean +1.96 (SD)
Mean -1.96 (SD)
With Diabetes
Without Diabetes
b
Without Diabetes
Mean +1.96 (SD)
Mean -1.96 (SD)
c
With Diabetes
Mean +1.96 (SD)
Mean -1.96 (SD)
a
Equation 33a
Mean +1.96 (SD)
Mean -1.96 (SD)
b
Without Diabetes
Mean +1.96 (SD)
Mean -1.96 (SD)
c
With Diabetes
Mean +1.96 (SD)
Mean -1.96 (SD)
40
20
0
-20
-40
-60
-80
200
250
300
350
400
Mean Osmolality & Osmolarity
Mean Osmolality & Osmolarity

Figure 21: (above): Bland-Altman plots demonstrating the relationship between measured serum osmolality and calculated osmolarity for equations with the lowest and most consistent mean of difference between osmolality and osmolarity. Regression coefficient and R^2 for these plots are listed below.

	Whole cohort (a)		**Without Diabetes (b)**		**With Diabetes (c)**	
	R^2	Regress coefficient (95% CI)	R^2	Regress coefficient (95% CI)	R^2	Regress coefficient (95% CI)
Equation 32[a]	0.25	-0.93 (-1.16 to -0.72)	0.12	-0.95 (-1.31 to -0.58)	0.25	-0.81 (-1.16 to -0.46)
Equation 33[a]	0.13	-0.69 (-0.93 to -0.45)	0.04	-0.53 (-0.93 to -0.13)	0.13	-0.60 (-0.99 to -0.22)

Equation 32[a] and 33[a] indicate glucose replaced with median population glucose of 8.5 mmol/l for patients with and mean population glucose of 6.4 mmol/l in patients without diabetes.

7.6.4 Diagnostic accuracy

Equations 32 (Khajuria and Krahn, 2005) and 33 (Bianchi *et al.,* 2009) demonstrated the greatest consistency and accuracy at diagnosing HD (Table 30). Overall, equation 32 had the greatest diagnostic accuracy at 300 mmol/l; with a sensitivity (95% CI) of 90% (86% to 94%) and specificity (95% CI) of 97.0% (95% to 99%) and positive and negative likelihood ratios of 30 and 0.1, respectively. Equation 32[a] demonstrated sensitivity (95% CI) of 80% (74% to 86%) and specificity of 95% (92% to 98%) at 297 mmol/l in patients without diabetes (Table 28).

7.6.5 Comparison with other published data

The absolute difference between measured and calculated osmolality in the present study was compared with those previously published by Siervo *et al.,* 2014 and Fazekas *et al.,* 2013 (Tables 29a to 29h). The present study demonstrates that equations 32 and 33 were likely the most accurate/consistent equations. The mean of the difference (95% CI) for equations 32 was -1.1 (-2.0 to -0.1) mmol/l and 0.2 (-0.7 to 1.2) mmol/l for equations 33. Siervo *et al.,* 2014 demonstrated comparable results with a mean (95% CI) of the difference of -0.4 (-1.0 to 0.2) mOsmol/kg for equation 32 and -0.5 (-1.1 to 0.1) mOsmol/kg for equation 33. However, the findings of Fazekas *et al.,* 2013 differed significantly, with a mean of the difference (95% CI) of -7.3 (-15.2 to 0.6) mOsmol/kg for equation 32 and -8.7 (-17.0 to -0.3) mOsmol/kg for equation 33.

Table 28: Sensitivity and specificity of equations at diagnosing hyperosmolar dehydration, serum osmolality >300 mOsmol/kg

	Whole cohort			Without diabetes			With diabetes		
Equation no.	**Osmolarity (mmol/l)**	**Sensitivity (95 % CI): %**	**Specificity (95 % CI): %**	**Osmolarity (mmol/l)**	**Sensitivity (95 % CI): %**	**Specificity (95 % CI): %**	**Osmolarity (mmol/l)**	**Sensitivity (95 % CI): %**	**Specificity (95 % CI): %**
4	295	83 (78 to 88)	94 (91 to 97)	295	83 (77 to 89)	94 (91 to 97)	297	96 (92 to 100)	91 (87 to 95)
21	297	88 (84 to 92)	96 (94 to 99)	294	83 (77 to 89)	92 (89 to 96)	297	96 (92 to 100)	94 (91 to 97)
32	300	90 (86 to 94)	97 (95 to 99)	296	87 (82 to 92)	97 (95 to 99)	301	96 (92 to 100)	97 (95 to 99)
33	297	88 (84 to 92)	95 (92 to 98)	301	83 (77 to 89)	99 (97 to 100)	299	93 (87 to 99)	97 (95 to 99)
32a	297	69 (63 to 75)	94 (91 to 97)	297	80 (74 to 86)	95 (92 to 98)	297	59 (47 to 71)	93 (89 to 96)
33a	296	66 (59 to 72)	92 (88 to 96)	299	70 (63 to 77)	95 (92 to 98)	294	62 (50 to 74)	91 (87 to 95)

Table 29a: Previously published work comparing the mean of the difference between measured serum osmolality and calculated osmolarity.

	Fazekas *et al, 2013*		Siervo *et al, 2014*[+]					
	All the cohort		All the cohort		Without diabetes		With diabetes	
Equations	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI) mmol/l**	**Absolute difference: mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***
1	23.1 (12.8 to 33.5)	7.6	30.9 (30.3 to 31.5)	0.2	30.6 (23. to 31.3)	1.1	32.3 (31.6 to 33.0)	1.2
2	-15.1 (-30.5 to 0.2)	10.4	-4.0 (-5.0 to -3.0)	0.6	−5.6 (-3.2 to -0.8))	5.2	3.0 (1.9 to 4.1)	12
3	17.7 (7.3 to 28.1)	8.6	25.9 (25.3 to 26.5)	0.4	25.5 (24.9 to 26.1)	0.2	27.5 (26.9 to 28.1)	1.5
4	-9.2 (-19.1 to 0.7)	8.7	-1.7 (-2.1 to -1.1)	1.2	−2.0 (-3.0 to -0.6)	1	-0.2 (-0.8 to 0.4)	1.2
5	7.8 (-6.3 to 21.8)	14.1	17.1 (16.2 to 18.0)	4.8	15.7 (15 to 16.4)	1.6	23.4 (22.4 to 24.4)	9.8

Table 29b: Previously published work comparing the mean of the difference between measured serum osmolality and calculated osmolarity.

	Fazekas *et al, 2013*		Siervo *et al, 2014*[+]					
	All the cohort		All the cohort		Without diabetes		With diabetes	
Equations	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI) mmol/l**	**Absolute difference: mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***
6	-1.4 (-11.3 to 8.4)	6.5	6.7 (6.0 to 7.4)	1.2	6.3 (5.6 to 7.0)	0.7	8.4 (7.8 to 9.0)	2
7	1.1 (-12.5 to 14.8)	13.8	10.1 (9.2 to 11.0)	4.8	8.7 (8.0 to 9.4)	1.6	16.4 (15.4 to 17.4)	9.8
8	-1.7 (-15.4 to 11.9)	10.2	7.1 (6.2 to 8.0)	4.8	5.7 (5.0 to 6.4)	1.6	13.4 (12.4 to 14.4)	9.8
9	1.9 (-11.1 to 14.9)	10.2	10.2 (9.5 to 10.9)	1.9	9.6 (8.9 to 10.3)	1.1	12.6 (11.9 to 13.3)	2.7
10	-5.7 (-19.5 to 8.2)	3	3.3 (2.4 to 4.2)	5.4	2.0 (1.3 to 2.7)	2.3	9.8 (8.8 to 10.8)	10.1

Table 29c: Previously published work comparing the mean of the difference between measured serum osmolality and calculated osmolarity.

	Fazekas *et al, 2013*		Siervo *et al, 2014*[+]					
	All the cohort		All the cohort		Without diabetes		With diabetes	
Equations	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI) mmol/l**	**Absolute difference : mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***
11	-1.2 (-11.2 to 8.9)	7	6.9 (6.2 to 7.6)	1.3	6.5 (5.8 to 7.2)	0.7	8.7 (8.1 to 9.3)	2.1
12	-4.8 (-14.4 to 4.8)	1	-2.6 (-3.2 to -2.0)	1.2	−2.3 (-3.5 to -1.1)	0.7	-4.3 (-4.9 to -3.7)	1.5
13	12.7 (2.3 to 23.0)	13.1	20.9 (20.3 to 21.5)	4.9	20.5 (19.9 to 21.1)	4.3	22.5 (21.9 to 23.1)	6.0
14	-0.6 (-10.6 to 9.4)	8.6	7.6 (6.9 to 8.3)	1.6	7.1 (6.4 to 7.8)	0.8	9.8 (9.2 to 10.4)	2.9
15	4.3 (-6.6 to 15.1)	13.5	13.6 (12.8 to 14.4)	4.2	12.4 (11.7 to 13.1)	1.2	19.3 (18.4 to 20.2)	9.0

Table 29d: Previously published work comparing the mean of the difference between measured serum osmolality and calculated osmolarity.

	Fazekas *et al, 2013*		Siervo *et al, 2014*[+]					
	All the cohort		All the cohort		Without diabetes		With diabetes	
Equations	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI) mmol/l**	**Absolute difference : mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***
16	-2.2 (-11.8 to 7.4)	4.7	5.9 (5.3 to 6.5)	1	5.6 (5.0 to 6.2)	0.6	7.3 (6.7 to 7.9)	1.4
17	4.5 (-5.1 to 14.2)	8.6	12.4 (11.8 to 13.0)	0.7	12.0 (11.4 to 12.6)	0.3	13.9 (13.3 to 14.5)	1.2
18	7.7 (-2.5 to 18.0)	11.4	18.7 (18.1 to 19.3)	0.4	18.4 (17.7 to 19.0)	0.4	20.3 (19.7 to 20.9)	1.5
19	8.7 (-1.5 to 19.0)	8.6	16.9 (16.3 to 17.5)	0.4	16.5 (15.9 to 17.1)	0.2	18.5 (17.9 to 19.1)	1.5
20	5.2 (-3.0 to 13.5)	8	13.4 (12.8 to 14.0)	0.2	13.2 (12.6 to 13.8)	0.7	14.3 (13.8 to 14.8)	0.8

Table 29e: Previously published work comparing the mean of the difference between measured serum osmolality and calculated osmolarity.

	Fazekas *et al, 2013*		Siervo *et al, 2014*[+]					
	All the cohort		All the cohort		Without diabetes		With diabetes	
Equations	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI) mmol/l**	**Absolute difference : mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***
21	-9.0 (-19.0 to 1.1)	8.8	-1.4 (-2.0 to -0.8)	1.2	−1.8 (-3.0 to -0.6)	0.8	0.1 (-0.5 to 0.7)	1.6
22	-3.1 (-10.8 to 4.7)	0.9	4.2 (3.6 to 4.8)	0.2	4.1 (3.5 to 4.7)	0.4	4.7 (4.2 to 5.2)	0.0
23	-2.5 (-10.2 to 5.1)	1.9	4.5 (4.0 to 5.1)	0.1	4.4 (3.8 to 5.0)	0.5	5.3 (4.8 to 5.8)	0.4
24	-8.3 (-18.8 to 2.2)	7.1	-0.4 (-1.1 to 0.3)	0.8	–0.8 (-2.1 to -0.6)	0.8	1.8 (1.2 to 2.4)	2.8
25	22.0 (12.3 to 31.7)	2.9	24.7 (24.1 to 25.3)	0.2	24.5 (23.9 to 25.1)	0.5	26 (25.4 to 26.6)	1.1

Table 29f: Previously published work comparing the mean of the difference between measured serum osmolality and calculated osmolarity.

	Fazekas *et al, 2013*		**Siervo *et al, 2014*[+]**					
	All the cohort		**All the cohort**		**Without diabetes**		**With diabetes**	
Equations	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI) mmol/l**	**Absolute difference: mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***
25a	-	-	28.7 (28.1 to 29.3)	0.1	28.4 (27.7 to 29.)	0.6	30 (29.4 to 30.6)	1.2
26	-5.8 (-16.6 to 5.0)	0.5	-0.9 (-1.6 to -0.2)	4.4	–0.5 (-2.0 to -1.0)	3.5	-2.5 (-3.3 to -1.7)	4.1
27	-34.9 (-43.5 to -26.3)	2.6	-32 (-32.6 to -31.3)	0.6	−32.2 (-33.9 to -31.0)	0.2	-31 (-31.5 to -30.4)	2.0
27a	-	26	-27.1 (-27.6 to -26.5)	1.1	−27.3 (-28.5 to -26.1)	0.3	-26.1 (-26.6 to -25.5)	2.0
28	-0.4 (-10.1 to 9.2)	7.6	7.3 (6.7 to 7.9)	0.7	6.9 (6.3 to 7.5)	0	8.9 (8.3 to 9.5)	1.7

Table 29g: Previously published work comparing the mean of the difference between measured serum osmolality and calculated osmolarity.

	Fazekas *et al, 2013*		Siervo *et al, 2014*[+]					
	All the cohort		All the cohort		Without diabetes		With diabetes	
Equations	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI) mmol/l**	**Absolute difference: mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***
29	-0.1 (-9.4 to 9.3)	8	7.4 (6.8 to 8.0)	0.7	7 (6.4 to 7.6)	0.3	8.9 (8.3 to 9.5)	1.2
30	6.7 (-1.6 to 15.0)	7.7	14.5 (13.9 to 15.1)	0.1	14.4 (13.8 to 15)	0.5	15.3 (14.8 to 15.8)	0.4
31	-5.8 (-14.0 to 2.5)	3.4	2.1 (1.5 to 2.7)	0.3	2.0 (1.4 to 2.6)	0.2	2.6 (2.0 to 3.2)	0.3
32	-7.3 (-15.2 to 0.6)	6.2	-0.4 (-1.0 to 0.2)	0.7	–0.4 (-1.5 to 0.7)	0.6	-0.3 (-0.8 to 0.2)	0.7

Table 29h: Previously published work comparing the mean of the difference between measured serum osmolality and calculated osmolarity.

	Fazekas *et al, 2013*		Siervo *et al, 2014*[+]					
	All the cohort		All the cohort		Without diabetes		With diabetes	
Equations	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***	**Mean of difference (95% CI) mmol/l**	**Absolute difference: mmol/l***	**Mean of difference (95% CI): mmol/l**	**Absolute difference mmol/l***
33	-8.7 (-17.0 to -0.3)	8.5	-0.5 (-1.1 to 0.1)	0.3	–0.8 (-2.0 to 0.4)	1.1	0.5 (-0.1 to 1.1)	1.2

*Data published by Fazekas et al., 2013 and Siervo et al., 2014.*Absolute difference between means of the difference published by Fazekas et al., 2013 and Siervo et al., 2014 subtracted from the mean of the difference between osmolality and osmolarity from the present study. [+]The online supplementary table published by Siervo et al., 2014 containing mean of the difference and SD was used. SD was converted to 95% CI using the following equation [95% CI = mean ± 1.96 x SE], [SE = SD ÷ √n].*

The present study demonstrates that equations 32 (Khajuria and Krahn, 2005) and 33 (Bianchi et al., 2009) were likely the most accurate/consistent equations.

7.7 Discussion

This study investigated the accuracy of previously published equations at calculating serum osmolarity in hospitalised older adults and has shown that the equation 33 (Bianchi *et al.,* 2009) was the most accurate when considering the overall mean of the difference (95% CI) between measured and calculated serum osmolality. However, the mean of the difference (95% CI) increased after stratification by diabetes status. Equation 32 (Khajuria and Krahn, 2005) had a greater overall mean of the difference that is within acceptable limits and showed little change after stratification for diabetes status. Moreover, equation 32 demonstrated the greatest diagnostic accuracy at predicting HD with over 90% sensitivity and 97% specificity at 300 mmol/l. This equation (Khajuria and Krahn, 2005) also demonstrated greatest diagnostic accuracy after stratification for diabetes status.

The findings of the present study are consistent with work published by Siervo *et al.,* 2014 who investigated the difference between measured serum osmolality and calculated osmolarity in community-dwelling older adults. The authors reported that equations 32 and 33 were associated with the lowest overall mean (SD) of the difference between osmolality and osmolarity. Moreover, the absolute difference between findings reported in the present study and those reported by Siervo *et al.,* 2014 were constantly low for most equations. Furthermore, Siervo *et al.,* 2014 reported similar diagnostic accuracy using this equation, with sensitivity of 97% with 76% specificity at 296 mmol/l. However, Fazekas *et al.,* 2013, reported greater mean of the

difference between measured osmolality and osmolarity calculated using equation 32 (Khajuria and Krahn, 2005). Although, it is important to note that the study by (Fazekas *et al.,* 2013) used serum samples from a relatively younger adult population (mean age 58).

The use of these equations is dependent on the availability of serum biochemistry including serum glucose measurements which are not always routinely performed. This study showed that equation 32^{a} maintained excellent levels of sensitivity (87%) and specificity (95%) at 297 mmol/l at diagnosing HD. These findings may be useful in clinical or research settings to assess and monitor changes in hydration status where serum glucose measurements are not available. This high level of sensitivity and specificity with equation 33^{a} is likely due to the tight regulation of serum glucose in non-diabetic patients. However, in patients with diabetes glycaemic control is less predictable where rapid increase in serum glucose concentrations occur in the post prandial period or as a result of ill health due to physiological stress. In these patients where formal laboratory glucose testing is unavailable, bedside glucose tests may prove a useful alternative if performed close to the time of blood sampling for biochemistry. Various reports have demonstrated excellent sensitivity and specificity of modern bedside glucose testing kits which are readily available and routinely used (Bala Raghavendra and Bhat, 2010). Therefore it may be feasible to use this result as an alternative to formal laboratory serum glucose testing. However, the present study did not test this hypothesis.

Knowing serum osmolality may be useful in the clinical setting to aid the assessment and diagnosis of dehydration. It is important to note however, that the present study did not investigate the clinical applicability of osmolality, further work is required to clarify this.

7.8 Conclusion

The findings reported in the present study together with previous work published by Siervo *et al.,* 2014 support the use of equation 32 (Khajuria and Krahn, 2005) as an alternative to serum osmolality, and may be used to screen and monitor hydration status in hospitalised older adults where serum osmolality is unavailable.

8. Hyperosmolar dehydration as a predictor of kidney injury and outcome in hospitalised older adults

8.1 Introduction

Increased age is associated with diminished physiological reserve and can result in physical as well as functional decline. Age-related pathophysiological changes (El-Sharkawy *et al.,* 2014) make the older adult increasingly vulnerable to fluid and electrolyte disturbance, particularly during periods of ill health or physiological stress.

Serum osmolality is the key regulated variable in fluid balance. Cheuvront *et al.,* 2010 demonstrated that serum osmolality of 297 mOsmol/kg had 90% sensitivity and 100% specificity in young adults dehydrated in a hot environment to between 2% and 7% of TBW. An additional benefit of serum osmolality is that it can be used to assess hydration status at a set point as well as to monitor hydration over time at any given time interval.

HD was reported in 37% of older adults at admission to hospital and was associated with a six-fold increase in mortality (El-Sharkawy *et al.,* 2015a). (Chapter 5) However, in Chapter 6, a review of 32,980 older adult hospital admissions demonstrated that 0.6% of patients had clinically reported dehydration as the primary cause of admission and 8.9% as a secondary diagnosis, associated with a 2.2 fold increase in mortality. However, it is unclear which of these findings represent a true reflection of the prevalence and impact on outcome. Both studies also reported higher prevalence of AKI associated with dehydration. However, the studies did not clarify whether AKI was a cause or effect of dehydration.

Serum osmolality, widely seen as the most reliable objective measure of hydration status (Bhalla *et al.,* 2000, Sollanek *et al.,* 2011, Cheuvront *et al.,* 2013, Cheuvront *et al.,* 2010, Stookey *et al.,* 2005) is not routinely measured in clinical practice. However, equations have been developed to estimate osmolality using routinely measured biochemistry including sodium, potassium, urea and glucose (Fazekas *et al.,* 2013, Siervo *et al.,* 2014). Some of these equations have been shown to be accurate enough to be used as a surrogate marker of serum osmolality (Chapter 7) (Fazekas *et al.,* 2013, Siervo *et al.,* 2014).

This study aimed to use the admission records from a large UK university teaching hospitals National Health Service (NHS) trust to estimate the prevalence of HD using the equation by Khajuria and Krahn, 2005 and to assess the impact on AKI, LOS and mortality in hospitalised older adults.

8.2 Hypothesis

We hypothesised that the prevalence of HD would be higher than previously reported clinical dehydration (Chapter 6) and similar to that reported in Chapter 5. Dehydration would be associated with increased LOS and increased risk of AKI and mortality.

8.3 Methodology

This retrospective cohort study in adult patients aged ≥ 65 years was conducted using data from a large UK university teaching hospitals NHS trust.

Details of the data selection methods, data validation and analysis are outlined in Chapter 3.

8.3.1 Osmolality estimate and outcome

Laboratory glucose measurements are not routinely performed on hospitalised patients as most patients undergo bedside "finger prick" glucose measurements. To investigate the effects of HD on a wider population of hospitalised older adults osmolarity was estimated using a constant value instead of serum glucose in Krah & Khajuria's equation for patients without diabetes. The constant value was derived from mean population values given that serum glucose is tightly regulated in patients without diabetes. All patients with serum glucose measurements were identified (n=23,979). Where multiple measurements were performed on the same patient during admission, the first measurement was selected, with a final sample of 13,673. The cohort was then stratified by diabetes status to measure the mean serum glucose (6.3 mmol/l) in patients without diabetes (n=9,536). The accuracy of this estimation was assessed and the effects on outcome reported in supplementary data. A similar approach was not possible in patients with diabetes due to the wide variation in serum glucose and thus the limited accuracy of this approach. Results from this analysis are listed in Appendix 1.

8.3.2 Inclusion/exclusion criteria

All older adult patients admitted to hospital as a medical emergency were included. Patients admitted with any alcohol related condition including alcohol intoxication were excluded to reduce the risk of artificially high osmolar gap, the difference between measured serum osmolality and calculated osmolarity. Patients admitted with bleeding or those admitted to surgery were also excluded, Figure 22. Patients who did not have measured serum biochemistry required for the equation by Krah and Khajuria, 2005 within 12 hours of admission were also excluded from the primary analysis.

HD was defined as serum osmolarity >300 mOsmol/kg calculated using the equation by Krahn and Khajuria, 2005 [1.86 x (Na + K) + 1.15 x glucose + urea + 14] for patients with relevant serum results, Figure 22 (Siervo *et al.,* 2014). Clinically reported dehydration (ICD-10 code E86.X) indicated severe dehydration or dehydration requiring intravenous fluids.

8.4 Results

8.4.1 Prevalence of dehydration

A total of 6632 patients were admitted between 1st May 2011 and 31st October 2013 who had all the serum parameters required for the equation by Krah & Khajuria at admission to hospital (Figure 22). Patient characteristics are summarised in Table 30.

Table 30: Demographics and characteristics of the study cohort, comparing those with and without hypertonic dehydration.

		All Patients (n=6632)	Euhydrated (n=4830)	Dehydrated# (n=1802)	*P* value*
Age	**65 – 75: n (%)**	2692 (40.6)	2103 (43.5)	589 (32.7)	**<0.001**
	76 - 85: n (%)	2555 (38.5)	1801 (37.3)	754 (41.8)	
	86 - 95: n (%)	1286 (19.4)	865 (17.9)	421 (23.4)	
	>95: n (%)	99 (1.5)	61 (1.3)	38 (2.1)	
Gender	**Female: n (%)**	3469 (52.3)	2596 (53.7)	873 (48.4)	**<0.001**
	Male: n (%)	3163 (47.7)	2234 (46.3)	929 (51.6)	
Charlson Comorbidity Index	**None: n (%)**	1135 (17.1)	910 (18.8)	225 (12.5)	**<0.001**
	Mild: n (%)	3117 (47.0)	2364 (48.9)	753 (41.8)	
	Moderate: n (%)	1265 (19.1)	780 (16.1)	485 (26.9)	
	Severe: n (%)	1115 (16.8)	776 (16.1)	339 (18.8)	
Admission Method	**Emergency Department: n (%)**	2496 (37.6)	1902 (39.4)	594 (33.0)	**<0.001**
	General Practitioner: n (%)	3626 (54.7)	2522 (52.2)	1104 (61.3)	
	Other: n (%)	510 (7.7)	406 (8.4)	104 (5.8)	
National Early Warning Score: Median (Q1, Q3)**		1 (0, 2)	1 (0, 2)	1 (0, 3)	**0.021**

P value comparing patients with and without dehydration. #Dehydration indicates hypertonic dehydration, serum osmolarity >300 mOsmol/l. +Osmolarity calculated using the equation by Krah & Khajuria, 2006 [1.86 x (Na + K) + 1.15 x glucose + urea + 14]. National Early Warning Score available in only 422 patients, 274 were euhydrated and 148 were dehydrated.*

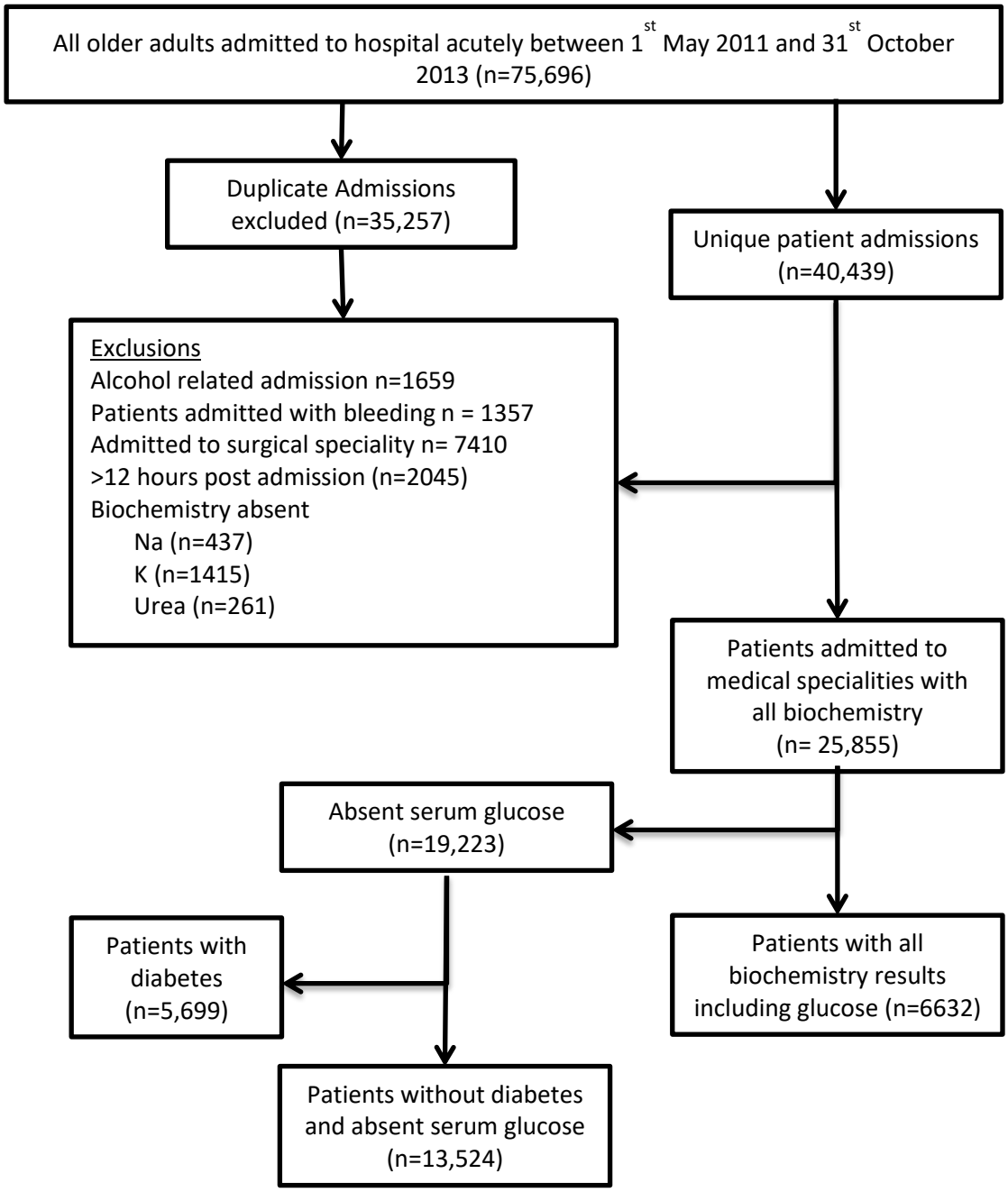
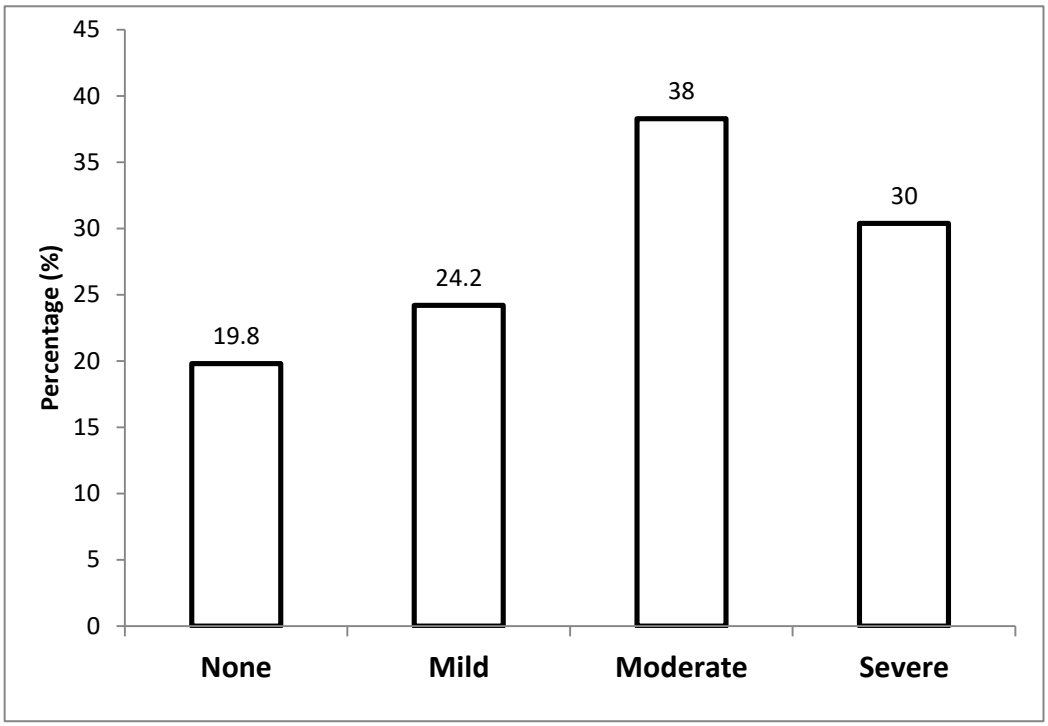


Figure 22: Data selection methods # First admission episode selected If a patient was admitted multiple times over the study period, the first admission where dehydration was diagnosed (ICD-10 code E86.X) was preferentially selected (dehydration as primary cause of admission where preferentially selected over secondary diagnosis of dehydration). If dehydration was not diagnosed during any of the admissions, the first admission was selected.* Dehydrated patient episodes selected over non dehydrated episodes and formal laboratory serum glucose measurement with performed on blood sampled at the same time as that used for other biochemistry analysis.

HD was noted in 1802 (27.2%) patients at admission compared with 676 (10.2%) with clinically reported dehydration. Of the 1802 patients with HD, 313 (17.4%) patients were diagnosed with dehydration by the clinical team compared with 363 (7.5%) patients in the euhydrated group, *P*<0.001. The mean (SD) osmolarity in patients who were clinically and biochemically dehydrated was 319 (22) compared with 308 (12) in those with HD and were not clinically diagnosed, *P*<0.001. The mean (SD) age of dehydrated patients was 79.0 (8.3) compared with 77.6 (8.1) in euhydrated patients. Similarly the median CCI (Q1, Q3) score were comparable between patients with and without hypertonic dehydration, 1 (0, 2) *vs*. 1 (1, 2) respectively. However, stratification by age and CCI revealed that the prevalence of dehydration increased with age and comorbidities, Figure 23. Of the 422 patients that had data allowing a NEWS calculation, 35% of which in the dehydrated group at admission who also had higher median (Q1, Q3) scores compared with the euhydrated group, 1 (0, 3) vs. 1 (0, 2), respectively, *P*=0.021.



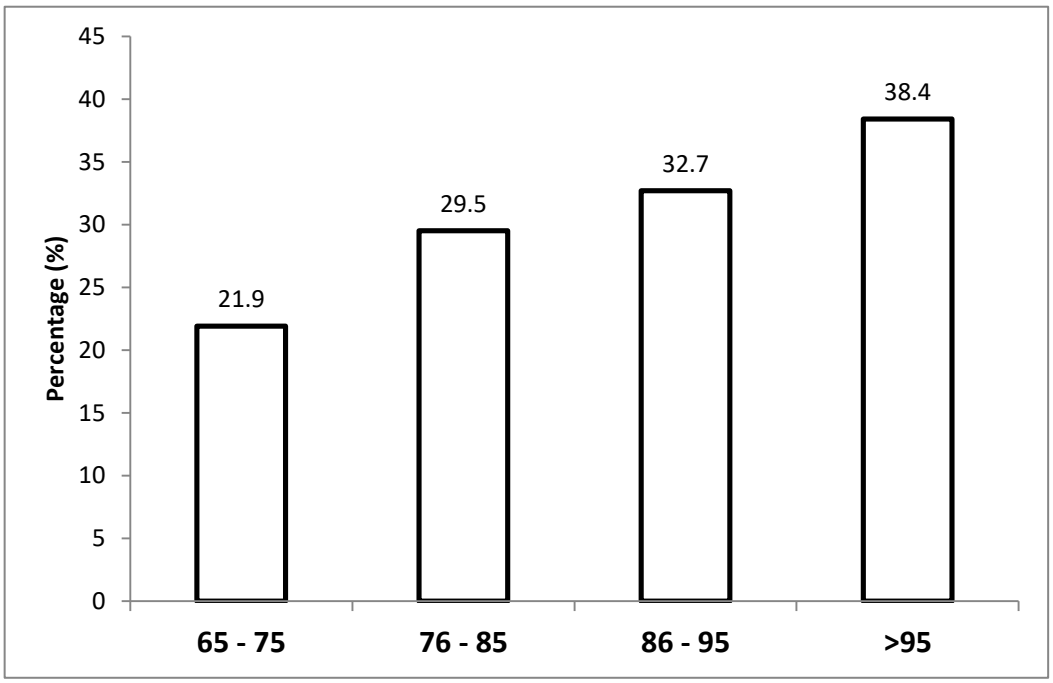


Figure 23: (top) Prevalence of dehydration with Charlson comorbidity index (age unadjusted). 'None' (no comorbidity, 0 points), 'Mild' (mild comorbidity, 1-2 points), 'Moderate' (moderate comorbidity, 3-4 points) and 'Severe' (severe comorbidity, ≥5 points). (bottom): Prevalence of dehydration with increased age.

8.4.2 Dehydration and acute kidney injury

AKI was reported in 710 (39.4%) patients with HD, compared with 818 (16.9%) patients who were biochemically euhydrated, *P*<0.001. Moreover, a greater proportion of those with HD had severe AKI, compared with those without dehydration, AKI stage 2 –160 (8.9) *vs.* 145 (3.0) and AKI stage 3 - 162 (9.0%) *vs.* 63 (1.3%), respectively, *P*<0.001. Patients with HD were at increased risk of developing AKI within 24 hours of admission, independent of age, gender and CCI, HR 4.45 (3.53 to 5.60), *P*<0.001. The risk of AKI was also independently greater 48 and 72 hours post admission in patients with HD compared with euhydrated individuals, Table 31a. Further analysis demonstrated that the risk of AKI associated with HD was also independent of NEWS, Table 31b.

8.4.3 Dehydration and mortality

Mortality rates at all time periods were consistently higher in patents with HD, Table 32a. Kaplan Meier survival plot demonstrates a significant drop in survival post admission in those diagnosed with HD, Figure 24. Cox regression analysis adjusted for age, gender and comorbidity (CCI) demonstrated that patients with HD were at higher risk of mortality 30 days post admission compared with those euhydrated at admission, HR 1.61 (1.36 to 1.89), *P*<0.001. Further analysis revealed that dehydration related 30-day mortality was also independent of NEWS, Table 32b.

Table 31a: Hyperosmolar dehydration and acute kidney injury (AKI) in hospitalised older adults – a) Whole cohort

a- Whole cohort (n=6632)							
AKI (hours from admission)	**Euhydrated (n=4830)**	**Dehydrated* (n=1802)**	***P* value**	**Unadjusted: HR (95% CI)**	***P* value**	**Adjusted[+:] HR (95% CI)**	***P* value**
All AKI	818 (16.9)	710 (39.4)	**<0.001**	-	-	-	-
12 to 24	*119 (2.5)*	*203 (11.3)*	**<0.001**	*4.79 (3.82 to 6.01)*	**<0.001**	*4.45 (3.53 to 5.60)*	**<0.001**
12 to 48	212 (4.4)	266 (14.8)	**<0.001**	3.59 (3.00 to 4.30)	**<0.001**	3.28 (2.73 to 3.94)	**<0.001**
12 to 72	272 (5.6)	303 (16.8)	**<0.001**	3.22 (2.73 to 3.79)	**<0.001**	2.93 (2.48 to 3.46)	**<0.001**

*AKI-Acute kidney injury*Dehydration indicated hyperosmolar dehydration, osmolarity >300mOsmolo/l. [+]Adjusted for age, gender, Charlson Comorbidity Index (CCI). [++]Adjusted for age, gender, CCI and National Early Warning Score (NEWS). HR-Hazard ratio. Patients with dehydration were at increased risk of developing AKI within 24 hours of admission, independent of age, gender and CCI. Patients with dehydration had higher incidence of AKI. Moreover, the risk of AKI was also independently greater 48 and 72 hours post admission in patients with dehydration compared with euhydrated individuals.*

Table 31b: Hyperosmolar dehydration and acute kidney injury (AKI) in hospitalised older adults – b) Whole cohort

b -Patients with National Early Warning Score (n=422)							
AKI (hours from admission)	**Euhydrated (n=274)**	**Dehydrated* (n=148)**	***P* value**	**Unadjusted: HR (95% CI)**	***P* value**	**Adjusted[++]: HR (95% CI)**	***P* value**
All AKI	54 (19.7)	58 (39.2)	**<0.001**	-	-	-	-
12 to 24	*6 (2.2)*	*16 (10.8)*	**<0.001**	*5.13 (2.01 to 13.12)*	**0.001**	*5.15 (1.8 to 14.64)*	**0.002**
12 to 48	15 (5.5)	22 (14.9)	**0.001**	2.90 (1.50 to 5.58)	**0.001**	2.74 (1.32 to 5.70)	**0.007**
12 to 72	22 (8.0)	29 (19.6)	**0.001**	2.64 (1.52 to 4.60)	**0.001**	2.54 (1.38 to 4.64)	**0.003**

*AKI-Acute kidney injury. *Dehydration indicated hyperosmolar dehydration, osmolarity >300mOsmolo/l. [+]Adjusted for age, gender, Charlson Comorbidity Index (CCI). [++]Adjusted for age, gender, CCI and National Early Warning Score (NEWS). HR-Hazard ratio. Patients with dehydration had higher incidence of AKI. Moreover, those with dehydration were at increased risk of developing AKI within 24 hours of admission, independent of age, gender, CCI and NEWS. The risk of AKI was also independently greater 48 and 72 hours post admission in patients with dehydration compared with euhydrated individuals.*

Table 32a: Hyperosmolar status and mortality in hospitalised older adults. a) Whole cohort

a- Whole cohort (n=6632)							
Mortality	**Euhydrated (n=4830)**	**Dehydrated* (n=1802)**	***P* value**	**Unadjusted: HR (95% CI)**	***P* value**	**Adjusted[+:] HR (95% CI)**	***P* value**
In-Hospital	381 (6.4)	231 (12.8)	**<0.001**	2.087 (1.752 to 2.48)	**<0.001**	1.723 (1.44 to 2.06)	**<0.001**
30-day	381 (7.9)	265 (14.7)	**<0.001**	1.929 (1.645 to 2.26)	**<0.001**	1.606 (1.36 to 1.89)	**<0.001**
90-day	679 (14.0)	306 (22.5)	**<0.001**	1.694 (1.50 to 1.92)	**<0.001**	1.404 (1.24 to 1.56)	**<0.001**
One-year	1224 (25.3)	629 (34.9)	**<0.001**	1.494 (1.36 to 1.65)	**<0.001**	1.231 (1.11 to 1.36)	**<0.001**

**Dehydration indicated hyperosmolar dehydration, osmolarity >300mOsmolo/l. [+]Adjusted for age, gender, Charlson Comorbidity Index(CCI) . [++]Adjusted for age, gender, CCI and National Early Warning Score. HR-Hazard ratio. Patients with dehydration had increased mortality rates and had increased risk of death (HR), independent of age, gender and, CCI.*

Table 32b: Hyperosmolar status and mortality in hospitalised older adults. b) Patients with National Early Warning Score

b- Patients with National Early Warning Score (n=422)							
Mortality	**Euhydrated (n=274)**	**Dehydrated* (n=148)**	***P* value**	**Unadjusted: HR (95% CI)**	***P* value**	**Adjusted[++]: HR (95% CI)**	***P* value**
In-Hospital	16 (5.8)	20 (13.5)	**0.007**	2.81 (1.23 to 6.42)	**0.014**	1.817 (0.94 to 3.56)	0.077
30-day	18 (6.6)	22 (14.9)	**0.005**	3.40 (1.62 to 7.14)	**0.001**	1.915 (1.03 to 3.56)	**0.039**
90-day	26 (9.5)	27 (18.2)	**0.009**	4.42 (2.40 to 8.15)	**<0.001**	1.634 (0.96 to 2.78)	0.071
One-year	56 (20.4)	44 (29.7)	**0.028**	3.19 (1.91 to 5.33)	**<0.001**	1.278 (0.85 to 1.91)	0.234

**Dehydration indicated hyperosmolar dehydration, osmolarity >300mOsmolo/l. [+]Adjusted for age, gender, Charlson Comorbidity Index (CCI). [++]Adjusted for age, gender, CCI and National Early Warning Score (NEWS). HR-Hazard ratio. Patients with dehydration had increased mortality rates and had increased risk of death (HR), independent of age, gender, CCI and NEWS.*

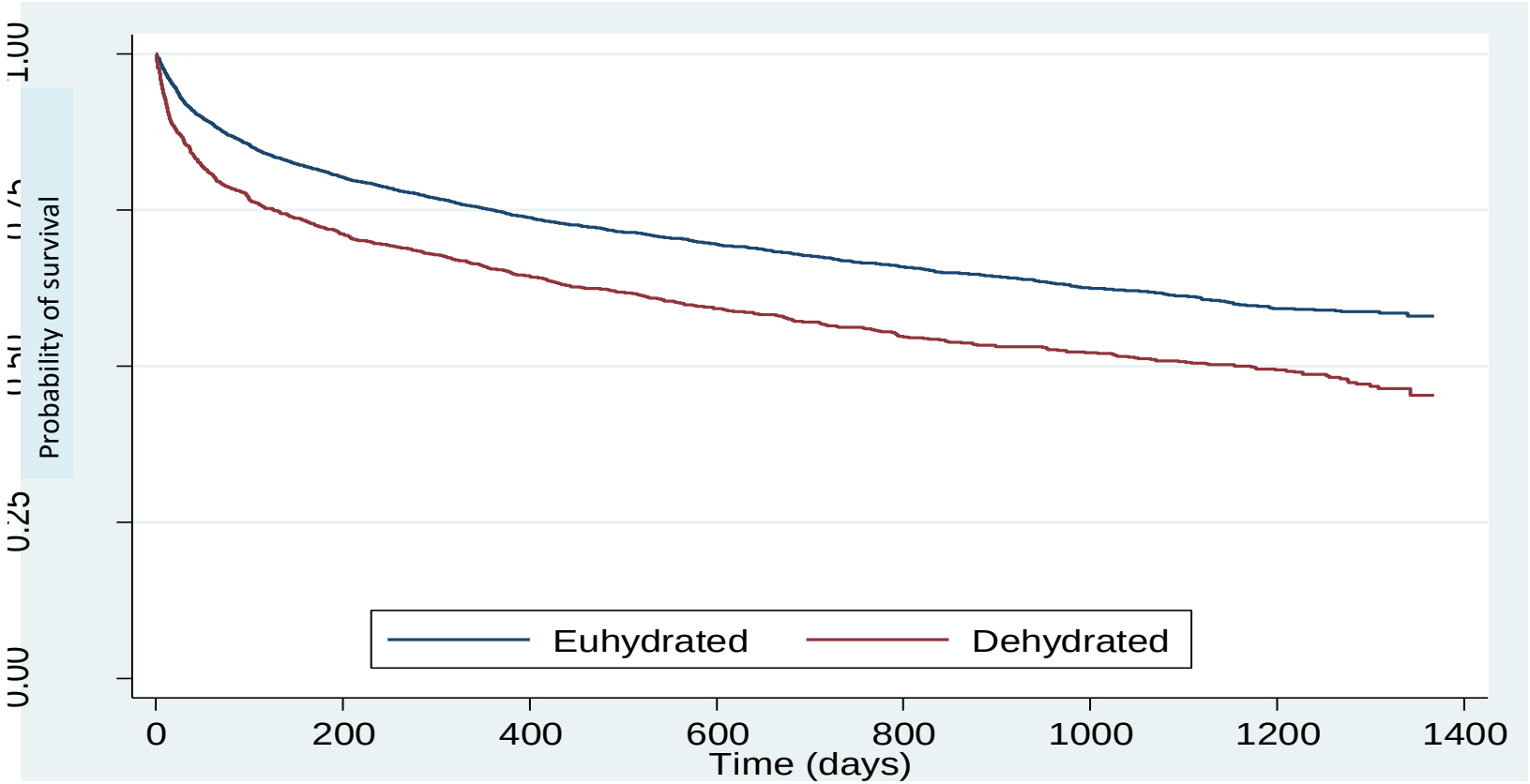


Figure 24: Kaplan-Meier survival plot demonstrating the relationship between hydration status and mortality

8.5 Discussion

HD occurred in over a quarter of hospitalised older adults, consistent with previously reported results using osmolality as the marker of hydration (El-Sharkawy *et al.,* 2015b). However, the prevalence of dehydration in the present study is significantly greater than clinically reported dehydration in Chapter 6 and that previously reported by Warren *et al.* (Warren *et al.,* 1994) These significant differences between clinically reported dehydration and HD are most likely the result of limited sensitivity of the clinical features of dehydration in this age group as well as the lack of screening and poor documentation.

The present study also demonstrated increased prevalence of dehydration with increased age and comorbidity similar to that shown in Chapters 5 and 6. This is a likely consequence of the disease process and polypharmacy, which result in physiological vulnerability and homeostatic irregularity as well as organ dysfunction. However, given the high prevalence of HD at admission, chronic or pre-existing dehydration should also be considered as a contributing factor. Studies have demonstrated that up to 60% of seemingly "well" community-dwelling older adults may be dehydrated (Stookey *et al.,* 2005).

In the present study, 39% of those who had HD also developed AKI and a significantly greater proportion had advanced (stage 3) AKI compared with those who were euhydrated, 9% *vs.* 1.3%, P<0.001. Moreover, regression

analysis revealed patients with HD were nearly five times more likely to be in AKI 12 to 24 hours post admission, adjusted HR 5.15 (1.8 to 14.64) $P<0.001$.), independent of age, gender, comorbidity and illness severity (NEWS). It is of course difficult to attribute cause and effect in this retrospective study. However, considering the age-related renal changes (El-Sharkawy *et al.,* 2014, Lindeman *et al.,* 1985, Davies and Shock, 1950, Hollenberg *et al.,* 1974, Beck, 2000), recognising and treating dehydration may help prevent AKI in some patients (National Confidential Enquiry into Patient Outcome and Death, 2009, Ftouh and Thomas, 2013). This is of particular relevance where patients are prescribed diuretics and nephrotoxic drugs, a common scenario in older adults.

Adverse events related to diuretics account for up to 25% of all adverse drug reactions in older adults mostly due to poor monitoring and difficulties in accurately assessing hydration status (Wierenga *et al.,* 2012, Sandhofer *et al.,* 2002, Klopotowska *et al.,* 2012). Currently many clinicians rely on changes in serum urea and creatinine to aid the assessment of hydration status and fluid balance. However, these are not sensitive to small changes in hydration status, and are features of AKI (Sandhofer *et al.,* 2002, Khwaja, 2012. (Sandhofer *et al.,* 2002, Khwaja, 2012) Moreover, there is evidence suggesting that changes in creatinine may lag several days behind actual changes in glomerular filtration rate (Moran and Myers, 1985, Star, 1998). Therefore, serum osmolality may facilitate diagnosis of HD as well as monitor and guide the prescription of diuretics and nephrotoxic drugs. This approach may help

prevent AKI, which is associated with high morbidity and mortality (Porter *et al.,* 2014, National Confidential Enquiry into Patient Outcome and Death, 2009, Ftouh and Thomas, 2013).

HD was also found to be associated with mortality. The 30-day mortality in the dehydrated group was nearly double that of the euhydrated group, 14.7% *vs.*7.9%, respectively, *P*<0.001. It was also independently associated with a greater risk of 30-day and 90-day mortality. These findings are consistent with previous reports (Chapter 5 and 6) and are unlikely to be unique to this cohort or this centre which was described by the Care Quality Commission (CQC) as "safe, caring, effective and well-led" and had a standardised mortality rate in keeping with the national average (Dr. Foster Intelligence, Commission). Studies in other centres have also shown that high osmolality at admission was associated with increased morbidity and mortality post ischaemic stroke and myocardial infarction (Rohla *et al.,* 2013, Villani *et al.,* 1978, Bhalla *et al.,* 2000). The higher mortality rates may be related to complications of dehydration and associated hypovolaemia such as AKI as well as other organ dysfunction.

This present study also demonstrates a significant difference in the median LOS by an extra two days in patients with HD and five days in those clinically diagnosed with dehydration compared with euhydrated patients, 5 *vs.* 3 and 8 *vs.* 3, respectively. These marked differences will further contribute to financial and resource pressures already facing the NHS.

8.6 Limitations

This study reports significant findings with potential clinical implications; however, there are clear limitations that need to be considered when interpreting the results. HD (serum osmolality >300 mOsmol/kg) is thought to be the most common form of dehydration in older adults, equivalent to a reduction of between 4 and 5% of body weight (Armstrong *et al.,* 1997, Cheuvront *et al.,* 2013). However, this does not represent all forms of dehydration and it is therefore important to consider salt and water balance when using serum osmolality to assess hydration status (Electrolytes and Water, 2005, Eaton *et al.,* 1994, Thomas *et al.,* 2008, Armstrong, 2007, Armstrong, 2005).

Osmolarity calculations have been shown to be comparable to measured serum osmolality and were also highly sensitive and specific at predicting HD in this cohort as shown in Chapter 7. These findings are also supported by Siervo *et al.,* 2014 who also showed this equation to be the most accurate at predicting HD in community-dwelling older adults. However, osmolarity is only an estimation of hydration status and may be influenced by various factors including serum alcohol concentrations. Efforts were made to exclude all alcohol related admissions to minimise bias.

HD may be a manifestation of disease severity, and an increase in LOS and mortality would therefore be expected, although attempts were made to

account for confounders including age, gender and comorbidities using the CCI and NEWS.

LOS analysis was based on admission and discharge date and not the date the patient was medically fit for discharge. The LOS results should therefore be interpreted with caution as delayed discharges are common in older adults, a result of complex, length discharge processes, which may attenuate or exacerbate the differences in LOS reported in this study. However, it may be reasonable to assume that the incidence of delayed discharge may be equal between dehydrated and euhydrated patients.

The study findings are based on data obtained from a large university teaching hospitals NHS trust, further work is therefore required to assess whether these findings are applicable to other hospitals. However, there are numerous reports (although less comprehensive) from hospital and community settings suggesting that fluid mismanagement may be more widespread. (Powell and Paterson-Brown, 2011, Leach *et al.,* 2013)

8.7 Conclusions

This study provides compelling evidence adding to the growing body of research highlighting limitations with the way hydration status is currently assessed and monitored in hospitalised older adults.

9. Discussion

It is widely accepted that good hydration is essential to healthy living. Dehydration has been linked with multiple system disorders including cardiovascular, gastrointestinal and urinary disorders (El-Sharkawy *et al.,* 2015a). Vulnerable groups such as older adults are at increased risk, particularly during periods of ill health as a result of age-related pathophysiological changes, multiple comorbidities and polypharmacy (El-Sharkawy *et al.,* 2015b).

Work done in this thesis demonstrates that healthy younger adult HCPs are also at risk. Over a third of the HCPs studied were dehydrated at the start of their shift, close to half at the end, and a third were oliguric. Interestingly, differences in the work patterns, speciality of work as well as level of experience influenced the hydration status of the participants. The reasons for this are likely to be multifactorial, with the difficulty in balancing adequate food and fluid consumption with the demands of a busy stressful shift in an often hot ward environment being significant contributing factors. Limited knowledge and awareness are also likely to be key contributors and addressing this has been shown to result in significant improvements in the hydration status of shift workers (Brake and Bates, 2003).

Furthermore, it was demonstrated that dehydration can negatively affect the way participants feel and may be associated with impaired cognitive function. Other work has shown that rehydration can reverse the cognitive impairment associated with dehydration, with the degree of improvement related to the severity of the thirst perception (Rogers *et al.,* 2001).

These findings may be of clinical significance given the relationship between subjective feelings and prescribing errors. A report commissioned for the UK General Medical Council investigating the prevalence and causes of prescribing errors, highlighted that physical and emotional well-being of the prescriber were amongst the five most common root causes (Avery *et al.,* 2012). The authors reported anxiety and tiredness as key factors that contribute to this common problem (Avery *et al.,* 2012). Similarly, findings from USA investigations into causes of errors, reported thirst, hunger and tiredness as leading causes of prescribing errors amongst interns (Coombes *et al.,* 2008). Links between poor quality clinical care, serious clinical errors and the physician wellbeing of the clinicians have also been described (Firth-Cozens and Greenhalgh, 1997). These findings emphasise the importance of HCPs maintaining a euhydrated state, given that prescribing and administering drugs are amongst the most common tasks undertaken in the clinical setting.

Others have gone further suggesting that employers should facilitate adequate hydration and encourage a culture of wellness amongst HCP's, given that the well-being of workers is an indicator of an organisation's well-being (Wallace *et al.,* 2009, Arnetz, 2005). Simple measures such as easy access to drinking water are likely to be a cost effective way to improve the health of workers, which has been shown to increase productivity (Linzer *et al.,* 2001) and may improve patient care.

It was also demonstrated in this thesis that HD is common in hospitalised older adults and is associated with AKI and poor outcome. Moreover, there

was a significant disparity between the prevalence of clinically diagnosed and biochemically measured dehydration. This may be explained by the challenges in assessing fluid status in the older adult. Current clinical methods of assessing and monitoring hydration status have been shown to be unreliable (Schols *et al.,* 2009, Shimizu *et al.,* 2012, Fortes *et al.,* 2014, Eaton *et al.,* 1994, Fletcher *et al.,* 1999, McGee *et al.,* 1999, Weinberg and Minaker, 1995). A study investigating the accuracy of seven clinical signs of dehydration against objective biochemical assessment using urea: creatinine ratio and serum osmolality, reported poor sensitivity and specificity of commonly assessed clinical features including increased CRT, dry mucus membranes, sunken eyes, dry axilla and reduced skin turgor, with sensitivity ranging from 0 to 44% (Fortes *et al.,* 2014). Common clinical features of dehydration are non-specific; dry skin and reduced skin turgor can occur with the normal ageing process and the commonest cause of dry mucus membrane in the older adult is mouth breathing. Additional features of dehydration include dizziness, postural hypotension, confusion, weakness and apathy, all of which may erroneously be attributed to other causes or simply ascribed to the aging process, meaning that HD may not be recognised (Schols *et al.,* 2009, Shimizu *et al.,* 2012, Fortes *et al.,* 2014).

Other markers such as acute changes in weight can also be useful, although this requires serial measurements, which can be a challenge in dependent older adults and requires specialist equipment and training. Furthermore, this

method is limited to changes over a short time period as weight fluctuates over longer time periods.

Urine parameters such as urine colour and specific gravity have been used to assess hydration status, but these lack sensitivity (Fortes *et al.,* 2014). However, urine osmolality and output are more sensitive and specific at assessing and monitoring hydration status when measured over 24 hours (Armstrong, 2007), though obtaining urine samples is often difficult in older adults and oliguria is a late feature of dehydration, associated with AKI (Lewington and Kanagasundaram, 2011).

These challenges in assessing hydration status and the absence of validated assessment tools results in undiagnosed and therefore underreported dehydration (Lobo *et al.,* 2001a). Limited awareness and poor knowledge together with the lack of comprehensive guidelines compound the problem.

Further findings from this thesis demonstrate that HD may be an independent risk factor for AKI, with many of the dehydrated patients also diagnosed with AKI. Dehydration was also shown to be a contributor to mortality, independent of the primary cause of hospitalization as well as age, gender and comorbidities. These findings suggest that missed or late diagnosis of severe dehydration that results in kidney injury; a likely contributing factor to the increased mortality rates reported.

The results of these studies are unlikely to be unique to this cohort or this centre which was described by the Care Quality Commission (CQC) as “safe,

caring, effective and well-led" and had a standardised mortality rate in keeping with the national average (Dr. Foster Intelligence, CQC 2014). The CQC also noted evidence in the acute setting "that staff assessed nutrition and hydration needs and that they put in place and followed care plans if specific needs were identified, for example, if a patient required assistance at mealtimes."(CQC, 2014)

Over the last four decades, numerous publications have highlighted the significance of hydration status in vulnerable groups particularly in older adults. Some reports have highlighted a clear need for improvement and lack of compliance with national care guidelines (National Confidential Enquiry into Patient Outcome and Death, 2009, Ftouh and Thomas, 2013). The CQC's Essential Standards of Quality and Safety clearly state that the nutrition and hydration needs of service users must be met (CQC, 2012), but the Health Ombudsman for England reported that there was a lack of access to fresh drinking water during her investigations into the care of older people. However, it is important to highlight the CQC investigation that reported 45 out of 100 acute NHS hospitals complied fully with their standards on participants' nutritional needs following unannounced inspections by an independent panel of representatives that included patient charities and advocates (CQC, 2011).

The link between AKI and dehydration demonstrated in this thesis are supported by the National Confidential Enquiry into Patient Death which reported that as many as 12,000 deaths annually could be prevented by

treating the causes of 'avoidable' AKI which include dehydration (National Confidential Enquiry into Patient Outcome and Death, 2009, Ftouh and Thomas, 2013).

Given the challenges highlighted in assessing and monitoring hydration status, serum osmolality may be a useful adjunct to current clinical care, as it is the key regulated variable in fluid balance and is widely seen as the most reliable objective measure of hydration status (Bhalla *et al.,* 2000, Sollanek *et al.,* 2011, Cheuvront *et al.,* 2013, Cheuvront *et al.,* 2010, Stookey *et al.,* 2005). It may also be useful to aid prescribing of diuretics and other nephrotoxic drugs given that changes in urea and creatinine may not be sensitive to small changes in hydration status (Sandhofer *et al.,* 2002, Khwaja, 2012). Therefore using serum osmolality in the clinical setting will not only help early detection of dehydration, it may also help prevent AKI. However, it is important to note a single measurement is unlikely to be useful due to the rapid fluctuation of body water through the different fluid compartments (Armstrong, 2007, Armstrong *et al.,* 2013b).

Despite the widespread use of serum osmolality in a variety of human physiological research settings, it has not been fully adopted in the clinical setting due to limited evidence and resources. However, it has been demonstrated that calculated osmolarity may be used as an alternative in hospital (Chapter 7) and community setting (Siervo *et al.,* 2014). Studies described in this thesis demonstrated that the equation by Khajuria and Krahn, 2005, had the greatest diagnostic accuracy at predicting HD with over

90% sensitivity and 97% specificity at 300 mmol/l, consistent with work done in community-dwelling older adults (Siervo *et al.,* 2014). This equation is a simple and cost effective way to allow screening, diagnosing and monitoring of patients. It is based on serum biochemistry, which is routinely measured when patients present to hospital and in many cases daily during hospitalisation. However, there is a clear need for prospective evaluation and validation of the clinical applicability of this approach in order to meet the basic needs for some of our most vulnerable patients.

Dehydration in older hospitalised patients is a major concern for patient safety and could also contribute to a significant public health burden. In the US it has been estimated that dehydration as a primary diagnosis costs the healthcare provider $2942 per admission based on 1991 estimates (Warren *et al.,* 1994). Furthermore, a study used the 2004 US National Hospital Discharge Survey of 518,000 hospitals and reported that dehydration as the primary cause of admission, cost $5.5 billion, describing the findings as “avoidable healthcare costs” (Kim, 2007). Given the projected increase in the UK older adult population, the financial and resource burdens are likely to increase significantly (Cracknell, 2010). However, cost implications related to dehydration are difficult to quantify and any figure estimating the financial implication is unlikely to account for under-reporting or dehydration-related conditions such as urolithiasis and AKI (El-Sharkawy *et al.,* 2015a).

10. Conclusions

Given that hydration and nutrition are the hallmarks of compassionate care, there is clear room for improvement. Our findings suggest the need for further investigations and interventions in both community and hospital settings. Our studies have highlighted that dehydration is still a common problem both in healthy individuals as well as hospitalised older adults and highlights the challenges in assessing, diagnosing and monitoring dehydration in older adults. Routine use of serum osmolality to assess and monitor hydration status in older adults may help prevent avoidable causes of kidney injury and may reduce morbidity and mortality. Knowing hydration status serum osmolality will not only facilitate rehydration, but may also help guide the prescription of diuretics and other potentially nephrotoxic mediation.

Work from this thesis highlights the need for further work to prospectively assess the use of serum osmolality as a predictor of dehydration, AKI and outcomes. Education of both patients and HCP is also needed in order to highlight the importance of good hydration. Co-ordinated efforts are necessary to develop comprehensive guidelines and hydration assessment tools together with methods to implement and monitor a real change in culture and attitude towards hydration in hospitalised older adults. Regular feedback audits and reviews of practice are likely to encourage implementation of guidelines and improvements in care and will help prevent avoidable morbidity, reduce mortality and reduce unnecessary costs.

11. Future Directions

The studies outlined in this thesis have highlighted the high prevalence of dehydration amongst HCPs and associated cognitive impairment. It has also highlighted that a significant proportion of hospitalised older adults are dehydrated, with significant discrepancy between clinically diagnosed and objectively measured dehydration. As a result, many may go unrecognised and if untreated can result in AKI and poor outcome. However, the work undertaken thus far also raises many new questions that we hope to address in future studies:

1. Whether the prevalence of dehydration reduces during normal working hours or with 'protected' breaks.

2. Whether better knowledge, awareness and access to fluids would reduce the prevalence of dehydration amongst HCPs, improve wellbeing scores and reverse cognitive impairment associated with dehydration.

3. Whether the prevalence of dehydration in 'well' community-dwelling older adults is as high as that reported in hospitalised older adults.

4. Whether the prevalence of dehydration amongst older adult patients undergoing elective surgery impacts on intraoperative fluid administration and postoperative outcome.

5. Whether better knowledge, awareness amongst HCPs, relatives and patients impacts on the prevalence of dehydration and associated adverse events in older adults.

6. Whether improved monitoring and access to fluids would reduce the prevalence of dehydration and improve outcome amongst hospitalised older adults.

7. Whether the use of osmolality as an adjunct to clinical assessment tools, to screen and monitor hydration status in older adults would reduce the prevalence of severe dehydration, AKI and improve clinical outcome.

12. Bibliography

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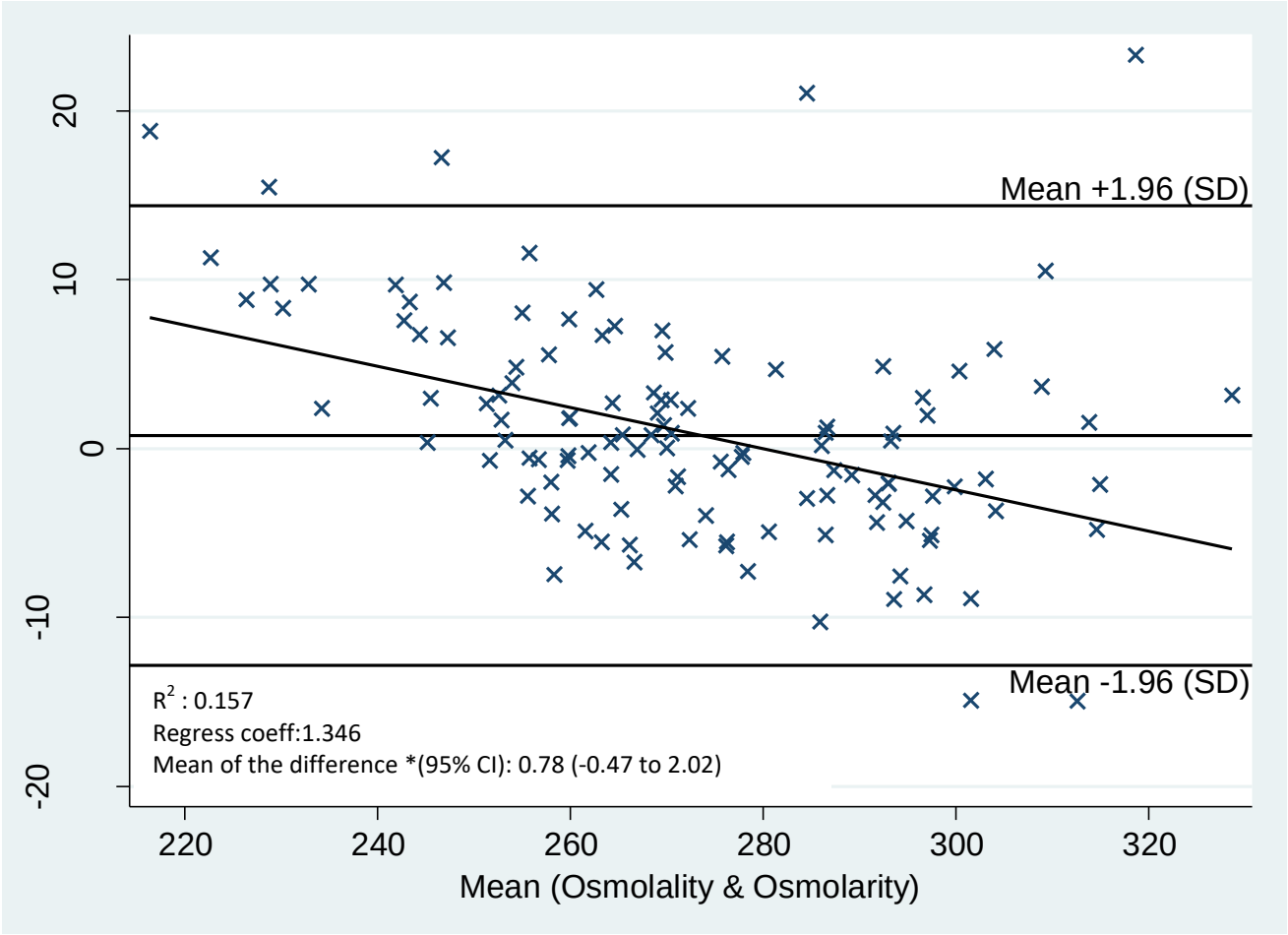
13. Appendix

13.1Appendix 1: Supplementary data analysis from chapter 8



Bland-Altman plot, mean difference and accuracy of osmolarity calculations using Krah & Khajuria's[16] equation [1.86 x (Na + K) + 1.15 x 6.3 + urea + 14] for patient without glucose. 6.3 a constant value obtained from the mean population (n=13,542) glucose of non-diabetic patients.

Supplementary Table 1: Demographics and characteristics of the study cohort. Comparing those with and without hypertonic dehydration during hospitalisation.

		All Patients (n=13542)	Euhydrated (n=9902)	Dehydrated[#] (n=3640)	*P* value*
Age	65 - 75	523 (3.9)	427 (4.3)	96 (2.6)	<0.001
	76 - 85	9295 (68.6)	6,974 (70.4)	2,321 (63.8)	
	86 - 95	3433 (25.4)	2,319 (23.4)	1,114 (30.6)	
	>95	291 (2.2)	182 (1.8)	109 (3.0)	
Gender	Female	7,715 (57.0)	5843 (59.0)	1,872 (51.4)	<0.001
	Male	5,827 (43.0)	4,059 (41.0)	1,768 (48.6)	
Charlson Comorbidity Index	None	4,327 (32.0)	3,329 (33.6)	998 (27.4)	<0.001
	Mild	6,095 (45.0)	4,524 (45.7)	1,571 (43.2)	
	Moderate	1,899 (24.0)	1,153 (11.6)	746 (20.5)	
	Severe	1,221 (9.0)	896 (9.1)	325 (8.9)	

**P value comparing patients with and without dehydration. [#]Dehydration indicates hypertonic dehydration, osmolarity >300mOsmol/l. [+]Osmolarity calculated using the equation by Krah & Khajuria's equation 2005 [1.86 x (Na + K) + 1.15 x glucose + urea + 14].*

Supplementary Table 3: Prevalence of conditions associated with dehydration.

	(a) Whole cohort (n=13542)							(b) Patients with National Early Warning Score (n=2346)						
AKI (hours from admission)	**Euhydrated (n=9902)**	**Dehydrated* (n=3640)**	***P* value**	**Unadjusted: HR (95% CI)**	***P* value**	**Adjusted[+]: HR (95% CI)**	***P* value**	**Euhydrated (n=3854)**	**Dehydrated* (n=1492)**	***P* value**	**Unadjusted: HR (95% CI)**	***P* value**	**Adjusted[++]: HR (95% CI)**	***P* value**
All AKI	*1276 (12.9)*	*1068 (29.3)*	<0.001	-	-	-	-	*364 (9.4)*	*316 (21.2)*	<0.001	-	-	-	-
12 to 24	*143 (1.4)*	*288 (7.9)*	<0.001	*2.96 (2.42 to 3.62)*	<0.001	*3.05 (1.48 to 3.75)*	<0.001	*44 (1.4)*	*93 (6.2)*	<0.001	*3.12 (2.18 to 4.46)*	<0.001	*3.21 (2.22 to 4.65)*	<0.001
12 to 48	313 (3.2)	429 (11.8)	<0.001	*2.33 (2.01 to 2.69)*	<0.001	2.34 (2.01 to 2.71)	<0.001	112 (2.9)	155 (10.4)	<0.001	2.43 (1.9 to 3.10)	<0.001	2.47 (1.92 to 3.19)	<0.001
12 to 72	420 (4.2)	486 (13.4)	<0.001	2.08 (1.82 to 2.37)	<0.001	2.10 (1.84 to 2.40)	<0.001	152 (3.9)	179 (12,0)	<0.001	2.22 (1.78 to 2.76)	<0.001	2.27 (1.81 to 2.85)	<0.001

**Dehydration indicated hyperosmolar dehydration, osmolarity >300mOsmo/l. [+]Adjusted for age, gender, Charlson Comorbidity Index . [++]Adjusted for age, gender, Charlson Comorbidity Index and National Early Warning Score.*

Supplementary Table 4: Hydration status and mortality.

	(a) Whole cohort (n=13542)							(b) With NEWS (n=2346)						
Mortality	**Euhydrated (n=9902)**	**Dehydrated* (n=3640)**	***P* value**	**Unadjusted: HR (95% CI)**	***P* value**	**Adjusted[+]: HR (95% CI)**	***P* value**	**Euhydrated (n=3854)**	**Dehydrated* (n=1492)**	***P* value**	**Unadjusted: HR (95% CI)**	***P* value**	**Adjusted[++]: HR (95% CI)**	***P* value**
In-Hospital	586 (5.9)	499 (13.7)	<0.001	2.39 (2.11 to 2.70)	<0.001	2.08 (1.83 to 2.36)	<0.001	184 (4.8)	164 (11.0)	<0.001	2.34 (1.88 to 2.91)	<0.001	2.11 (1.69 to 2.65)	<0.001
30-day	724 (7.3)	568 (15.6)	<0.001	2.23 (1.99 to 2.50)	<0.001	1.95 (1.74 to 2.19)	<0.001	229 (5.9)	191 (12.8)	<0.001	2.23 (1.83 to 2.71)	<0.001	2.02 (1.65 to 2.48)	<0.001
90-day	1244 (12.6)	820 (22.5)	<0.001	1.91 (1.75 to 2.09)	<0.001	1.67 (1.53 to 1.83)	<0.001	397 (10.3)	270 (18.1)	<0.001	1.84 (1.58 to 2.16)	<0.001	1.65 (1.40 to 1.94)	<0.001
One-year	2078 (21.0)	1188(32.6)	<0.001	1.70 (1.58 to 1.83)	<0.001	1.47 (1.37 to 1.58)	<0.001	681 (17.7)	438 (29.4)	<0.001	1.79 (1.59 to 2.02)	<0.001	1.58 (1.40 to 1.80)	<0.001

**Dehydration indicated hyperosmolar dehydration, osmolarity >300mOsmo/l. [+]Adjusted for age, gender, Charlson Comorbidity Index . [++]Adjusted for age, gender, Charlson Comorbidity Index and National Early Warning Score.*

13.2 Appendix 2: Subjective feelings questionnaire

10 cm visual analogue scale to measure subjective feelings

Study ID: ____ Initials: _____ Date of Birth: _____

How thirsty do you feel now?

Not at all (0)  *(10)* very thirsty

How hungry do you feel now?

Not at all (0)  *(10)* very hungry

How tired do you feel now?

Not at all (0)  *(10)* very tired

How alert do you feel now?

Not at all (0)  *(10)* very alert

How well can you concentrate just now?

Not at all (0)  *(10)* very well

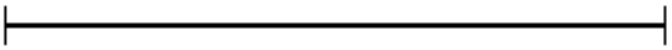
How stressed do you feel now?

Not at all (0)  *(10)* very stressed

How does your head feel now?

Not at all (0)  *(10)* very sore

How refreshed do you feel now?

Not at all (0)  *(10)* very refreshed

13.3 Appendix 3: Charlson Comorbidity Index

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.

Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

13.4Appendix 4: Rockwood Frailty Scale

Box 1: The CSHA Clinical Frailty Scale

1 *Very fit* — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age

2 *Well* — without active disease, but less fit than people in category 1

3 *Well, with treated comorbid disease* — disease symptoms are well controlled compared with those in category 4

4 *Apparently vulnerable* — although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms

5 *Mildly frail* — with limited dependence on others for instrumental activities of daily living

6 *Moderately frail* — help is needed with both instrumental and non-instrumental activities of daily living

7 *Severely frail* — completely dependent on others for the activities of daily living, or terminally ill

Note: CSHA = Canadian Study of Health and Aging.

13.5 Appendix 5: Barthel Activities of Daily Living Index

	Please tick one
1. In the bath or shower, do you:	
Manage on your own?	
Need help?	
Never have a bath or shower?	
2. Do you go up and down stairs:	
Without any help?	
With help (either supervision or assistance)?	
Not at all?	
3. Do you get dressed:	
Without any help (including buttons, zips, laces etc)?	
With help, but can do at least half on your own?	
With help for almost everything?	
4. Do you get about indoors:	
Walking with no-one helping? (with stick or frame)	
Walking with the help or supervision of one person?	
Propelling you with a wheelchair?	
Not at all?	
5. Do you move from bed to chair:	
On your own?	
With a little help from one person?	
With a lot of help from one or two people?	
Not at all?	
6. Do you feed yourself:	
Without any help?	
With a little help (e.g. cutting up food)?	
With a lot of help?	
7. Do you use the toilet or commode:	
Without any help?	
With a little help (e.g. wiping)?	

With a lot of help?	
8. Do you wash your face, brush your hair and teeth, (for men, shave): Please tick one	
Without help?	
With help?	
9. Are you incontinent of urine (wet your bed or clothes):	
Never?	
Occasional “accident”?	
More often than occasional “accident”?	
Have a catheter which you manage yourself?	
Have a catheter managed by someone else?	
10. Are you incontinent of your bowels (soil yourself):	
Never?	
Occasional “accident”?	
More often than occasional “accident”?	
Need regular enemas?	

13.6 Appendix 6: Mini Mental State Examination

(adapted from Folstein *et al.*)

	Section	Questions:	points	score
			Max score	**Patient score**
1	**Orientation**	a) Can you tell me today's (date)/ (month)/ (year)? Which (day of the week) is it today? Can you also tell me which (season) it is?	5	
		b) What city/town are we in? What are the (county)/ (country)? What (building) are we in and on what (floor)?	5	
2	**Registration**	I should like to test your memory. (name 3 common objects: e.g. "ball, car, man") Can you repeat the words I said? ***score 1 point for each word*** (repeat up to 6 trials until all three are remembered) (record number of trials needed here:)	3	
3	**Attention & Calculation**	a) From 100 keep subtracting 7 and give each answer: Stop after 5 answers. (93...86…79...72...65). ***Alternatively*** b) Spell the word 'WORLD' backwards. (D_L_R_O_W).	5	
4	**Recall**	What were the three words I asked you to say earlier? (skip this if all three objects were not remembered during registration test)	3	
5	**Language Naming**	Name these objects (show a watch) (show a pencil)	2	
	Repeating	Repeat the following: "no ifs, ands or buts"	1	
6	**Reading**	(show card or write "CLOSE YOUR EYES") - see over Read this sentence and do what it says.	1	
	Writing	Now can you write a short sentence for me?	1	

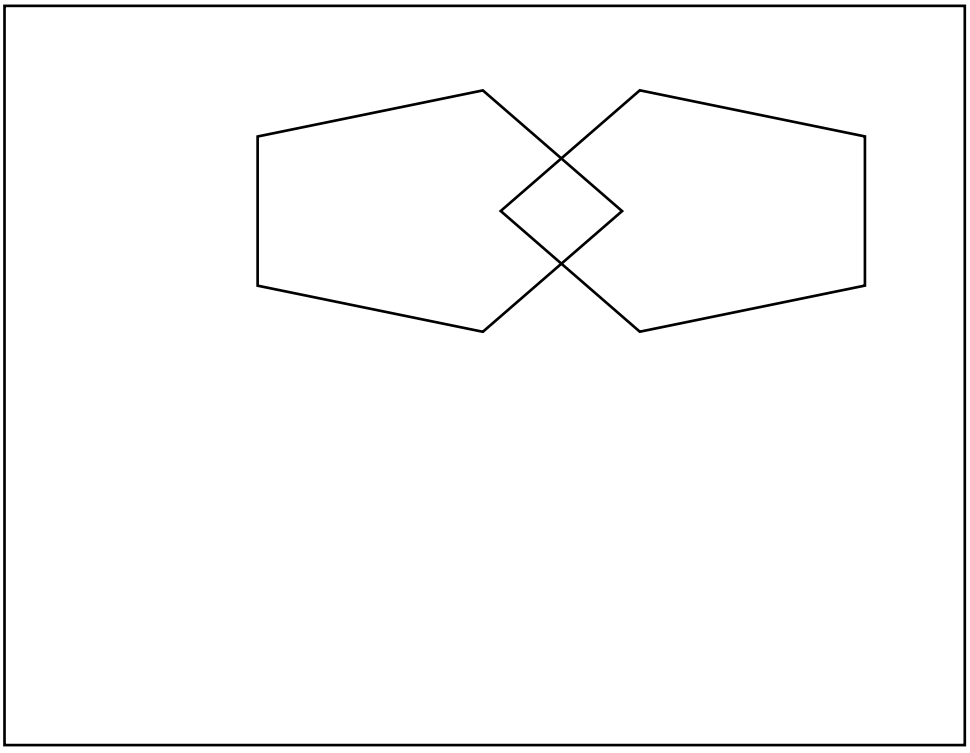
7	**Three stage command**	(Present paper) Take this paper in your left (or right) hand, fold it in half, and put it on the floor.	3	
8	**Construction**	Will you copy this drawing please? – see below	1	
	Total Score		30	
		Notes		

Question 6 – Writing

_____

___

Question 8 - Construction



13.7 Appendix 7: Nutritional Risk Screening Tool

Nutritional Risk Screening (NRS 2002)

Table 1 Initial screening			
1	Is BMI <20.5?	Yes	No
2	Has the patient lost weight within the last 3 months?		
3	Has the patient had a reduced dietary intake in the last week?		
4	Is the patient severely ill ? (e.g. in intensive therapy)		
Yes: If the answer is 'Yes' to any question, the screening in Table 2 is performed. **No**: If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

Table 2 Final screening			
Impaired nutritional status		**Severity of disease (≈ increase in requirements)**	
Absent **Score 0**	Normal nutritional status	Absent **Score 0**	Normal nutritional requirements
Mild **Score 1**	Wt loss >5% in 3 mths or Food intake below 50–75% of normal requirement in preceding week	Mild **Score 1**	Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*. *Chronic hemodialysis, diabetes, oncology*
Moderate **Score 2**	Wt loss >5% in 2 mths or BMI 18.5 – 20.5 + impaired general condition or Food intake 25–60% of normal requirement in preceding week	Moderate **Score 2**	Major abdominal surgery* Stroke* *Severe pneumonia, hematologic malignancy*
Severe **Score 3**	Wt loss >5% in 1 mth (>15% in 3 mths) or BMI <18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week in preceding week.	Severe **Score 3**	Head injury* Bone marrow transplantation* *Intensive care patients (APACHE>10).*
Score:	+	**Score:**	**=Total score**
Age	if ≥70 years: add 1 to total score above	**=age-adjusted total score**	
Score ≥3: the patient is nutritionally at-risk and a nutritional care plan is initiated **Score <3**: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

NRS-2002 is based on an interpre-tation of available randomized clinical trials.
*indicates that a trial directly supports the categorization of patients with that diagnosis. Diagnoses shown in *italics* are based on the prototypes given below.
Nutritional risk is defined by the present **nutritional status** and risk of impairment of present status, due to **increased requirements** caused by stress metabolism of the clinical condition.

A nutritional care plan is indicated in all patients who are

(1) severely undernourished (score = 3), or (2) severely ill (score = 3), or (3) moderately undernourished + mildly ill (score 2 + 1), or (4) mildly undernourished + moderately ill (score 1 + 2).

Prototypes for severity of disease
Score = 1: a patient with chronic disease, admitted to hospital due to complications. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.

Score = 2: a patient confined to bed due to illness, e.g. following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.

Score = 3: a patient in intensive care with assisted ventilation etc. Protein requirement is increased and cannot be covered even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.