Clinical and physical signs for identification of impending and current water-loss dehydration in older people (Protocol)

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Clinical and physical signs for identification of impending and current water-loss dehydration in older people

Lee Hooper[1], Natalie J Attreed[1], Wayne W Campbell[2], Adam M Channell[1], Philippe Chassagne[3], Kennith R Culp[4], Stephen J Fletcher [5], Nigel Fuller[1], Phyllis M Gaspar[6], Daniel J Gilbert[1], Adam C Heathcote[1], Gregor Lindner[7], Gary W Mack[8], Janet C Mentes[9], Rowan A Needham[10], Marcel GM Olde Rikkert[11], Sheila C Ranson[1], Patrick Ritz[12], Anne M Rowat[13], Alexandra C Smith[1], Jodi JD Stookey[14], David R Thomas[15], Bonnie J Wakefield[16], Sean Ward[1], John F Potter[17], Paul R. Hunter[18]

[1]Norwich Medical School, University of East Anglia, Norwich, UK. [2]Department of Nutrition Science, Purdue University, West Lafayette, IN, USA. [3]Geriatrics Department, Rouen University Hospital, Rouen Cedex, France. [4]College of Nursing, University of Iowa, Iowa City, IA, USA. [5]Department of Anaesthesia and Intensive Care Medicine, Bradford Teaching Hospitals NHSFT, Bradford, UK. [6]Colleges of Medicine and Nursing, University of Toledo, Toledo, OH, USA. [7]Department of Nephrology and Hypertension, Inselspital Bern, University of Bern, Bern, Switzerland. [8]Brigham Young University, Provo, UT, USA. [9]University of California Los Angeles, Los Angeles, CA, USA. [10]Gateshead NHS Trust, Gateshead, UK. [11]Department of Geriatrics, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands. [12]Department of Endocrinology, Nutrition and Metabolic Diseases, Chu de Toulouse, Toulouse, France. [13]School of Nursing, Midwifery and Social Care, Edinburgh Napier University, Edinburgh, UK. [14]Childrens Hospital Oakland Research Institute (CHORI), Oakland, CA, USA. [15]Department of Medicine, Saint Louis University, St Louis, MO, USA. [16]Sinclair School of Nursing, University of Missouri, Columbia, MO, USA. [17]Ageing & Stroke Medicine, Norwich Medical School, University of East Anglia, Norwich, UK. [18]The Norwich School of Medicine, University of East Anglia, Norwich, UK

Contact address: Lee Hooper, Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ, UK. l.hooper@uea.ac.uk.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the diagnostic accuracy of state, minimally invasive clinical and physical signs (or sets of signs) to be used as screening tests for detecting impending or current water-loss dehydration, or both, in older people by systematically reviewing studies that have measured a reference standard and at least one index test in people aged 65 years and over.

1. To assess the effect of different cut offs of index test results assessed using continuous data on sensitivity and specificity in diagnosis of impending or current water-loss dehydration.

2. To identify clinical and physical signs that may be used in screening for impending or current water-loss dehydration in older people.

3. To identify clinical and physical signs that are not useful in screening for impending or current water-loss dehydration in older people.

4. To directly compare promising index tests (sensitivity $\geq$ 0.60 and specificity $\geq$ 0.75) where two or more are measured in a single study (direct comparison).

5. To carry out an exploratory analysis to assess the value of combining the best three index tests where the three tests each have some predictive ability of their own, and individual studies include participants who had all three tests.

We will explore sources of heterogeneity of diagnostic accuracy of individual clinical and physical signs that show some evidence of discrimination by the reference standard used, cut off value for tests providing continuous data, type of participants (community-dwelling older people, those in residential care, and those in hospital), sex, and baseline prevalence of dehydration.

BACKGROUND

Target condition being diagnosed

Dehydration is defined as "loss or removal of fluid" from the body and occurs when fluid intake fails to fully replace fluid losses in the body (Churchill Livingstone Medical Dictionary 2008). Causes in older people may include diarrhoea, exudation (from burns or other raw areas), increased sweating, polyuria (frequent urination), bleeding, vomiting and/or inadequate fluid intake. The resultant hypovolaemia (decrease in blood plasma volume) is accompanied by electrolyte balance disruption (Churchill Livingstone Medical Dictionary 2008). The most extreme manifestation of dehydration is hypovolaemic shock, which requires emergency medical treatment. Hypovolaemic shock symptoms can include cool and clammy skin, reduced urine output, flattening of veins in the neck, altered mental state, low pulmonary wedge pressure, low cardiac index and high systemic vascular resistance index (Goldman 2004). Milder dehydration is common in older people.

The Dehydration Council suggests that dehydration is a complex condition resulting in a reduction in total body water (TBW) (Thomas 2008). It can be classified as water-loss dehydration (due to water deficit, which can be hypernatraemic (high blood sodium levels) or hyponatraemic (low blood sodium levels) in the presence of hyperglycaemia (high blood glucose)); or salt-loss dehydration (due to salt and water deficit, generally hyponatraemic, rarely isotonic (the same concentration of solutes as blood)). Serum osmolality is the osmolar concentration or osmotic pressure of serum, so reflects the number of dissolved particles (whether they are able to permeate cell membranes or not) per kilogram of serum. Serum osmolality of 275 to < 295 mOsmol/kg is considered normal; 295 to 300 mOsmol/kg suggests impending water-loss dehydration; and > 300 mOsmol/kg suggests current water-loss dehydration. In water-loss dehydration either serum sodium or glucose levels are raised and hypotonic fluids must be given. Impending (mild or pre-clinical) water-loss dehydration is an intermediate stage that may indicate long term chronic fluid deficiency, which may not progress, or an early stage of dehydration before onset of current dehydration. Impending dehydration may indicate a point at which an intervention to reverse dehydration, prevent medical emergency and reduce the risk of current dehydration, can be applied. Rapid medical intervention is needed for current (severe or clinical) water-loss dehydration because electrolyte disturbance and volume reduction is a significant health risk.

Dehydration in older people is associated with high risk of adverse health outcomes and death (Waikar 2009; Warren 1994). Dehydration contributes to many of the major causes of death and morbidity in older people. Adverse health outcomes associated with dehydration in older people include falls, fractures, heart disease, confusion, delirium, heat stress, constipation, kidney failure, pressure ulcers, poor wound healing, suboptimal rehabilitation outcomes, infections, seizures, drug toxicity, and reduced quality of life (Chan 2002; DoH and Nutrition Summit 2007; Mentes 2006a; Olde Rikkert 2009; Rolland 2006; Thomas 2008; Wakefield 2008). There are consistent data from high quality prospective studies (appropriately adjusted for concurrent risk factors and disease) indicating that raised serum osmolality and tonicity (indicating water-loss dehydration) are associated with increased risk of mortality in a general elderly US population, UK stroke patients and US older people with diabetes (Bhalla 2000; Stookey 2004; Wachtel 1991), and with poorer functional status in US older people (Stookey 2004). In 2004, John Reid, UK Secretary of State for Health, stated that high numbers of unplanned hospital admissions among the at-risk elderly were for entirely preventable conditions such as dehydration (Reid 2004). The estimated avoidable cost to the 1999 US healthcare system of older people admitted to hospital with primary diagnoses of dehydration was USD1.1 to USD1.4 billion annually, and admission rates appeared to be rising (Xiao 2004). Early identification, prevention and treatment of dehydration in the community would benefit older people and reduce healthcare costs.

The prevalence of dehydration in frail older people varies by setting and level of care required, as well as how hydration status is assessed. It has been asserted that hydration is well maintained in older people living independently, maintaining normal patterns of eating and drinking, but dehydration can develop following illness, depression, surgery, trauma or other physically stressful situations (Luckey 2003). However, recent evidence suggests that the prevalence of dehydration in independent community-dwelling older people is higher than previously thought. Plasma osmolality, measured in a US population of 15,000 people aged from 20 to 90 years (from the NHANES III cohort), found that 40% of those aged 70 to 90 years had impending water-loss dehydration, and a further 28% had current dehydration (high plasma tonicity, > 300 mmol/L) (Stookey 2005a). Another large US survey found that 50% of older people had elevated plasma tonicity. Both findings may relate to a high prevalence of elevated glucose, rather than hypernatraemia (Stookey 2005b; Thomas 2008). Dehydration becomes more common as people age because the thirst response decreases (De Castro 1992), ability to retain salt and fluid falls as kidney function decreases, kidney and urinary disease increase (Davies 1995; Lindeman 1985), and total body fluid reduces (Olde Rikkert 1997; Olde Rikkert 2009). Medications such as diuretics, laxatives, angiotensin-converting enzyme inhibitors (ACEi), psychotropic medications and polypharmacy (Mentes 2006a), as well as increased dependence on carers to provide drinks, also increase dehydration risk.

Older people living in residential care represent an extremely frail population. In the UK, 4% of the growing number of older people live in care homes or long-stay hospitals; rising to 21% of those aged 85 years and over (National Care Homes R&D Forum 2007). In our own research in Norfolk (UK) aged care homes we found that on a single assessment of 56 residents (from six institutions), 17 (30%) residents were dehydrated (with a furrowed tongue). A year later rates were lower (21%) and the risk of being dehydrated

at the second visit did not relate to hydration status at first visit (Kenkmann 2010). A Californian nursing home study found that 31% of residents were dehydrated (11% of elderly residents were hospitalised for dehydration, 6% were given intravenous rehydration, and 14% were found to have blood urea nitrogen/creatinine ratio greater than 25 mg/dL) at some point over six months (Mentes 2006a). However, point prevalence dehydration was reported to be 1.4% in Missouri nursing homes (Thomas 2008). A small study of US nursing home residents suggested that most participants did not drink enough fluid (39/40 drank less than 1.5 L/day), and drank little between meals. Factors contributing to low fluid intake included clinical (dysphagia, functional impairment, dementia, and pain); social (lack of attention to drink preferences, inability of residents to communicate with staff, and lack of social support); and institutional factors (untrained and unsupervised staff).

Suggested interventions to help prevent dehydration in older adults living in care homes include education and involvement of staff, use of social times, drinks carts and water jugs to support drinking habits, encouraging relatives to offer residents drinks, monitoring urine colour, drinking more in hot weather, being aware of medications and health conditions that increase fluid requirements, and providing specific support for those with swallowing problems (Mentes 2006a; Water UK 2006). However, many interventions have not been tested or were tested using methodology with moderate risk of bias such as before-after studies (Robinson 2002) or provided equivocal results (Culp 2003; Mentes 2003). A systematic review that aimed to "identify the factors that increase the risk of dehydration in older adults, how best to assess the risk and manage oral fluid intake" concluded that few data were available to answer these questions (Hodgkinson 2003). Perhaps the first stage in prevention of dehydration in older people is recognising the condition when it occurs, so that is it clear whether it is an institutional problem and if measures to reduce dehydration have been successful. Additionally, recognising early signs of dehydration (impending dehydration) would enable early intervention of preventive measures.

This review will focus on the clinical and physical signs of water-loss dehydration as distinct from salt-loss dehydration or volume depletion due to blood loss because it is likely that with underlying differences in physiology and impact, there will be differences in clinical and physical signs.

Reference standard for dehydration

In the absence of a consensus definition or gold standard test of dehydration, we will use two reference standards for water-loss dehydration. There are several approaches in situations where a reference standard is imperfect, but generally involve creation of a feasible reference standard (Reitsma 2009b). For dehydration due to reduced fluid intake, feasible reference standards for initial assessment of dehydration include raised serum osmolality or a large and rapid change in body weight (McGee 1999).

Serum osmolality has a clinical advantage in that it can be assessed as a single measure (does not require prior knowledge or measurements), and because osmolality is controlled by the body, any change suggests problems in body biochemistry. Disadvantages are that if body fluids are lost along with electrolytes (through loss of blood or sweat) then fluid may be lost without alteration of osmolality. However, this review is concerned with reductions in body fluid relating to conscious or unconscious reductions in fluid intake with or without increased losses due to variables such as use of diuretics, fever, diabetes insipidus, dysregulated diabetes mellitus, increased perspiration, or hot dry surroundings. In such situations where body fluids are lost overall, the response is likely to be increased osmolality (Thomas 2008). Serum and plasma osmolality appear to be useful markers of water-loss dehydration in the absence of tracking over time (Cheuvront 2010).

Total body weight is the sum of body fluid, fat, muscle, organs and bone, and the weight of body fluid is difficult to disentangle from total weight. However, fluid is the body component with the ability to alter most quickly, so that a substantial change in body weight over a short period of time will relate most directly to fluid status (Cheuvront 2010; Shirreffs 2003). For this reason, a reduction of $\geq$ 3% of body weight within seven days may be considered to be a clear sign of dehydration, as would an increase of $\geq$ 3% of body weight on rehydration within seven days. This relies on more than one assessment, and the assessments need to be accurate and account for issues such as constipation or oedema (Cheuvront 2010).

TBW can be estimated by deuterium oxide dilution and therefore change in TBW can be assessed over time (Schloerb 1950). A fall in body water of 2% or more could be considered to constitute dehydration, however due to the variance in assessment of TBW (1% to 2%), this will not be used as a reference standard. A single measure of TBW has not been correlated with hydration status in older people, so cannot be used as a reference standard on its own.

Index test(s)

To protect the health of older people, and prevent emergency hospital admissions, primary and care home staff must recognise and treat dehydration early. While a biochemical assessment may be the best state (one time) indicator of dehydration in a clinical setting (Thomas 2008) these tests are not generally available in community, primary or residential care settings (Leibovitz 2007). A systematic review of the diagnostic accuracy of physical signs of hypovolaemia, which included studies published to late 1997, found that in the few relevant studies there was limited evidence that in older people with vomiting, diarrhoea or reduced fluid intake that dry armpits (axilla) supported the diagnosis of hypovolaemia (positive likelihood ratio 2.8, 95% CI 1.4 to 5.4), and moist mucous membranes or a tongue without furrows supported lack of hypovolaemia (negative likelihood ratio for each 0.3, 95% CI 0.1 to 0.6). Capillary refill time and poor skin turgor (elasticity)

were not diagnostic (McGee 1999). A recent Australian cohort study found that systolic blood pressure drop on standing, sternal skin turgor, tongue dryness and body mass index were good indicators of early dehydration on hospital admission. However, these factors were compared with physician assessment of hydration status that may have included some or all of these clinical signs (Vivanti 2008).

Other state methods proposed to diagnose dehydration include assessment of urine colour, urine specific gravity, saliva osmolality, urine volume, sunken eyes, rapid pulse, postural pulse increment, severe postural dizziness, fluid balance charts, upper body weakness, bioelectrical impedance, and checklists of risk factors (Cheuvront 2010; Eaton 1994; Gross 1992; Mentes 2006a; Mentes 2006b; Schut 2005; Thomas 2008; Vivanti 2008). A systematic review that searched literature to 1995 found that early diagnosis of dehydration in older adults can be difficult because "the classical physical signs of dehydration may be absent or misleading in an older patient" suggesting that even index tests established in younger people cannot be assumed to be useful in older people (Weinberg 1995). Although some tests are probably not useful in older people, others may indicate dehydration risk, early stages of dehydration, or current dehydration. It is likely that a portfolio of assessments would be needed to usefully assess stage and type of dehydration among people in residential care without indicating that all residents are at high risk (Wotton 2008).

Rationale

Currently available evidence on water-loss dehydration in older people is inconsistent. It is vital both for the health and well-being of older people and to reduce unplanned emergency hospital admissions, that the risk of water-loss dehydration is reduced, methods of assessing dehydration risk are developed, impending dehydration in older people in the community and residential care are recognised, and early referral for diagnosis and treatment is carried out where appropriate. A valid, simple and non-invasive screening test for dehydration for older adults in the community would better enable:

- identification of older adults with impending water-loss dehydration so that measures can be taken to improve fluid status;
- monitoring progress of such older people;
- identification of older adults with likely current water-loss dehydration so that further testing or rapid medical support or both can be provided;
- identification of settings where there is a high risk of dehydration so that public health measures to improve hydration may be taken; and
- assessment of effects of interventions to improve hydration in individuals and populations.

OBJECTIVES

To determine the diagnostic accuracy of state, minimally invasive clinical and physical signs (or sets of signs) to be used as screening tests for detecting impending or current water-loss dehydration, or both, in older people by systematically reviewing studies that have measured a reference standard and at least one index test in people aged 65 years and over.

Secondary objectives

1. To assess the effect of different cut offs of index test results assessed using continuous data on sensitivity and specificity in diagnosis of impending or current water-loss dehydration.
2. To identify clinical and physical signs that may be used in screening for impending or current water-loss dehydration in older people.
3. To identify clinical and physical signs that are not useful in screening for impending or current water-loss dehydration in older people.
4. To directly compare promising index tests (sensitivity $\geq$ 0.60 and specificity $\geq$ 0.75) where two or more are measured in a single study (direct comparison).
5. To carry out an exploratory analysis to assess the value of combining the best three index tests where the three tests each have some predictive ability of their own, and individual studies include participants who had all three tests.

Investigation of sources of heterogeneity

We will explore sources of heterogeneity of diagnostic accuracy of individual clinical and physical signs that show some evidence of discrimination by the reference standard used, cut off value for tests providing continuous data, type of participants (community-dwelling older people, those in residential care, and those in hospital), sex, and baseline prevalence of dehydration.

METHODS

Criteria for considering studies for this review

Types of studies

Diagnostic studies that compare an index test with a reference standard for impending dehydration or current dehydration or both in older people will be included. We will also include non-diagnostic accuracy studies such as cohort and cross-sectional studies where at least one reference standard and at least one index test

were measured in at least 10 participants aged 65 years or over and with at least two participants with impending or current water-loss dehydration and at least two participants without water-loss dehydration. These studies will be included where the authors are able to provide a relevant 2 x 2 table comparing a reference with an index test, or a data set from which relevant 2 x 2 tables can be calculated. Where we have access to the full study data set we will exclude any participants who did not receive both the index test and the reference standard. We will attempt to access the full data sets (such as Excel spreadsheets or SPSS files) of all included studies.

Participants

People aged 65 years and over who are hospitalised, living in the community, or in institutions, in a developed country will be included. Participants will not have diagnosed kidney failure, heart failure, will not have recently been prepared for surgery or undergone surgery, but may have other chronic or acute illnesses, such as stroke, fracture, or infection. For mixed populations of older people that include participants aged under 65 years, we will exclude participants aged less than 65 years where we have access to the full data set; but, where only summary data are available, the study will only be included where the proportion of those under 65 years is less than 10%. In the same way, when using published data we will exclude studies with more than 10% of participants having one or more of the following: kidney failure, heart failure or a recent operation; and when using full study data sets, participants diagnosed with any of these conditions (according to individual study criteria) will be excluded from analysis.

Index tests

Single clinical or physical signs or a portfolio of signs and/or a checklist. Potential index tests for dehydration will include dry axilla and other markers of transepidermal water loss; dry mucous membranes; dry or furrowed tongue; extended capillary refill time and measures of skin blood flow; poor sternal skin turgor; systolic blood pressure drop on standing; urine colour; urine specific gravity; saliva osmolality; urine volume; sunken eyes; rapid pulse; postural pulse increment; postural dizziness; fluid balance charts; thirst; bad taste in the mouth; upper body weakness; measures of thermoregulation; bioelectrical impedance; and checklists of risk factors.

Target conditions

Water-loss dehydration (including both impending and current water-loss dehydration) is the primary target condition. Impending water-loss dehydration and current water-loss dehydration (treated as two separate conditions) will be secondary target conditions.

Reference standards

We will include studies that use either of two reference standards for water-loss dehydration, ordered in terms of their importance to make best use of the reference standard better able to represent water-loss dehydration in frail older people. The primary standard will be raised serum osmolality, followed by weight change.

Serum osmolality

- 295 to 300 mOsmol/kg suggests impending water-loss dehydration.
- Serum osmolality greater than 300 mOsmol/kg suggests current dehydration.

Weight change

Weight change may be naturally occurring or follow encouragement to limit fluid intake for a period, but not result from unusual levels of exercise or saunas (because these may result in dehydration that is metabolically distinct from naturally occurring dehydration).

- We will define impending dehydration as a reduction of 3% to 5% of body weight within seven days or less, or an increase of 3% to 5% of body weight within seven days as a sign that a person was dehydrated before rehydration.
- Current dehydration corresponds to changes of more than 5% of body weight.
- Weight change over a period less than seven days will not be multiplied up to the seven day equivalent.

Search methods for identification of studies

Search methods used will be based on guidelines for Cochrane diagnostic test accuracy reviews (de Vet 2008).

Electronic searches

A structured search strategy has been developed for MEDLINE (OvidSP), and adapted for EMBASE (OvidSP), CINAHL, BIOSIS Previews and LILACS. The strategies for MEDLINE, EMBASE and CINAHL are shown in Appendix 1. The DARE and HTA databases (in *The Cochrane Library*) will be searched for any relevant non-Cochrane reviews using a strategy adapted from the MEDLINE strategy. The International Clinical Trials Registry Platform (ICTRP) will be searched for ongoing studies using keywords derived from this search strategy. The CENTRAL database in *The Cochrane Library* will not be searched because research has shown that it does not contribute relevant studies for diagnostic test accuracy reviews (Whiting 2008). We will seek assistance from the Cochrane Renal Group's Trials Search Co-ordinator to search the *Cochrane Register of Diagnostic Test Accuracy Studies* for further relevant studies. No diagnostic methodology search filters will be

employed as these appear unhelpful in reducing sensitivity (de Vet 2008; Whiting 2011).

Searching other resources

Reference lists of included studies and identified relevant reviews will be handsearched. Authors of included studies will be contacted for details of further relevant studies.

Data collection and analysis

Selection of studies

Titles and abstracts will be scanned and all potentially relevant studies will be obtained as full text studies. Inclusion of full text studies will be assessed independently in duplicate, and disagreements resolved by a third author. We will write to authors of all studies that appear to have collected data on at least one reference standard and at least one index test, and in at least 10 people aged 65 years and over, even where no comparative analysis has been published, requesting either that the original authors supply the relevant 2 x 2 table or the original data set so that we can create 2 x 2 tables. The latter is preferable because it enables the review authors to remove data relating to any participants aged under 65 years, or with heart failure or kidney disease, as well as providing potential to explore effects of different cut points for index tests that provide continuous data.

Data extraction and management

A data extraction form, including validity criteria, will be developed for the review and tested by all data extractors on two or three included studies. We will collect age, gender, health, functional status, and level of independence data for participants, as well as how each test was performed and assessed, timing of each test including how far apart in time the different tests were taken, and at what time of day.

The data extraction form will be refined (with definitions and explanations added as required by the team), then data extraction will be carried out in duplicate for each included study. Authors who extract data will confer to agree on a final data extraction and validity data set for the review. Where items required for data extraction or validity assessment are designated as unclear, original study investigators will be contacted to obtain further details.

Where complete data sets for included studies are sought from original investigators, we will request data on sex, age, presence or absence of diseases such as kidney and heart failure, and use of medications as well as results of our index tests and reference standards. In processing the data sets, we will ensure that details of each component of the data set are understood (when tests were taken, units, serum or urinary measures and so forth) by analysing the publication and from contact with original investigators. The data set will then be cleaned by removing data of participants aged less than 65 years; those with kidney disease, heart failure, or oedema; or who are perioperative or postoperative; and participants who have no reference standard data (the process, including losses of participants, will be logged). We will construct 2 x 2 tables (no dehydration versus impending or current dehydration) for each index test, one table for each dichotomous index test for each study, and three tables per continuous index test (one table for each of three cut off points). The three cut off points for continuous index tests will be consistent for all studies measuring that index test, and based on recommended cut offs in the literature (ideally), reference ranges (where recommended cut offs are not available) or will be data driven (taking a median, high and low data point, where no other source of cut offs exist). Data driven cut points will be set as the median in the data set, plus a value higher than the median and lower than the median. The higher cut point will be chosen as the point midway between the median and highest value present in the data set, and the lower cut point as the point midway between the median and the lowest value present. We will calculate sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and diagnostic odds ratio for each 2 x 2 table.

This final data set for each included study will be used to complete tables of characteristics and validity.

Assessment of methodological quality

Assessment of methodological quality will be carried out independently in duplicate as part of data extraction. It will be based on the characteristics suggested by QUADAS, and reflected in the RevMan 5 program (Reitsma 2009a; Whiting 2006). Additionally, we will record whether the study was free of commercial funding. The qualities assessed are described in further detail in Appendix 2.

Statistical analysis and data synthesis

Analysis will be performed according to descriptions in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Macaskill 2010). Diagnostic accuracy of each clinical or physical sign will be assessed against the best available reference standard for impending and current water-loss dehydration (ideally serum osmolality, but weight change where osmolality is not available) within each study.

The main analysis for each index test will assess ability to diagnose either impending or current dehydration (no dehydration versus impending plus current dehydration). Secondary analyses for each index test will assess ability to diagnose current dehydration (no or impending dehydration versus current dehydration) and to diagnose impending dehydration (no dehydration versus impending dehydration). Secondary analyses and exploration of heterogeneity will be conducted for index tests only where some evidence of discrimination is observed in the main analysis.

Individual study data for each index test will be presented in forest plots of sensitivity and specificity and in receiver operating characteristic (ROC) space, subgrouped by cut off for continuous index tests.

We will conduct bivariate random-effects meta-analyses in Stata/IC (StataCorp) for index tests where there are at least four studies or data sets on a single index test and data sets can be pooled (Reitsma 2005) to construct sensitivity and specificity summary estimates, and summary ROC curves. We will assign the same approach for index tests with continuous outcome data for each of the three cut off points investigated. Covariates will be incorporated into the bivariate model to examine the effects of factors that may be responsible for heterogeneity.

The principal aim of this review is to identify the potential usefulness of index tests to identify or rule out impending or current dehydration. Because the index tests will be used to screen for dehydration in populations with little or no current screening, but among whom there are likely to be high levels of dehydration, initial tools will need to be quite specific. This will help to limit numbers of false positive results that may discredit future time spent in responding to positive results. Any level of sensitivity would be an improvement on the current lack of ability to detect most episodes of dehydration in the community, but clearly, the higher the sensitivity the better, while maintaining high specificity. We suggest that minimum specificity of a useful test would be 0.75, and minimum sensitivity would be 0.60 for both impending and current dehydration. These levels will be used as standards against which the utility of minimally invasive clinical and physical signs will be assessed.

We will directly compare index tests that fulfil the minimum criteria of sensitivity $\geq$ 0.60 and specificity $\geq$ 0.75 where two or more are measured in a single study (direct comparison). The tests will be compared at their best cut off point, that is, the point that provides the best discrimination, its threshold nearest to the upper left quadrant of the ROC curve. We will also conduct bivariate meta-regression to explore including a binary covariate for index test to understand if the expected sensitivity and specificity or both differs between index tests (Macaskill 2010).

An exploratory analysis will assess the value of combining the best three index tests where each have some individual predictive ability, and studies included participants who had all three tests (or the value of combining two of the three best tests where this is feasible and assessing three is not).

Investigations of heterogeneity

Heterogeneity will be examined by considering study characteristics, visual inspection of forest plots of sensitivities and specificities, and examining ROC curves of raw data. Heterogeneity due to different cut off values for each index test will be examined by comparing results of the bivariate random-effects meta-analyses at each cut off point. The effects of reference standard type (serum osmolality or weight change), participant type (community-dwelling older people, those in residential care or in hospital), sex, and baseline prevalence of dehydration will be assessed (Leeflang 2009). Most will be study-level variables, but for mixed sex studies where we have the full study data set, we will produce separate 2 x 2 tables for men and women to enable more complete analysis.

Sensitivity analyses

We will assess the effect of four quality items: acceptable delay between tests; incorporation avoided; partial verification avoided; and withdrawals explained; on the results by using each quality assessment item as a covariate in bivariate regression. These four items have been chosen for sensitivity analyses because they are not explored within the investigations of heterogeneity and are potentially troublesome even though we will have access to full data sets for most included studies.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategy

Database	Search terms
MEDLINE (Ovid)	1. exp Aged/ 2. aged.tw. 3. (older adult* or older people or older person* or older patient* or older women or older men).tw. 4. elder*.tw. 5. "65 and over".tw. 6. "sixty five and over".tw. 7. sixty five years.tw. 8. (geriatric or geriatrics).tw. 9. (senile or senility).tw. 10. old age.tw. 11. nursing home*.tw. 12. care home*.tw. 13. or/1-12 14. exp Infant/ or exp Child/ or Adolescent/ 15. 13 not 14 16. (Adult/ or Middle Aged/) not ((Adult/ or Middle Aged/) and (Aged/ or "Aged, 80 and Over"/ or Frail Elderly/)) 17. 15 not 16 18. Dehydration/ 19. Water-electrolyte Imbalance/ 20. Water-electrolyte Balance/

(*Continued*)

	21. Hyperkalemia/ 22. Hypokalemia/ 23. Hypernatremia/ 24. Hyponatremia/ 25. Osmolar Concentration/ 26. Hypovolemia/ 27. (dehydrat* or hydrat*).tw. 28. ((fluid* or water) adj3 (balance* or imbalance* or status or body or extracellular or intracellular)).tw. 29. (hypokal* or hyperkal* or hyponatr* or hypernatr*).tw. 30. (plasma* adj3 (tonicit* or hypertonic* or hypotonic*)).tw. 31. h?emoconcentrat*.tw. 32. osmolalit*.tw. 33. hypovol?emi*.tw. 34. or/18-33 35. and/17,34 36. Tongue/ 37. Axilla/ 38. Skin/ 39. Mucous Membrane/ 40. Mouth Mucosa/ 41. Respiratory Mucosa/ 42. exp Nasal Mucosa/ 43. (mucous membrane* or mucosal tissue* or mucosa).tw. 44. (tongue* or axilla* or armpit* or skin).tw. 45. or/36-44 46. (dry or dried or furrow* or turgid or turgor or damp*).tw. 47. and/45-46 48. exp Eye/ 49. (eye or eyes).tw. 50. or/48-49 51. (dry or dried or sunk*).tw. 52. and/50-51 53. Urine/ 54. (urin* adj3 (volume* or colo?r or dark* or gravit* or concentration)).tw. 55. Heart Rate/ 56. Pulse/ 57. ((pulse or heart) adj3 (rapid* or change* or fast)).tw. 58. exp Blood Pressure/ 59. ((systolic or diastolic) adj3 pressure*).tw. 60. Dizziness/ 61. (dizz* or lightheaded* or orthostasis).tw. 62. or/55-61 63. (postural or stand* or upright*).tw. 64. and/62-63 65. Upper Extremity/ or Arm/ 66. Muscle Weakness/ 67. 65 and 66 68. ((weak or weakness) adj3 (arm* or upper limb* or upper extremit*)).tw.

(*Continued*)

	69. ((fluid* or water) adj3 (balance or chart* or record* or diary or diaries)).tw. 70. Body Weight Changes/ 71. Weight Loss/ 72. ((weight or BMI or body mass index) adj3 (loss or lost or lose or losing or fall* or reduc* or chang*)).tw. 73. (capillar* adj3 refill*).tw. 74. Electric Impedance/ 75. Plethysmography, Impedance/ 76. (impedance* or bioimpedance or BIA).tw. 77. Physical Examination/ 78. ((clinical* or physical) adj3 (sign* or symptom* or exam* or finding* or assess*).tw. 79. Water Loss, Insensible/ 80. ((epiderm* or skin* or transepiderm* or transderm*) adj3 (water* or fluid* or temperature)).tw. 81. Body Temperature Regulation/ 82. Sweating/ 83. Thermogenesis/ 84. Skin Temperature/ 85. (thermoregulat* or thermogenesis or sweating).tw. 86. ((thermal or temperature*) adj3 (regulat* or control*)).tw. 87. (blood flow* adj3 (skin or epiderm* or dermal)).tw. 88. or/47,52-54,64,67-87 89. and/17,34,88 90. Animals/ not (Humans/ and Animals/) 91. 89 not 90 92. case report.ti. 93. 91 not 92
EMBASE (Ovid)	1. exp Aged/ 2. aged.tw. 3. (older adult* or older people or older person* or older patient* or older women or older men).tw. 4. elder*.tw. 5. “65 and over”.tw. 6. “sixty five and over”.tw. 7. sixty five years.tw. 8. (geriatric or geriatrics).tw. 9. (senile or senility).tw. 10. old age.tw. 11. nursing home*.tw. 12. care home*.tw. 13. or/1-12 14. exp Child/ or exp Newborn/ or Adolescent/ 15. 13 not 14 16. (Adult/ or Middle Aged/) not ((Adult/ or Middle Aged/) and exp Aged/) 17. 15 not 16 18. Dehydration/ 19. Electrolyte Disturbance/ 20. Electrolyte Balance/ 21. Hyperkalemia/ 22. Hypokalemia/ 23. Hypernatremia/

(*Continued*)

	24. Hyponatremia/ 25. Osmolarity/ 26. Hypovolemia/ 27. (dehydrat* or hydrat*).tw. 28. ((fluid* or water) adj3 (balance* or imbalance* or status or body or extracellular or intracellular)).tw. 29. (hypokal* or hyperkal* or hyponatr* or hypernatr*).tw. 30. (plasma* adj3 (tonicit* or hypertonic* or hypotonic*)).tw. 31. h?emoconcentrat*.tw. 32. osmolalit*.tw. 33. hypovol?emi*.tw. 34. or/18-33 35. and/17,34 36. Tongue/ 37. Axilla/ 38. Skin/ 39. Mucosa/ 40. exp Mouth Mucosa/ 41. Respiratory Tract Mucosa/ 42. (mucous membrane* or mucosal tissue* or mucosa).tw. 43. (tongue* or axilla* or armpit* or skin).tw. 44. or/36-43 45. (dry or dried or furrow* or turgid or turgor or damp*).tw. 46. and/44-45 47. Dry Skin/ 48. Skin Turgor/ 49. or/46-48 50. Eye/ 51. (eye or eyes).tw. 52. or/50-51 53. (dry or dried or sunk*).tw. 54. and/52-53 55. Dry Eye/ 56. or/54-55 57. Urine/ 58. (volume* or colo?r or dark* or gravit* or concentration).tw. 59. 57 and 58 60. Urine Color/ 61. Urine Volume/ 62. (urin* adj3 (volume* or colo?r or dark* or gravit* or concentration)).tw. 63. or/59-62 64. Heart Rate/ 65. (rapid* or fast).tw. 66. and/64-65 67. Heart Rate Variability/ 68. Pulse Rate/ 69. (rapid* or fast).tw. 70. and/68-69 71. ((pulse or heart rate) adj3 (rapid* or fast)).tw.

(*Continued*)

	72. Blood Pressure/ 73. Systolic Blood Pressure/ or Diastolic Blood Pressure/ or Orthostatic Blood Pressure/ 74. (systolic blood pressure or diastolic blood pressure or orthostatic blood pressure).tw. 75. Dizziness/ 76. (dizz* or lightheaded* or orthostasis).tw. 77. or/66-67,70-76 78. Standing/ 79. (postural or stand* or upright*).tw. 80. or/78-79 81. and/77,80 82. Positional Dizziness/ 83. or/81-82 84. Arm/ 85. Muscle Weakness/ 86. and/84-85 87. Arm Weakness/ 88. ((weak or weakness) adj3 (arm* or upper limb* or upper extremit*)).tw. 89. or/86-88 90. ((fluid* or water) adj3 (balance or chart* or record* or diary or diaries or chart*)).tw. 91. Weight Change/ 92. Weight Reduction/ 93. ((weight or BMI or body mass index) adj3 (loss or lost or lose or losing or fall* or reduc* or chang*)).tw. 94. (capillar* adj3 refill*).tw. 95. Impedance/ 96. Impedance Plethysmography/ 97. (impedance* or bioimpedance or BIA).tw. 98. ((clinical* or physical) adj (sign* or symptom* or exam* or finding*)).tw. 99. Thermoregulation/ 100. Sweating/ 101. Skin Temperature/ 102. Thermogenesis/ 103. ((epiderm* or skin* or transepiderm* or transderm*) adj3 (water* or fluid* or temperature)).tw. 104. (thermoregulat* or thermogenesis or sweating).tw. 105. ((thermal or temperature*) adj3 (regulat* or control*)).tw. 106. (blood flow* adj3 (skin or epiderm* or dermal)).tw. 107. or/46,49,56,63,83,89-106 108. and/17,34,107 109. (Animal/ or Rat/ or Mouse/) not (Human/ and (Animal/ or Rat/ or Mouse/)) 110. 108 not 109 111. case report.ti. 112. 110 not 111
CINAHL	S55 S51 NOT S54 S54 S53 NOT S52 S53 MH “Adult” OR MH “Middle Age” S52 (MH “Adult” OR MH “Middle Age”) AND MH “Aged+” S51 S49 NOT S50 S50 (MH “Adolescence+”) OR (MH “Young Adult”) OR (MH “Child+”) S49 S43 AND S48 S48 S21 OR S47

(*Continued*)

	S47 S44 OR S45 OR S46 S46 AB ("65 and over" OR "sixty five years" OR geriatric OR geriatrics OR senile OR senility OR old age) S45 AB elder* S44 AB (older adult* OR older people OR older person OR older patient* OR older women OR older men) S43 S14 OR S42 S42 S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 S41 AB osmolalit* S40 AB (hemoconcentrat* OR haemoconcentrat*) S39 AB (water N3 intracellular) S38 AB (water N3 extracellular) S37 AB (water N3 body) S36 AB (water N3 status) S35 AB (water N3 imbalance*) S34 AB (water N3 balance*) S33 AB (plasma* N3 hypertonic*) S32 AB (plasma* N3 hypotonic*) S31 AB (plasma* N3 tonicit*) S30 AB (hypokal* OR hyperkal* OR hyponatr* OR hypernatr* OR hypovolemi* OR hypovolaemi*) S29 AB (fluid* N3 intracellular) S28 AB (fluid* N3 extracellular) S27 AB (fluid* N3 body) S26 AB (fluid* N3 status) S25 AB (fluid* N3 imbalance*) S24 AB (fluid* N3 balance*) S23 AB (dehydrat* OR hydrat*) S22 S14 and S21 S21 S15 or S16 or S17 or S18 or S19 or S20 S20 (MH "Gerontologic Nursing+") S19 TI ("65 and over" OR "sixty five years" OR geriatric OR geriatrics OR senile OR senility OR old age) S18 TI elder* S17 TI (older adult* OR older people OR older person OR older patient* OR older women OR older men) S16 (MH "Nursing Homes+") OR (MH "Nursing Home Patients") S15 (MH "Aged+") OR (MH "Aged, 80 and Over") OR (MH "Aged, Hospitalized") OR (MH "Assisted Living") OR (MH "Gerontologic Care") OR (MH "Gerontologic Nursing+") S14 S1 or S2 or S3 or S4 or S7 or S8 or S11 or S12 or S13 S13 TI osmolalit* S12 TI (hemoconcentrat* OR haemoconcentrat*) S11 S9 and S10 S10 TI (tonicit* OR hypertonic* OR hypotonic*) S9 TI plasma* S8 TI (hypokal* OR hyperkal* OR hyponatr* OR hypernatr* OR hypovolemi* OR hypovolaemi*) S7 S5 and S6 S6 TI balance* OR TI imbalance* OR TI status OR TI body OR TI extracellular OR TI intracellular S5 TI fluid* OR TI water S4 TI dehydrat* OR TI hydrat* S3 (MH "Osmolar Concentration+")

(*Continued*)

	S2 (MH "Fluid-Electrolyte Imbalance") OR (MH "Fluid-Electrolyte Balance+") S1 (MH "Dehydration") OR (MH "Hyperkalemia") OR (MH "Hypokalemia") OR (MH "Hypernatremia") OR (MH "Hyponatremia")

MEDLINE

- Lines 1-17 = terms for the participants
- Lines 18-34 = terms for the Target Condition
- Line 35 = Participants and Target Condition
- Lines 36 to 88 = Index Tests, grouped by type.
- Line 89 = Participants and Target Condition and Index Tests
- Lines 90-91 = removing studies indexed as Animal/ only from search (retains Humans/ and Animals/, or studies with neither index term)
- Line 92-93 = removes studies with Case Report in the title of the article.

EMBASE

This strategy has been constructed along similar lines to MEDLINE, but using available EMTREE terms.

CINAHL

Due to current difficulties in searching the EBSCO interface for CINAHL (the only interface available) we have used terms only for Participants and Target Condition. Title words/phrases and Abstract words phrases are grouped separately. This was done to get some idea of the yield from leaving out the index tests. There is a risk that some relevant studies may have been missed, but the search interface cannot cope with complex Boolean searching or large numbers of search lines, and failed when this was attempted.

- Lines S1-S14 = CINAHL headings and word in Title for the Target Condition
- Lines S15-S21 = CINAHL headings and words in Title for Participants
- Lines S22 = Target Condition and Participants combined (to get some idea of yield)
- Lines S23-S42 = Abstract words for Target Condition
- Line S43 = CINAHL headings or Title or Abstract words for Target Condition
- Lines S44-S47 = Abstract words for Participants
- Line S48 = CINAHL headings or Title or Abstract words for Participants
- Line S49 = Target Condition and Participants
- Line S50-S55 = removal of articles indexed only with CINAHL headings for people younger than 65 years

Appendix 2. Criteria for assessment of study validity

Quality assessment area	Score	Criteria
Representative spectrum	Yes	Where participants were older people living in the community independently or with care (for example, sheltered housing, communities for older people or in residential care homes, NOT in hospital or other medical settings or where people were chosen for the presence of a risk factor, medical condition or illness) AND the method of recruitment was consecutive, or random samples were taken from consecutive series
	No	One or more of the above criteria clearly not met
	Unclear	Where it is unclear whether either or both criteria were met

(*Continued*)

Acceptable reference standard	Yes	Cut offs used to define dehydration were: Serum or plasma osmolality - Impending dehydration: serum or plasma osmolality 295 to 300 mOsmol/kg Serum or plasma osmolality - Current dehydration: serum or plasma osmolality > 300 mOsmol/kg
	No	The definition was similar, but not exactly the same OR serum osmolality was calculated rather than measured, or the reference standard was weight change
	Unclear	It is not clear whether the definition is exactly the same, or that the serum osmolality was measured (rather than calculated)
Acceptable delay between tests	Yes	Delay ≤ 2 hours between the index text(s) and the reference standard (for at least 90% of participants)
	No	Delay > 2 hours for over 10% of the participants
	Unclear	Any delay not stated or variable
Partial verification avoided	Yes	All, or a random selection of, participants who received the index test went on to receive verification of their disease status using a reference standard, even if the reference standard was not the same for all participants. For this to be assumed the study design should be prospective
	No	Some patients who received the index test did not receive the reference standard, and the selection of patients to receive the reference standard was not random
	Unclear	Unclear
Differential verification avoided	Yes	The same reference standard was used in all patients
	No	Different reference standards were used in some patients
	Unclear	Unclear
Incorporation avoided	Yes	The index test did not form part of the reference standard
	No	The index test was formally part of the reference standard
	Unclear	Unclear
Reference standard results blinded	Yes	Reference standard results were interpreted blind to the results of the index test(s), or blinding was dictated by the test order
	No	The reference standard results were interpreted with knowledge of the index test(s) results
	Unclear	Unclear

(*Continued*)

Index test results blinded	Yes	Index test results were interpreted blind to the results of the reference test, or blinding was dictated by the test order
	No	The index test results were interpreted with knowledge of the reference test results
	Unclear	Unclear
Relevant clinical information	Yes	Interpretation of the index and reference tests were without reference to other potentially relevant clinical data, such as knowledge of previously dehydrated episodes and/or current risk factors for dehydration (such as fever, vomiting, diarrhoea, lack of appetite, dementia, depression etc)
	No	Data were interpreted only with added clinical data
	Unclear	Unclear
Uninterpretable test results reported	Yes	The number of uninterpretable test results was stated, or the number of results reported agreed with the number of patients recruited (indicating no uninterpretable test results)
	No	Uninterpretable test results occurred or were excluded but it was not reported how many tests were uninterpretable
	Unclear	It is unclear uninterpretable results occurred
Withdrawals explained	Yes	It was clear what happened to all patients who entered the study (e.g. flow diagram of study participants explains any withdrawals or exclusions), or the numbers recruited match those in the analysis
	No	Some of the people who entered the study did not receive both index test and reference standard, or were not included in the analysis, and were not accounted for
	Unclear	Unclear
Was the study free of commercial funding?	Yes	Funding was stated, and it was clear that this was not from a source likely to benefit from a specific study result AND author allegiances stated and none allied to a source likely to benefit from specific study result
	No	Study funding or author allegiance from a source likely to benefit from a specific study result
	Unclear	Funding and/or allegiances not stated or their link to study results not clear

HISTORY

Protocol first published: Issue 2, 2012

CONTRIBUTIONS OF AUTHORS

Lee Hooper conceived the review and drafted the protocol. All authors contributed to refining and correcting the protocol and have agreed the final text.

DECLARATIONS OF INTEREST

- Natalie J Attreed: None known
- Wayne W Campbell: None Known
- Adam M Channell: None known
- Philippe Chassagne: None known
- Kennith R Culp: None known
- Stephen J Fletcher: None known
- Nigel Fuller: None known
- Phyllis M Gaspar: None of the consulting or research funding received presents a potential conflict of interest.
- Daniel J: Gilbert: None known
- Adam C Heathcote: None known
- Lee Hooper: LH's institution has received funding to allow her and her PhD student to investigate dehydration in older people - this primary research follows on from this systematic review.
- Paul R Hunter: PRH has been chair of the executive board of the Institute of Public Health and Water Research, Chicago, and was chair of the Science Advisory Council for Suez Environment until 2010. He has also given expert medical opinion in relation to outbreaks of waterborne disease.
- Gregor Lindner: None known
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- David R Thomas: Dr Thomas has given lectures to educational seminars, provided expert legal testimony, and is author of a textbook Geriatric Nutrition.
- Bonnie J Wakefield: None known
- Sean Ward: None known

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