Check for updates

PROFESSOR CARSTEN FLOHR (Orcid ID : 0000-0003-4884-6286)

Article type : Original Article-Clinical Mechanisms in Allergic Disease

DR ZARIF K JABBAR-LOPEZ (ORCID: 0000-0003-4127-8263)
PROF CARSTEN FLOHR (ORCID: 0000-0003-4884-6286)
DR SIMON DANBY (ORCID: 0000-0001-7363-140X)
PROF JANET PEACOCK (ORCID: 0000-0002-0310-2518)

The effect of water hardness on atopic eczema and skin barrier function: A systematic review and meta-analysis

Running head: Water hardness and atopic eczema

Z.K. Jabbar-Lopez[1], C.Y. Ung[1], H. Alexander[1], N. Gurung[1], J. Chalmers[2], S. Danby[3], M.J. Cork[3], J.L. Peacock[4,5], C. Flohr[1]

1. Unit for Population-Based Dermatology, St John's Institute of Dermatology, King's College London and Guy's and St Thomas' NHS Foundation Trust, London UK
2. Centre of Evidence Based Dermatology, University of Nottingham, Nottingham UK
3. Sheffield Dermatology Research, Department of Infection, Immunity & Cardiovascular Diseases, The University of Sheffield Medical School, Sheffield UK
4. School of Population Health and Environmental Sciences, King's College London, London, United Kingdom
5. Department of Epidemiology, Geisel School of Medicine at Dartmouth, United States

Corresponding author:
Prof Carsten Flohr, MA MSc PhD FRCP FRCPCH
Unit for Population-Based Dermatology Research, St John's Institute of Dermatology, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH. United Kingdom
Tel: +44 (0) 20 7188 7188 ext. 51162, Fax: +44 (0)20 7188 6379

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CEA.13797

This article is protected by copyright. All rights reserved

Accepted Article

Email carsten.flohr@kcl.ac.uk

Word count: 4,548
Tables: 5
Figures: 3

Funding:
This work was funded through a National Institute for Health Research (NIHR) Career Development Fellowship (CDF-2014-07-037) and also supported by the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the UK NIHR, MRC or the UK Department of Health.

Author contribution:
The study was conceptualised and designed by CF. The literature search and data collection was performed by ZKJ-L and CYU. The data analysis was performed by ZKJ-L. The manuscript was drafted by ZKJ-L and then revised by all co-authors. All authors reviewed the final version and approved its submission.

Conflicts of interest:
ZKJ-L is an employee of Galderma. CF has received departmental investigator-led research funding from Sanofi for skin microbiome work. MJC is/has been an Investigator and/or Consultant for the following organisations: Astellas, Boots, Dermavant, Galapagos, Galderma, Harvey Water Softeners, Hyphens, Johnson & Johnson, Kymab, Leo Pharma, L'Oreal, Menlo, Novartis, Oxagen, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron, Sanofi Genzyme. MJC and SGD have received funding for research from Harvey Water Softeners. CYU, NG, HA, JC and JP - none.

Accepted Article

This article is protected by copyright. All rights reserved

ABSTRACT

Background

Hard domestic water has been reported to worsen atopic eczema (AE) and may contribute to its development in early life.

Objective

To review the literature on the relationship between the effect of water hardness (high calcium carbonate; $CaCO_3$) on a) the risk of developing AE, b) the treatment of existing AE, and c) skin barrier function in human and animal studies.

Design, data sources and eligibility criteria

We systematically searched databases (MEDLINE, Embase, Cochrane CENTRAL, GREAT and Web of Science) from inception until 30/6/2020. Human and animal observational and experimental studies were included. The primary outcomes were risk of AE and skin barrier function. Studies were meta-analysed using a random-effects model. Evidence certainty was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Results

Sixteen studies were included. Pooled observational data from 7 studies on 385,901 participants identified increased odds of AE in children exposed to harder versus softer water (odds ratio 1.28, 95% CI 1.09, 1.50; GRADE certainty: very low). Two mechanistic studies in humans reported higher deposition of the detergent sodium lauryl sulphate in those exposed to harder versus softer water. Two randomized controlled trials comparing water softeners with standard care did not show a significant difference in objective AE severity with softened water (standardised mean difference 0.06 standard deviations higher, 95% CI 0.16 lower to 0.27 higher; GRADE certainty: moderate).

Conclusions & Clinical Relevance

There was a positive association between living in a hard-water (range: 76 to >350 mg/L $CaCO_3$) area and AE in children. There is no evidence that domestic water softeners improve objective disease severity in established AE. There may be a role of water hardness in the initiation of skin inflammation in early life, but there is a need for further longitudinal and interventional studies.

Systematic review registration: PROSPERO (CRD42016051528)

This article is protected by copyright. All rights reserved

INTRODUCTION

Atopic eczema (AE, syn. atopic dermatitis) is a chronic inflammatory skin condition with a multifactorial aetiology and a high level of disease burden among both adults and children. The rising incidence of AE in many countries around the world over the past decades has raised the question of whether environmental factors may be contributing to this growing public health problem.[1] Given the ubiquity of bathing around the world, there has long been an interest in the relationship between the water and wash products that we bathe with and their effects on the skin.

Rainwater is naturally soft due to low mineral content. As rainwater falls to the ground and percolates through the rock it dissolves minerals and may become hard. This is particularly the case when water percolates through limestone where the water picks up calcium carbonate ($CaCO_3$). Thus the level of water hardness can vary considerably depending on the local geology and the proportion of groundwater that constitutes the household water supply. The UK has a very wide range of water hardness levels: from very hard water in south-east England ($CaCO_3$ >400 mg/L) to very soft water in Scotland (≤60 mg/L $CaCO_3$). Such variation in water hardness levels can be observed even within small geographical proximity. For instance, variation in the levels of water hardness across the county of Nottinghamshire was associated with significant differences in the prevalence of AE among primary school children in the late 1990s.[2]

Consequently, a number of studies have sought to explore the hypothesis that skin exposure to hard water leads to skin barrier dysfunction and an increased risk of AE. Various potential mechanisms for this have been proposed, including a direct effect of calcium carbonate on the skin. As calcium has a natural gradient in the epidermis, disruption of this gradient might lead to abnormalities in keratinocyte differentiation.[3] In culture, low concentrations of calcium stimulate the growth of primary keratinocytes and increasing calcium concentrations promote terminal differentiation.[4] Exogenous calcium applied to murine skin has been shown to inhibit the repair process of the epidermis following acute barrier disturbance with organic solvents.[5] Calcium also has a role in the binding of lamellar bodies to the granular cell layer membranes and, therefore, in the formation of the bilayer lipid water barrier. Disruption of this barrier is thought to be a key step in the early development of AE.[6] Furthermore, hard water is more alkaline than soft water resulting in increased buffering capacity, i.e. the ability to resist pH changes. This means hard water may be able to modify skin surface pH. Changes in pH influence skin barrier function through altering the activity of epidermal enzymes such as the lymphoepithelial Kazal-type 5 serine protease inhibitor (LEKTI). LEKTI cleaves profilaggrin into filaggrin as well as inhibiting kallikrein (KLK) proteases KLK5 (stratum corneum tryptic enzyme, SCTE), KLK7 (stratum corneum chymotryptic enzyme, SCCE), and KLK14, important for desquamation. LEKTI activity is enhanced in more acidic conditions.[7] Additionally, there is a chemical interaction between some surfactants in everyday wash products and hard water which results in increased deposition of metallic surfactants on the skin.[8] The repeated nature of such exposures may have a cumulative detrimental effect on skin barrier integrity.

This article is protected by copyright. All rights reserved

Such hypotheses are of interest to clinicians keen to advise their patients on the best approach to bathing, particularly in people who have or who may be at risk of AE. We therefore systematically appraised the literature on the relationship between the effect of water hardness on a) the risk of developing AE, b) existing AE, and c) skin barrier function.

Accepted Article

This article is protected by copyright. All rights reserved

METHODS

Literature search and study selection

A systematic literature search was performed to answer the question 'What is the effect of water hardness on skin barrier function and AE?'. The conduct and reporting of this review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[9] and the Meta-analyses of Observational Studies (MOOSE) checklist.[9,10] The protocol was registered with PROSPERO (CRD42016051528). Systematic searches were conducted in MEDLINE, Embase, Cochrane CENTRAL, GREAT and Web of Science (including the Conference Proceedings Citation Index) from inception to 30th June 2020 using MESH terms such as 'Eczema' 'Atopic dermatitis' 'water' 'water softening' calcium' 'magnesium' and combinations of related free text keywords (full search strategy see Supplementary Appendix S1). Searches were performed by a researcher trained in systematic reviews (ZKJ-L). No language restrictions were used. References of included studies were reviewed for additional papers of relevance.

Inclusion and exclusion criteria

We included human and animal observational and experimental studies evaluating water hardness (calcium carbonate), water softening and/or filtration devices vs. naturally soft water, softened water, chlorine-free water, deionised water, filtered water. All study types were included, including conference abstracts. There were no language restrictions and no other exclusion criteria.

Outcome measures

The primary outcomes were risk of AE and skin barrier function impairment, as measured by raised transepidermal water loss (TEWL). No standardised definition of AE was specified. Secondary outcomes were also extracted, including clinician-assessed AE severity, patient-reported AE severity, AE disease control, time to onset of AE, wash product use including traditional alkyl carboxylate soaps and newer synthetic detergents (syndets), biological and cellular measures of skin barrier function, such as cutaneous cytokine release, and detergent deposition.

Data abstraction and risk of bias assessment

After de-duplication, abstracts and titles were screened independently by two different researchers (ZKJ-L and CYU). Full-text articles of selected titles/abstracts were reviewed against *a priori* defined inclusion and exclusion criteria, again independently by two different researchers (ZKJ-L and CYU). Discrepancies were resolved by discussion with the senior author (CF). Data extraction and quality assessment were performed by one researcher and checked by another against the original article.

Randomised controlled trial (RCT) risk of bias was assessed using the Cochrane Risk of Bias tool.[11] Study quality for other study types was assessed using domain-based approaches with tools appropriate to the

This article is protected by copyright. All rights reserved

specific designs of the included studies. The Newcastle-Ottawa Scale[12] was used for cohort studies without calculating a summary score. The Klimisch code was used to assess the quality of animal and *in vitro* studies using ToxRTool (available from https://eurl-ecvam.jrc.ec.europa.eu/about-ecvam/archive-publications/toxrtool). Data on outcomes were summarised and quality assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[13] Non-randomised studies were considered low-quality evidence unless there was a compelling reason to grade up.[14]

Data synthesis and statistical analysis

Human and animal data were analysed separately. Where appropriate, quantitative synthesis was performed using an inverse-variance weighted random effects model using RevMan v5.0 (Cochrane Collaboration)[15] and Open Meta-Analyst (Brown University)[16]. Otherwise, a narrative synthesis was used. Where a quantitative synthesis was performed, heterogeneity was explored by visual inspection of the forest plots and through the calculation of the I-squared (I^2) measure of heterogeneity.[17] Where non-trivial heterogeneity (I^2 >50%) was identified, this was explored through analysis of pre-defined subgroups: Infants (<1 year); primary school-aged children (5 to 11 years of age), secondary school-aged children (11-16 years), adults (>16 years of age); filaggrin loss of function (LOF) mutation status; clinician-reported versus patient-reported diagnosis AE. Water hardness exposure was considered “hard” or “soft” according to the definitions reported in each study. Where water hardness was reported in >2 categories, the highest category was compared to the lowest. AE risk data were summarised as odds ratios (ORs) with 95% confidence intervals (CIs). Wherever possible, adjusted estimates were synthesised in preference. In the GRADE tables, anticipated absolute effects were calculated based on the assumed pooled risk in the comparison group and the relative effect of the intervention or exposure (and its 95% CI). Where different scales were reported for a particular outcome, comparisons were made using standardised mean differences with 95% CIs. When interpreting outcomes, a two-sided P value of less than 0.05 was considered statistically significant. We planned to assess publication bias using funnel plots for quantitative syntheses of ≥10 studies.

Accepted Article

This article is protected by copyright. All rights reserved

RESULTS

Studies included in the review

The literature search identified 5,981 studies. Fifty studies were selected for full review; 16 were included: 2 RCTs[18,19], 8 observational studies[2,20-26], 2 experimental studies with a randomised component[8,27], 3 experimental non-randomised studies[28-30], 2 animal studies[30,31]. Study characteristics are presented in Table 1. Figure 1 represents the PRISMA flow diagram for study selection.

Studies in humans

Hard water exposure and risk of atopic eczema

The pooled estimate based on 385,901 participants in five cross-sectional and two birth cohort studies[2,20-25] showed statistically significant increased odds of AE in infants and children exposed to harder (range: 76 to >350 mg/L $CaCO_3$) versus softer (range: 35.2 to 256 mg/L $CaCO_3$) water (OR 1.28, 95% CI 1.09, 1.50) (Figure 2). No studies were identified that examined the risk of AE with hard water exposure in adults. Certainty in this estimate is very low due to high risk of bias and heterogeneity (I^2 63%; GRADE profile; Table 2). Time to AE development was not reported.

Hard water exposure and risk of atopic eczema in infants

Two studies[22,25] reported a higher risk of AE in infants living in a hard water area and one[23] reported no statistically significant difference in AE risk between harder and softer water areas (Figure 2). These studies adjusted for potential confounders, including geographical location (Table 1). The pooled estimate based on 27,892 infants was almost identical to that for all children but was not significant (OR 1.29, 95% CI 0.89, 1.86). Certainty in this estimate is very low due to high risk of bias and heterogeneity (I^2 68%; Table 2). This heterogeneity may be explained by the different populations studied – younger infants (3 months) in the Perkin[25] cross-sectional study, older infants in the Engebretsen[22] (<18 months) and Font-Ribera (<14 months) birth cohort studies. The use of different diagnostic criteria, i.e. questionnaire-derived diagnosis vs skin examination by a physician following validated diagnostic criteria, as well as covariates adjusted for, might also have contributed to the heterogeneity (Table 1). Importantly, there were also differences in the precision of water hardness estimation – postcode-based (around 100 m) in the Perkin study compared with wider, municipality-based estimates in the Engebretsen and Font-Ribera studies. Interestingly, the Font-Ribera study reported no significant variation in water hardness with repeat measurements over one year, suggesting that season is less likely to be a significant source of heterogeneity. A longitudinal analysis of data from the Perkin study by our group found no overall statistically significant association between exposure to harder versus softer water and parent-reported AE (adjusted HR 1.07, 95% CI 0.92, 1.24).[26]

Hard water exposure and risk of atopic eczema in non-infant children

This article is protected by copyright. All rights reserved

Five studies[2,20-24] reported on the risk of AE in children exposed to harder versus softer water. The pooled estimate based on 358,009 participants showed a statistically significant increased risk of AE in children exposed to hard water (OR 1.27; 95% 1.03, 1.57). Two studies[2,20] reported different risks in primary and secondary school-aged children and so these differences were explored further using a post hoc analysis of subgroups based on these categories.

Hard water exposure and risk of atopic eczema in primary school children

Three cross-sectional studies[2,20,24] reported a higher risk of AE and two studies[21,23] reported no statistically significant difference in AE risk in primary school children living in harder versus softer water areas (Figure 2). Studies adjusted for potential confounding covariates, such as socio-economic status (Table 1). The pooled estimate based on 353,573 participants showed a statistically significant increased risk of AE in primary school-aged children exposed to hard water (OR 1.43; 95% CI 1.09, 1.87). Certainty in this estimate is very low due to high risk of bias and heterogeneity (I^2 68%; Table 2). This heterogeneity may partly be explained by global differences in what is considered 'hard' water: up to 100 mg/ml $CaCO_3$ in the highest quartile in the Miyake et al.[24] study in Japan, compared to up to 341 mg/ml $CaCO_3$ in the highest quartile in the McNally et al.[2] study in the UK. Removing the large Miyake study[24] in a post hoc leave-one-out sensitivity analysis increased the pooled effect estimate (OR 1.59, 95% CI 1.29, 1.97) (Supplementary Figure 1).

Hard water exposure and risk of atopic eczema in secondary school children

Two cross-sectional studies[2,20] in the UK and Spain reported no statistically significant difference in AE risk in secondary school children living in harder versus softer water areas. The pooled estimate based on 4,436 participants also showed no statistically significant effect of hard water exposure on ISAAC questionnaire-based AE risk among secondary school-aged children (OR 0.80, 95% CI 0.35, 1.79) (Figure 2). However, certainty in this estimate is very low due to high risk of bias, moderate heterogeneity (I^2 52%) and imprecision (Table 2).

Effect of FLG mutation status on risk of atopic eczema in infants exposed to hard water

Perkin et al. investigated the interaction between hard water and the presence of a loss-of-function mutation in the filaggrin (*FLG*) gene in 1,303 healthy, breastfed 3-month olds but this was not statistically significant (OR 2.10 95% CI 0.74, 5.99). A longitudinal analysis of infants aged 3-36 months in the same study showed that, after adjustment for confounders, there was a significantly higher risk of parent-reported, doctor-diagnosed AE in infants with *FLG* mutations exposed to hard water, compared to those with wild-type *FLG* living in softer water areas (adjusted HR 2.72 [95%CI 2.03, 3.66]).[26]

Hard water compared to deionised water and skin barrier dysfunction in adults

TEWL was measured by Danby et al.[8] in 80 adults with or without AE, with and without *FLG* loss-of-function mutations. After 72 hours, mean TEWL at the volar forearm skin sites washed with hard water was

This article is protected by copyright. All rights reserved

2.76 g/m^2/h significantly higher than in those washed with deionised water (Table 3). Danby et al. reported no statistically significant effects of hard water on skin surface pH or IL-1α. Warren et al.[27] washed the forearms of 36 healthy adult female volunteers with various types of soap and hard (188 mg/L) or deionised water. There was no difference in skin hydration between washing with hard and deionised water (Table 3). However, skin rinsed in hard water had a 1.9 pF lower (95% CI -2.59, -1.21) mean level of skin hydration at five days. Both studies reported statistically significant increased erythema 72 hours to 5 days after washing with hard water. Overall, due to the small sample size and non-randomised experimental design, there is a very low certainty of the evidence for these estimates (Table 3).

Engebretsen et al.[28] studied the short-term effect of hard water on TEWL, NMF and cytokines in 40 healthy adults without *FLG* mutations using Finn chambers on the volar forearm. At 24 hours there was no difference between mean (SD) TEWL in volar forearm skin exposed to soft 13.0 (±6.2) g/m2/h and hard 13.1 (±6.1) g/m2/h compared with occlusion alone 11.8 (±3.3) g/m2/h. At 48 hours there was a statistically significant difference between soft 9.1 (±3.0) g/m2/h and hard 9.2 (±2.8) g/m2/h individually compared with occlusion alone 8.2 (±2.2) g/m2/h. At 24 hours, a significant decrease in NMF on tape strips was observed for soft (0·51 (0·19) mmol/g) and hard water (0·61 (0·32) mmol/g) compared with occlusion alone (0·71 (0·18) mmol/g), but no significant difference in mean NMF was found between hard and soft water. At 24 hours, there was a significant increase in mean interleukin-4 (IL-4), interferon-gamma (IFN-y) and interleukin-10 (IL-10) on tape strips after exposure to hard water compared to the control. No significant increase was found for soft water compared to control. The study did not report a direct comparison of the effect between hard and soft water. Matsuda et al.[29] studied the effect of ultra-pure softened water (UPSW) on skin hydration in 15 elderly care home residents without a history of skin diseases. Statistically significantly ($P<0.01$) higher mean skin hydration was reported at 12 weeks in adults bathed with UPSW compared to those bathed with tap water (Table 3). However, there was no statistically significant difference in mean TEWL or skin dryness between the groups at 12 weeks.

Water softeners and usual care compared to usual care alone in treating atopic eczema

Two RCTs[18,19] compared water softeners plus usual skincare to usual skincare alone in the treatment of AE in children. Thomas et al.,[18] found no objective improvement in disease severity from the addition of an ion-exchange water softener to usual care in 323 children aged 6 months to 16 years with moderate AE after 12 weeks (mean change in SASSAD 0.66 [95% CI -1.37, 2.69]). A smaller study by Togawa et al.[19] subsequently reported a non-statistically significant reduction in mean EASI of -2.61 points (95% CI -7.03, 1.81) at 6 weeks in 12 children aged 3-6 years with mild AE. The pooled estimate of objective AE severity across both RCTs showed no statistically significant additional benefit of ion-exchange water softeners in the treatment of AE (standardised mean difference (SMD) 0.06, 95% CI -0.16, 0.27) (Figure 3). Certainty in this estimate is moderate (Table 4). Thomas et al.[18] reported an improvement in subjective AE severity (POEM) with the use of an ion-exchange water softener in addition to usual care (mean reduction -2.03 points, 95% CI -3.55, -0.51, GRADE: moderate certainty). Slight improvement in disease control as

This article is protected by copyright. All rights reserved

measured by well-controlled weeks (WCW) was reported with the use of an ion-exchange water softener in addition to usual care (mean increase in WCW 0.99 week, 95% 0.04, 1.95, GRADE: moderate certainty). Totally-controlled weeks (TCW) also increased (mean 1.19 weeks, 95% CI 0.43, 1.95, GRADE: moderate certainty) (Table 4).

In Togawa et al. the changes in mean TEWL were not statistically significant at abdominal (-5.77 g/m2/h; 95% CI -13.9, 2.41) or upper back sites (2.26 g/m2/h; 95% CI -16.9, 21.4) over 12 weeks. The same study reported a statistically significant reduction in mean pruritus visual analogue scale (-2.1 points, 95% CI -4.14, -0.063, GRADE: low certainty) (Table 4).

Studies in animals

Animal studies of softened water and skin barrier dysfunction

Ohmori et al.[31] conducted a randomised crossover study of 11 dogs with AE. Dogs received a weekly shampoo for 4 weeks using either hard (158 mg/L $CaCO_3$) or UPSW (<1 mg/L $CaCO_3$) followed by a washout period of at least 12 weeks before switching to the other water type. The authors reported the changes in skin barrier dysfunction in each treatment period separately but did not directly compare the changes overall using a within-subject statistical analysis. The authors reported significantly improved canine eczema severity (CADESI) score and TEWL after shampoo treatment with soft water and no significant change after tap water (table 1), but with no direct, within-subject comparison these results cannot be used to infer a significant benefit of soft water and certainty in the reported findings is very low (Table 5).

Tanaka et al.[30] examined the effects of treatment with UPSW, tap water versus no treatment on the skin of 30 NC/Tnd mice with phenotypic eczema (Table 1). The graphical results showed the change in clinical severity score over time but are difficult to interpret since there is no overall analysis of the trend over time in the three groups.

Publication bias

Publication bias was not formally assessed due to the limited number of studies included in the quantitative syntheses (<10).

This article is protected by copyright. All rights reserved

DISCUSSION

We performed a systematic literature review and meta-analysis of the relationship between water hardness and the primary outcomes of AE and skin barrier function. Overall, in non-infant children exposed to harder versus softer water, there were slightly increased odds of AE, although there is very low certainty in the evidence. In infants and secondary school-aged children, there was no clear evidence of overall increased risk of AE with hard water exposure. However, infants with *FLG* mutations exposed to hard water may be at a higher risk of AE. In adults, hard water may result in skin barrier dysfunction, as measured by slight increases in short-term TEWL and skin erythema, with a more marked effect seen in adults with AE who have *FLG* mutations. Hard water appears to result in little to no difference in skin IL-1α release or skin surface pH but may reduce short-term skin hydration slightly. Secondary outcomes of clinician- and patient-reported AE severity and control were also reviewed. There is evidence that water softeners provide no objective improvement in AE severity when used in addition to usual care, with low certainty in the evidence. However, there is moderate-quality evidence that water softeners reduce patient-reported AE severity slightly and improve AE disease control slightly in addition to usual care.

Strengths and limitations

We conducted a comprehensive systematic search with the inclusion of the 'grey' literature. We assessed risk of bias for included studies and rated the certainty of the evidence for each outcome using the GRADE approach. There were key methodological limitations in the studies of AE risk that preclude firm conclusions being drawn regarding the role of hard water exposure on AE risk in children. There was a lack of studies in very young children and in adults. Definitions of hard water and AE varied across studies, potentially leading to misclassification. Most studies used questionnaire-based child- or parent-reported AE to determine AE status, some of which were based on the validated ISAAC questionnaire. Exposure to hard water is a product of water hardness and bathing frequency. Observational studies only look at the association between living in a hard water area and developing AE, rather than the effect of hard water exposure *per se* on the risk of AE development. Some studies included adjustment for confounders, however, the studies were mainly of a cross-sectional design and therefore do not allow causal interpretations to be made. Furthermore, the definition and nature of the confounders accounted for in the different studies varied, and so as with any observational study, there is a risk of bias due to residual confounding.

A limitation of this review is that single, rather than double, data extraction was used. There was a high degree of heterogeneity between studies that persisted after subgroup analyses, suggesting that the results must be interpreted with caution. An obvious difference between studies is in the levels of hard water between study areas. It could be that the baseline is too high, and/or that the comparator is too low. Indeed, removing the Miyake study where the comparison was between 70 mg/L CaCO3 and <48 mg/L CaCO3 increases the overall pooled OR to 1.53 (95% CI 1.29, 1.97) (see Supplementary Figure S1). The observed

This article is protected by copyright. All rights reserved

heterogeneity between studies may also be driven by differences in study design, for example, cross-sectional versus cohort design.

Interpretation of main findings

The development of AE is multifactorial and likely due to genetic determinants of skin barrier function and immunity along with environmental exposures that initiate and perpetuate the cycle of inflammation and skin barrier damage seen in chronic AE. The potential effect of environmental exposures, such as hard water, on skin barrier function has been hypothesised to be greater in early life because the skin barrier is immature. Our finding of an increased risk of AE in younger rather than older children fits with this hypothesis. Data from the Warren et al and Danby et al studies suggest that detergents in wash products may interact with hard water resulting in deposition of detergents on the skin leading to a detrimental effect on skin barrier function. Whilst the focus in the literature has been on calcium carbonate as the main determinant of water hardness, magnesium also influences hardness. Evidence from *in vitro* studies suggests that magnesium has a beneficial effect on skin barrier function. Furthermore, this effect may be enhanced by the addition of calcium, so long as the ratio of calcium to magnesium is <1.[32] Dead Sea water has a very high calcium level (17,600 mg/L) yet it is reported as having beneficial properties for the skin. This may in part be because the magnesium ion concentration is higher still at 45,900 mg/L, i.e. a ratio of 0.38.[33] As ion-exchange water softeners remove both calcium and magnesium, along with other divalent cations such as iron, zinc, and manganese, this may partly explain the lack of efficacy of water softeners in the treatment of AE. Softened water is different from naturally soft water in both its mineral content and pH, in that softened water retains the alkaline pH of the original hard water, whereas naturally soft water has a lower (more acidic) pH due to lower alkalinity. The short-term data from the study by Danby et al, however, suggest that in normal skin hard water does not make a significant difference to the pH of the skin surface, which may be due to the innate buffering potential of the skin.[8] Wash products have a major effect on skin surface pH and are also the source of irritant surfactants that bind to calcium. In recent years, the use of mild syndet liquid soaps has increased whereas the use of traditional alkyl carboxylate bars of soap has declined, probably leading to lower skin pH levels. This change in practice, in addition to varying early skincare advice around the world, make wash product use an important potential confounder to be considered when measuring the effect of water hardness on skin surface pH.

Clearly, people living in softer water areas also develop AE, suggesting that hard water is not a necessary cause. However, hard water may be a component cause. For example, following an initial barrier insult, either chemical or physical, there may be impaired barrier repair due to exposure to high levels of calcium. How much of a contribution to this initial barrier insult is made directly by hard water or indirectly through increased detergent deposition remains unclear. Further complicating the picture, some cleansers may reduce free calcium ion concentrations in water.[34] However, the effect of such calcium-surfactant complexes on the skin also remains unclear.

This article is protected by copyright. All rights reserved

Experimental studies in controlled environments in humans and animals provide some evidence for short-term irritant effects of hard water on the skin. It is unclear how this translates into real-world exposure to hard water where there is repeated exposure at varying frequencies and duration and in combination with multiple wash products that, again, may be used in varied ways.

Implications for clinical practice and future research

Water hardness needs to be considered in the context of other risk factors for the development of AE, both genetic and environmental, particularly in younger children. Based on the evidence, it is unclear how the evidence may be used practically for clinicians working in hard water areas. While there is good evidence that water softeners do not help in the treatment of AE, there is an open question as to whether water softeners may reduce the risk of AE in children. This review has highlighted a need for RCT evidence and has helped to shape the design of a randomised controlled trial of water softeners for the prevention of AE in newborn babies that is currently underway (ClinicalTrials.gov: NCT03270566).

Conclusions

Our findings have highlighted a lack of high-quality evidence on the effect of water hardness exposure on AE risk in adults and very young children. There is evidence for an increased risk of AE in primary-school-aged children exposed to harder water (range: 76 to >350 mg/L $CaCO_3$). Water softeners provide no additional objective benefit in the treatment of AE, however, they may provide subjective improvements in AE severity. There may be a role of water hardness in the initiation of skin inflammation in early life, but there is a need for further longitudinal and interventional studies to test this.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

REFERENCES

1 Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 2014; **69**: 3-16.

2 McNally NJ, Williams HC, Phillips DR *et al.* Atopic eczema and domestic water hardness. *Lancet* 1998; **352**: 527-31.

3 Elias P, Ahn S, Brown B *et al.* Origin of the epidermal calcium gradient: regulation by barrier status and role of active vs passive mechanisms. *J Invest Dermatol* 2002; **119**: 1269-74.

4 Fluhr J.W. B, L., Elias, P. *Stratum Corneum pH and Ions - Distribution and Importance*, 2nd edn. USA: CRC Press. 2004.

5 Lee SH, Elias PM, Proksch E *et al.* Calcium and potassium are important regulators of barrier homeostasis in murine epidermis. *J Clin Invest* 1992; **89**: 530-8.

6 Weidinger S, Beck LA, Bieber T *et al.* Atopic dermatitis. *Nat Rev Dis Primers* 2018; **4**: 1.

7 Deraison C, Bonnart C, Lopez F *et al.* LEKTI fragments specifically inhibit KLK5, KLK7, and KLK14 and control desquamation through a pH-dependent interaction. *Mol Biol Cell* 2007; **18**: 3607-19.

8 Danby SG, Brown K, Wigley AM *et al.* The effect of water hardness on surfactant deposition after washing and subsequent skin irritation in atopic dermatitis patients and healthy control subjects. *J Invest Dermatol* 2018; **138**: 68-77.

9 Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.

10 Stroup DF, Berlin JA, Morton SC *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-12.

11 Higgins JP, Altman DG, Gotzsche PC *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.

12 GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell, . The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. In.

13 Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**: 924-6.

14 Schunemann HJ, Cuello C, Akl EA *et al.* GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol* 2018.

15 Review Manager (RevMan). In, 5.3 edn. Copenhagen: The Cochrane Collaboration. 2014.

16 Wallace BC, Dahabreh, I., Trikalinos, T., Lau, J., Trow, P., Schmid, C. Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. *Journal of Statistical Software* 2012; **49**.

17 Higgins JP, Thompson SG, Deeks JJ *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-60.

This article is protected by copyright. All rights reserved

18 Thomas KS, Dean T, O'Leary C *et al.* A randomised controlled trial of ion-exchange water softeners for the treatment of eczema in children. *Plos Medicine* 2011; **8**: 11.
19 Togawa Y, Kambe N, Shimojo N *et al.* Ultra-pure soft water improves skin barrier function in children with atopic dermatitis: A randomized, double-blind, placebo-controlled, crossover pilot study. *Journal of Dermatological Science* 2014; **76**: 269-71.
20 Arnedo-Pena A, Bellido-Blasco J, Puig-Barbera J *et al.* Domestic water hardness and prevalence of atopic eczema in Castellon (Spain) schoolchildren. [Spanish]. *Salud Publica de Mexico* 2007; **49**: 295-301.
21 Chaumont A, Voisin C, Sardella A *et al.* Interactions between domestic water hardness, infant swimming and atopy in the development of childhood eczema. *Environmental Research* 2012; **116**: 52-7.
22 Engebretsen KA, Bager P, Wohlfahrt J *et al.* Prevalence of atopic dermatitis in infants by domestic water hardness and season of birth: Cohort study. *J Allergy Clin Immunol* 2017; **139**: 1568-+.
23 Font-Ribera L, Gracia-Lavedan E, Esplugues A *et al.* Water hardness and eczema at 1 and 4y of age in the INMA birth cohort. *Environmental Research* 2015; **142**: 579-85.
24 Miyake Y, Yokoyama T, Yura A *et al.* Ecological association of water hardness with prevalence of childhood atopic dermatitis in a Japanese urban area. *Environmental Research* 2004; **94**: 33-7.
25 Perkin MR, Craven J, Logan K *et al.* Association between domestic water hardness, chlorine, and atopic dermatitis risk in early life: A population-based cross-sectional study. *J Allergy Clin Immunol* 2016; **138**: 509-16.
26 Jabbar-Lopez Z, Perkin M, Strachan D *et al.* Longitudinal analysis of the effect of water hardness on atopic eczema: evidence for gene-environment interaction. *British J Dermatol* 2019 Oct 10 doi: 10.1111/bjd.18597. online ahead of print.
27 Warren R, Ertel KD, Bartolo RG *et al.* The influence of hard water (calcium) and surfactants on irritant contact dermatitis. *Contact Dermatitis* 1996; **35**: 337-43.
28 Engebretsen KA, Kezic S, Jakasa I *et al.* Effect of atopic skin stressors on natural moisturizing factors and cytokines in healthy adult epidermis. *Br J Dermatol* 2018; **179**: 679-88.
29 Matsuda K, Makita Y, Nagaoka T *et al.* Improved effect of ultra-pure soft water on skin water content in older adults. *Geriatr Gerontol Int* 2018; **18**: 364-5.
30 Tanaka A, Matsuda A, Jung K *et al.* Ultra-pure Soft Water Ameliorates Atopic Skin Disease by Preventing Metallic Soap Deposition in NC/Tnd Mice and Reduces Skin Dryness in Humans. *Acta Dermato-Venereologica* 2015; **95**: 787-91.
31 Ohmori K, Tanaka A, Makita Y *et al.* Pilot evaluation of the efficacy of shampoo treatment with ultrapure soft water for canine pruritus. *Veterinary Dermatology* 2010; **21**: 477-83.
32 Denda M, Katagiri C, Hirao T *et al.* Some magnesium salts and a mixture of magnesium and calcium salts accelerate skin barrier recovery. *Arch Dermatol Res* 1999; **291**: 560-3.

Accepted Article

This article is protected by copyright. All rights reserved

33 Proksch E, Nissen HP, Bremgartner M *et al.* Bathing in a magnesium-rich Dead Sea salt solution improves skin barrier function, enhances skin hydration, and reduces inflammation in atopic dry skin. *Int J Dermatol* 2005; **44**: 151-7.

34 Walters RM, Anim-Danso E, Amato SM *et al.* Hard water softening effect of a baby cleanser. *Clin Cosmet Investig Dermatol* 2016; **9**: 339-45.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

This article is protected by copyright. All rights reserved

TABLES

TABLE 1 – Characteristics of included studies

TABLE 2 – GRADE Summary of findings table – hard water exposure and risk of atopic eczema

TABLE 3 - GRADE Summary of findings table – hard water exposure and skin barrier function

TABLE 4 - GRADE Summary of findings table – water softeners for the treatment of atopic eczema

TABLE 5 - GRADE Summary of findings table – water softeners for the treatment of atopic eczema in animals

Accepted Article

This article is protected by copyright. All rights reserved

FIGURE LEGENDS

FIGURE 1 - PRISMA Flow diagram of studies

FIGURE 2 - Forest plot of observational studies of water hardness and atopic eczema risk

FIGURE 3 - Forest plot of RCTs comparing water softeners to usual care on eczema severity

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

TABLES

TABLE 1 – Characteristics of included studies

Author, Year Country Report type	Design	N	Population	Exposure(s) Comparator(s)	Outcome(s)	Covariates adjusted for	Effect (adjusted, where reported)
Hard water exposure and risk of atopic eczema							
McNally et al, 1998[2] UK Full paper	Observational, Cross-sectional	4,141	Primary school children (4-11 years)	$CaCO_3$ categories (mg/L): I) 118-135, II) 151-157 III) 172-214 IV) 231-341	Questionnaire-based parent-reported lifetime occurrence and 1-year-period prevalence of atopic eczema, defined by International Study of Asthma and Allergies in Childhood (ISAAC) study-based questionnaire	-Age -Sex -Socio-economic status -Health care status	1-year period prevalence of AE: adjusted OR = 1.54 (95%CI 1.19-1.99) Lifetime prevalence of AE (highest vs lowest hardness category): OR 1.28 (95%CI 1.04-1.58)
		3,499	Secondary school children (11-16 years)				1-year period prevalence of AE: adjusted OR = 1.03 (95%CI 1.79-1.33) Lifetime prevalence of AE (highest vs lowest hardness category): OR 0.99 (95%CI 0.80-1.23)
Miyake et al, 2004[24]	Observational, Cross-sectional	458,284	Primary and secondary school	$CaCO_3$ categories (mg/L) I) 35.2-48	Questionnaire-based parent-reported	-Smoking in the household	OR 1.12 (95% CI 1.06-1.18) for AE in highest vs lowest category of water

This article is protected by copyright. All rights reserved

Accepted Article

Japan Full paper			children (6-12 years)	II) 48-53.9 III) 54-75.9 IV) 76-100 Yearly average of water hardness levels supplied to municipalities	physician-diagnosed atopic eczema since birth	-Pollution due to traffic around residential area -Medical conditions -Socioeconomic status -Health care status	hardness *P* value for linear trend <0.0001
Arnedo-Pena et al, 2007[20] Spain Full paper	Observational, Cross-sectional	3,024	Primary school children (6-7 years)	CaCO3 level (mg/L) Zone1: <200 Zone 2: 200-250 Zone3: >300 Water hardness based on average levels measured between 1993-2002 across the Castellon region	Questionnaire-based parent-reported lifetime occurrence and 1-year-period prevalence of atopic eczema, defined by ISAAC questionnaire	-Age -Sex -Family history of atopic eczema -Social class -Number of siblings -History of otitis	Age 6-7 1-year period prevalence of AE (highest vs lowest hardness category): OR 2.29 (95%CI 1.19-4.42) Lifetime prevalence of AE (highest vs. lowest hardness category): OR 1.58 (95%CI 1.04-2.39)
		3,112	Secondary school children (13-14)				Age 13-14 1-year period prevalence of AE (highest vs lowest hardness category): OR 0.41 (95% CI, 0.12, 1.33) Lifetime prevalence of AE (highest vs lowest hardness category): OR 0.89 (95% CI 0.53, 1.49)
Chaumont et al, 2012[21] Belgium	Observational Cross-sectional	358	Primary school children (mean age 5.7 years)	3 categories of $CaCO_3$ (mg/L) Soft <150 Moderately hard 150-350,	Questionnaire-based parent-reported physician-diagnosed atopic eczema at any point	-Pool attendance during infancy -Parental AD and/or allergy -Breastfeeding	Prevalence of eczema (highest vs. lowest hardness category): OR 1.97 (95% 0.97-3.96) *P* trend = 0.08

This article is protected by copyright. All rights reserved

Accepted Article

Full paper				Very hard >350 Municipality-based average water hardness levels between 2003-2007		-Parent's education level -Presence of older siblings -Passive smoking -Maternal smoking during pregnancy	In atopic* individuals only (highest vs. lowest hardness category): OR 3.36 (95% CI 1.02-11.1) *defined as positive Rhinostick test to common allergens or reports receiving allergy medication
Font-Ribera et al, 2015[23] Spain Full paper	Observational, Birth cohort	1,638	Infants (14 months) Children (4 years)	$CaCO_3$ levels in tertiles: <173 173-209 >209 Water hardness level based on address of residence	Questionnaire-reported 'ever eczema' (based on ISAAC) Current eczema at 4 years if responded as having used eczema medication in last 12 months	-Cohort (geographical location) -Sex -Maternal allergy -Maternal education	'Eczema ever' at 14 months (highest vs. lowest hardness tertiles): OR 0.79 (95%CI 0.45, 1.39) "Eczema ever" at 4 years (highest vs. lowest hardness tertiles): OR 0.94 (95% CI 0.57,1.53) "Current eczema" at 4 years (highest vs. lowest hardness tertiles): OR 1.25 (95% CI 0.71, 2.20)
Perkin et al, 2016[25] UK Full paper	Observational, Cross-sectional	1,303	3 month-old infants	Categories based on water hardness & chlorine: 1) Low $CaCO_3$/ low total chlorine 2) High $CaCO_3$/ low total chlorine 3) Low $CaCO_3$/ high chlorine 4) High $CaCO_3$/ high chlorine	Atopic eczema using UK diagnostic criteria-based photographic protocol adapted for infants	-Sex -Ethnicity -Home location -Maternal age -Socioeconomic status (maternal age at leaving full-time education) -Water softener installation -Family history of	H $CaCO_3$/L Chlorine OR 1.87, 95%CI 1.25-2.80 H $CaCO_3$/H Chlorine OR 1.61, 95%CI 1.09-2.38

This article is protected by copyright. All rights reserved

Accepted Article

						AD or other atopy -Frequency of bathing and the use of emollients and bathing products	
Engebretsen et al, 2017[22] Denmark Full paper	Observational, Birth cohort	52,950	Children aged up to 18 months	Water hardness in German degrees	Parent-reported physician-diagnosed atopic eczema	- Sex - Maternal history of eczema - Maternal socioeconomic status - Maternal education - Urban location	Relative prevalence of atopic eczema during the first 18 months of life: 1.05 (95% CI: 1.03, 1.07) for every 5-degree increase in hardness
Jabbar-Lopez et al, 2019[26] UK Full paper	Observational, Cohort	958	Infants aged 3-36 months enrolled in the Enquiring About Tolerance study without atopic eczema by 3 months of age	Harder water (>255 mg/L $CaCO_3$) versus softer water (<255 mg/L $CaCO_3$)	Composite of atopic eczema using UK diagnostic criteria-based photographic protocol adapted for infants and parent-reported, doctor-diagnosed atopic eczema between 3-36 months of age	Adjustment for: - Ethnicity - Home location (urban vs. rural) - presence of a water softener	Adjusted HR 1.07 (95% CI 0.92, 1.24) Stratification by *FLG* mutation status showed a significant interaction with water hardness: adjusted HR 2.72 (95% CI: 2.03, 3.66).
Hard water exposure and skin barrier function							
Warren et al, 1996[27] *Part A*	Experimental	36	Healthy female volunteers	Forearm controlled application test (FCAT)	Visual assessment of erythema by	None	Mean dryness grade: 1.75 (SEM 0.07) with 11 gr rinse versus 1.14 (SEM

This article is protected by copyright. All rights reserved

Accepted Article

	Order of forearm testing sites was randomly determined		Aged 18 to 65 years	Controlled wash volar forearm with 3 test cleanser bars: 1) Sodium cocoate 2) Triethanolamine-coconut (TEA) 3) Sodium cocoyl isethionate (syndet) twice daily for two 5-day periods along with 4 wash/rinse water combinations: 1) 0 gr/0 gr 2) 0 gr/11 gr 3) 11 gr/0 gr 4) 11 gr/11gr (1 grain = 6.86 mg/L $CaCO_3$)	expert grader pre-wash and after final wash (>3 h), dryness, skin capacitance		0.07) with 0 gr water, P<0.001 Mean erythema grade: 1.2 (SEM 0.07) with 11 gr rinse versus 0.80 (SEM 0.07) with 0 gr rinse Mean capacitance (pF): 15.38 (SEM 0.25) with 11 gr versus 17.28 (SEM 0.25) with 0 gr rinse No statistically significant difference in dryness, erythema or capacitance with 11 gr versus 0 gr wash water hardness Statistically significantly higher dryness (P<0.01), erythema (P<0.05) and lower capacitance (P<0.01) with hard (11 gr) water rinse and syndet. Statistically significantly higher dryness, erythema and lower capacitance with sodium soap and TEA soap.
USA Full paper							
Warren et al, 1996[27] *Part B* USA Full paper	Experimental Subjects were randomly assigned to a water hardness group	24	Healthy volunteers aged 18 to 65 years	Flex wash Test bar rubbed with a sponge 3 x per day, each followed by 10s rinse for 5 days	Visual assessment of erythema by expert grader pre-wash and after 3rd wash each day, dryness, capacitance, soap deposition	None	In 11 gr water: Erythema grade 2.19 with TEA soap versus 0.77 with syndet (P<0.01). In 0 gr water: Erythema grade 2.08 with TEA soap versus 0.67 with syndet (P<0.01).
Warren et al, 1996[27]	Experimental	30, divided	Healthy volunteers	Forearm rinse with 70%	Soap deposition	None	When hard water rinse was preceded

This article is protected by copyright. All rights reserved

Accepted Article

Part C USA Full paper	Subjects were randomly assigned to different wash waters	into 3 groups		isopropyl alcohol followed by a wash with sodium cocoate soap bar and 0 gr or 8 gr (tap) water Group 1a: wash 0 gr, rinse 15 s 8 gr Group 1b: wash 0 gr, rinse 15 s 0 gr followed by 15 s 8 gr Group 2a: wash 8 gr, rinse 15 s8 gr Group 2b: wash 8 gr, rinse 15 s 0 gr followed by 15 s 8 gr Group 3a: wash 0 gr, rinse 30 s 8 gr Group 3b: wash 0 gr, rinse 15 s 0 gr followed by 15 s 8 gr	using Fourier transform infrared spectroscopy (FTIR)	by a 0 gr rinse there was significantly less soap deposition Distilled wash water wash followed by hard (8 gr) rinse mean soap deposition: 0.12 (±0.04) versus soft (0 gr) rinse mean soap deposition 0.07 (±0.02) (P<0.01). Hard (8 gr) wash water followed by hard (8 gr) mean soap deposition 0.09 (±0.04) versus hard then soft (0 gr) water rinse mean soap deposition 0.05 (±0.02) (P<0.05) Distilled wash water wash followed by hard (8 gr) water longer rinse mean soap deposition: 0.10 (±0.04) versus hard (8 gr) then soft (0 gr) rinse mean soap deposition 0.05 (±0.03) (P<0.05).
Tanaka et al, 2015[30] (human) Japan Full paper	Experimental, non-randomised	10 Group 1: UPSW Group 2: Tap water	Eight female patients with mild AE, median age 37 years Healthy volunteers	Daily showering with UPSW for 4 weeks	Dryness Scaling Pruritus Skin hydration TEWL Lauric acid residue on tape stripping determined by gas chromatography	Pruritus “almost completely resolved in this cohort of 8 females with mild AD and dry skin.” Showering with UPSW also significantly (P<0.001) increased the water content of the stratum corneum from a median of 21 to 30 arbitrary units at Day 29. This was associated with a significant (P<0.05) reduction in TEWL at 29 days compared to both

This article is protected by copyright. All rights reserved

Accepted Article

							before and after 15 days of UPSW treatment When the skin was rinsed with UPSW, the lauric acid was almost completely gone by 90 s, while even after 180 s of washing with tap water over 80% of the fatty acid remained in the stratum corneum
Danby et al, 2018[8] UK Full paper	Experimental Allocation of the test water to the test areas was randomized	Group 1: n=26; Group 2: n=8; Group 3: n=24; Group 4: n=22	Adult volunteers Group 1: healthy skin Group 2: *FLG* LOF mut without current/past AE Group 3: AE and normal *FLG* Group 4: AE and *FLG* LOF mut	Volar forearm skin washing with SLS 10% solution and one of: Hard domestic tap water Softened water using ion-exchange water softener Deionised water With or without chlorine (1.5 ppm) Patch testing	Visual grading of erythema Objective redness (Mexameter) TEWL (AquaFlux AF 200) Skin surface pH (PH905) Detergent deposition using FTIR Soluble IL-1a (ELISA) *FLG* genotyping	None	Objective erythema: statistically significantly lower skin redness with deionised versus hard water. TEWL: mean 10.19 (SEM 0.74) g/m2/h with hard water, versus 7.43 (SEM 0.74) g/m2/h with deionised water SLS deposition 2.8 +/-0.6-fold greater with hard water versus deionised water. Chlorine level in water did not affect SLS deposition AD patients carrying the FLG gene mutation were affected by SLS deposits to a significantly greater extent compared to individuals with no FLG mutation and healthy skin
Engebretsen et al, 2018[28] Denmark	Experimental, non-randomised	40	Healthy volunteers aged 18-49 years without *FLG* mutations	Exposure to different water types using Finn chambers:	Skin measurements taken from volar forearms 24 hours and 48 hours after	None	Mean (SD) TEWL at 24 hours: No difference between soft 13.0 (±6.2) g/m2/h and hard 13.1 (±6.1) g/m2/h compared with occlusion alone 11.8

This article is protected by copyright. All rights reserved

Accepted Article

	Hard water	application.	(±3.3) g/m2/h.
Full paper	Soft water		
	Chlorinated water	Transepidermal	Mean (SD) TEWL at 48 hours:
	0.5% sodium lauryl sulfate	water loss (TEWL)	Significant difference between soft 9.1 (±3.0) g/m2/h and hard 9.2 (±2.8) g/m2/h individually compared with occlusion alone 8.2 (±2.2) g/m2/h.
		Tape stripping for NMF, cytokines	Mean (SD) NMF at 24 hours: soft 0·51 (± 0·19) mmol/g and hard water (0·61 (± 0·32) mmol/g compared with occlusion alone 0·71 (± 0·18) mmol/g. No difference in NMF was found between hard and soft water.
			Mean (SD) NMF at 48 hours: soft 0.64 (± 0·22) mmol/g and hard water 0·61 (± 0·19) mmol/g compared with occlusion alone 0·82 (± 0·17) mmol/g. No difference in NMF was found between hard and soft water.
			There was an increase in mean (SD) stratum corneum cytokine levels: IL-4 -1.69 (±0.25) log(pg/µg protein), IFN- γ -1.12 (±0.22) log(pg/µg protein), and IL-10 -1.90 (±0.24) log(pg/µg protein) after 24 hours with exposure to hard water compared to the control. There was no significant increase in IL-1α, IL-β.

This article is protected by copyright. All rights reserved

Accepted Article

							No significant increase in IFN-γ, IL-4, IL-1α, IL-β, IL-10 was found for soft water compared to the control. No direct comparison was reported between hard and soft water.
Matsuda et al, 2018[29] Japan Full paper	Experimental, non-randomised	26 recruited, 15 participants with data Group 1: n=7 Group 2: N=8	Elderly care home residents aged 67-97 years with no history of skin diseases.	Twice-weekly bathing Group 1: Twice-weekly bathing with UPSW (<0.1 mg/L $CaCO_3$) Group 2: Twice-weekly bathing with tap water (79.9 mg/L $CaCO_3$)	Skin measurements taken from volar forearm 1.5 hours after bathing: Stratum corneum water content (Skicon-200EX) Transepidermal water loss (AquaFlux AF200) Dermatologist-assessed skin dryness	None	Statistically significantly higher skin hydration at 12 weeks in adults bathed with UPSW compared to those bathed with tap water (P<0.01). No statistically significant difference in TEWL or skin dryness between groups at 12 weeks.
Water softeners for the treatment of atopic eczema							
Thomas et al, 2011[18] UK Full paper	RCT (Parallel groups)	336 Group A: 159 Group B: 164	Children with atopic eczema aged 6 months to 16 years	Group A: ion-exchange water softener + normal eczema care for 12 weeks Group B: Usual eczema care for 12 weeks, then 4 weeks of softened water	Mean change in Six Area Six Sign Atopic Dermatitis (SASSAD) score Mean change in	N/A	Mean (SD) SASSAD improvement: Group A -5.0 (8.8) Group B -5.7 (9.8) Mean change (A-B) in SASSAD between 2 groups at 12 wk = 0.66 (95% CI -1.37, 2.69) Mean (SD) POEM improvement:

This article is protected by copyright. All rights reserved

Accepted Article

					Patient-Oriented Eczema (POEM) score		Group A -5.7 (7.2) Group B -3.6 (6.7) Mean change (A-B) in POEM between groups at 12 wk = -2.03 (95% CI -3.55, -0.51)
					Well-controlled weeks (WCW)		Mean (SD) WCW Group A 8.3 (3.8) weeks Group B 7.3 (4.1) weeks Mean difference (A-B) in WCW 0.99 (95% CI 0.04, 1.95) weeks
					Totally-controlled weeks (TCW)		Mean (SD) TCW Group A 2.9 (3.5) weeks Group B 1.7 (2.8) weeks Mean difference (A-B) in TCW 1.19 (95% CI 0.43, 1.95) weeks
Togawa et al, 2014[19] Japan Full paper	RCT (Crossover)	12 Group 1: 5 Group 2: 6	3-6-year-olds with mild-moderate eczema	Group 1: UPSW by cation-exchange resin 6-week shower treatment Group 2: Standard tap water (mean 91.67 mg/L $CaCO_3$)	Eczema Area and Severity Index (EASI)	N/A	Non-significant difference in mean change in EASI between groups: -2.61 (95% CI -7.03, 1.81) in UPSW group versus tap water group
					Pruritus visual analogue scale (VAS)		Mean difference in pruritus VAS in the UPSW group was -2.1 points (95% CI -4.14 to -0.063)
					Transepidermal water loss (TEWL)		Abdominal region: Mean difference in TEWL in the UPSW group: -5.77

This article is protected by copyright. All rights reserved

Accepted Article

							g/m^2h (95% CI -13.9 to 2.41) Upper back region: Mean difference in TEWL in the UPSW group: 2.26 g/m^2h (95% CI -16.9 to 21.4)
Animal studies							
Ohmori et al, 2010[31] Japan Full paper	Experimental, randomised	11	Dogs with atopic eczema	Tap water: hardness 158 mg/L $CaCO_3$ UPSW: hardness <1 mg $CaCO_3$ mg/L Group1: weekly shampoo wash with UPSW for 4 weeks, then washout period 12 weeks then tap water 4 weeks Group 2: weekly shampoo wash with tap water for 4 weeks then washout period 12 weeks, then UPSW 4 weeks	Pruritus visual analogue scale (PVAS) 0-10 Canine Atopic Dermatitis Extent and Severity Index (CADESI-03) Transepidermal Water Loss (TEWL)	N/A	PVAS -UPSW mean 4.7±0.6 -Tap water mean 5.3±0.6 CADESI scores -UPSW, mean 76.5±20.7 range (14-195) -Tap water, mean 88.1±18.9 range (24-199) TEWL -UPSW mean 12.5±2.3 g/m^2/h; range (3.2-27.2 g/m2/h) -Tap water, , mean 17.8±4.6 g/m^2/h (range 5.2-54.5 g/m2/h)
Tanaka et al, 2015[30] (animal) Japan Full paper	Experimental, non-randomised	15-16 mice in each group	NC/Tnd mice with moderate atopic dermatitis	Clipped dorsal skin washed with soap and rinsed with hard tap water (151.9 mg/L CacO3) or UPSW (<1 mg/L) daily for 3 weeks	Dermatitis severity score Scratching frequency Total scratching duration TEWL	N/A	Statistically significantly lower clinical severity scores in mice treated with UPSW versus tap water No statistically significant difference in TEWL between groups. Statistically significant reduction in TEWL pre- to post-treatment in UPSW group (P<0.05).

This article is protected by copyright. All rights reserved

Accepted Article

Abbreviations: AE – atopic eczema; CaCO3 - calcium carbonate; CADESI – canine atopic dermatitis extent and severity index; EASI – eczema area and severity index; *FLG* – filaggrin gene; gr – grain: HR – hazard ratio; ISAAC - International Study of Asthma and Allergies in Childhood; LOF mut – loss of function mutation; NMF – natural moisturising factor; OR – odds ratio; POEM – patient-oriented eczema measure; PVAS – pruritus visual analogue scale; SASSAD – six area, six sign atopic dermatitis severity score; SD – standard deviation; SEM – standard error of the mean; TEA - triethanolamine TEWL – transepidermal water loss; UPSW – ultrapure softened water

This article is protected by copyright. All rights reserved

Accepted Article

TABLE 2 – GRADE Summary of findings table – hard water exposure and risk of atopic eczema

What is the effect of hard water exposure on the risk of atopic eczema?

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with soft water	**Risk with hard water**				
Risk of atopic eczema in infants and children assessed with: Parent-reported doctor-diagnosed eczema or visible dermatitis Follow up: birth to 16 years	211 per 1,000	**255 per 1,000** (226 to 286)	**OR 1.28** (1.09 to 1.50)	385901 (7 observational studies)[2,20-25]	⨁◯◯◯ VERY LOW [a,b]	Hard water may increase the risk of atopic eczema in children but we are very uncertain.
Risk of atopic eczema in infants assessed with: Parent-reported, doctor-diagnosed eczema or visible dermatitis Follow up: birth to 18 months	126 per 1,000	**157 per 1,000** (114 to 212)	**OR 1.29** (0.89 to 1.86)	27892 (3 observational studies)[22,23,25]	⨁◯◯◯ VERY LOW [a,b]	We are very uncertain about the effect of hard water on the risk of atopic eczema in infants.
Risk of atopic eczema in primary school-aged children assessed with: Parent-reported physician-diagnosed Follow up: lifetime prevalence up to 7 years	227 per 1,000	**296 per 1,000** (243 to 355)	**OR 1.43** (1.09 to 1.87)	353573 (5 observational studies)[2,20,21,23,24]	⨁◯◯◯ VERY LOW [a,b]	Hard water may increase the risk of atopic eczema in primary school-aged children but we are very uncertain.

This article is protected by copyright. All rights reserved

Accepted Article

What is the effect of hard water exposure on the risk of atopic eczema?

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with soft water	Risk with hard water				
Risk of atopic eczema in secondary school-aged children assessed with: Child-reported doctor-diagnosed atopic eczema Follow up: lifetime prevalence up to 16 years	70 per 1,000	**63 per 1,000** (46 to 86)	**OR 0.90** (0.65 to 1.25)	4436 (2 observational studies)[2,20]	⨁◯◯◯ VERY LOW [a]	We are very uncertain about the effect of hard water on risk of atopic eczema in secondary school-aged children.
Risk of atopic eczema in adults - not measured	-	-	-	-	-	No studies identified reporting the risk of atopic eczema in adults

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed pooled risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Rated down for high risk of bias due to study design

b. Rated down for inconsistency due to high heterogeneity in effect estimates (I2 = 63%)

This article is protected by copyright. All rights reserved

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

TABLE 3 - GRADE Summary of findings table – hard water exposure and skin barrier function

Hard water compared to Deionised water for Skin barrier dysfunction

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Deionised water	**Risk with Hard water**				
Transepidermal water loss at volar forearm (TEWL) follow up: mean 72 hours	The mean transepidermal water loss at volar forearm was **10.19** g/m^2/h	The mean transepidermal water loss at volar forearm in the intervention group was 2.76 g/m^2/h higher (0.71 higher to 4.81 higher)	-	80 (1 observational study)[8]	⨁◯◯◯ VERY LOW[a]	Hard water may increase short-term transepidermal water loss at volar forearm slightly but we are very uncertain.
Transepidermal water loss at volar forearm (TEWL) follow up: 12 weeks	Matsuda et al: "There was no significant difference in TEWL between the two groups"		-	15 (1 observational study)[29]	⨁◯◯◯ VERY LOW[a]	We are very uncertain about the medium-term effect of hard water on transepidermal water loss.

This article is protected by copyright. All rights reserved

Accepted Article

Hard water compared to Deionised water for Skin barrier dysfunction

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Deionised water	Risk with Hard water				
Erythema (Erythema) assessed with: Mexameter/visual erythema scale 0-6 follow up: range 72 hours to 5 days	Danby, et al: "There was a significant effect of water type on skin redness (repeated measures analysis of variance, p<0.0001)." A larger change in skin redness was seen in the skin sites exposed to hard water compared to those exposed to deionised water. Warren, et al: no statistically significant difference between hard and deionised water used for washing, but statistically significant (p<0.001) higher erythema with skin washed with hard water (1.20) compared to deionised water (0.80).			116 (2 observational studies)[8,27]	⨁◯◯◯ VERY LOW[a]	Hard water may increase short-term skin erythema slightly but we are very uncertain.
Skin cytokine release assessed with: IL-1a follow up: mean 72 hours	"The use of hard water without chlorine did not lead to elevated IL-1a levels compared with the deionised water control."			80 (1 observational study)[8]	⨁◯◯◯ VERY LOW[a]	We are very uncertain about the effect of hard water on skin (stratum corneum) cytokine release.
Skin surface pH assessed with: pH probe follow up: mean 72 hours	No apparent statistically significant difference in skin surface pH between sites exposed to hard water compared to those exposed to deionised water.			80 (1 observational study)[8]	⨁◯◯◯ VERY LOW[a]	Hard water appears to result in little to no difference in skin surface pH but we are very uncertain.

This article is protected by copyright. All rights reserved

Accepted Article

Hard water compared to Deionised water for Skin barrier dysfunction

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Deionised water	Risk with Hard water				
Skin hydration follow up: mean 5 days	The mean skin hydration was **17.28** pF	The mean skin hydration in the intervention group was 1.9 pF lower (95% CI -2.59, -1.21).	-	36 (1 observational study)[8,27]	⨁◯◯◯ VERY LOW[a]	Hard water may reduce short-term skin hydration slightly but we are very uncertain.
Skin hydration follow up: 12 weeks	"Water content was increased on 8 and 12 weeks in the older adults with UPSW bathing as compared with those with tap water that contained 79.9 mg $CaCO_3$/L." P<0.01 at 12 weeks between groups.		-	15 (1 observational study)[29]	⨁◯◯◯ VERY LOW[a]	Hard water may increase medium-term skin hydration slightly but we are very uncertain.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed pooled risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Rated down for imprecision due to small study size

TABLE 4 - GRADE Summary of findings table – water softeners for the treatment of atopic eczema

This article is protected by copyright. All rights reserved

Accepted Article

Water softeners for the treatment of atopic eczema

Outcomes	**Anticipated absolute effects*** (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with water softeners**			
Atopic eczema severity assessed with: SASSAD, EASI follow up: mean 12 weeks	-	SMD 0.06 SD higher (0.16 lower to 0.27 higher)	335 (2 RCTs)[18,19]	⨁⨁⨁◯ MODERATE [a]	Water softeners in addition to usual care probably do not reduce atopic eczema severity.
Skin barrier function (TEWL) assessed with: Transepidermal water loss (TEWL) (Abdominal region), g/m^2h follow up: mean 12 weeks	The mean change in TEWL was **-0.037** g/m^2h	The mean change in TEWL in the intervention group was 5.77 g/m^2h lower (13.9 lower to 2.41 higher)	11 (1 RCT)[19]	⨁◯◯◯ VERY LOW [a, b, c]	Water softeners in addition to usual care may result in little to no difference in skin barrier function in children with atopic eczema.
Skin barrier function (TEWL) assessed with: Transepidermal water loss (TEWL) (Upper back region), g/m^2h) follow up: mean 12 weeks	The mean skin barrier function was **-4.62** g/m^2h	The mean skin barrier function in the intervention group was 2.26 g/m^2h higher (16.9 lower to 21.4 higher)	11 (1 RCT)[19]	⨁◯◯◯ VERY LOW [a, b, c]	Water softeners in addition to usual care may result in little to no difference in skin barrier function in children with atopic eczema.

This article is protected by copyright. All rights reserved

Accepted Article

Water softeners for the treatment of atopic eczema

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with water softeners**			
Patient-reported eczema severity (Pruritus VAS) assessed with: Pruritus Visual Analogue Scale Scale from: 0 to 9 follow up: mean 12 weeks	The mean change in patient-reported eczema severity was **0.56** points	The mean change in patient-reported eczema severity in the intervention group was 2.1 points lower (4.14 lower to 0.063 lower)	11 (1 RCT)[19]	⊕◯◯◯ VERY LOW [a, b, c]	Water softeners may reduce patient-reported pruritus slightly.
Patient-reported atopic eczema severity assessed with: Patient-oriented eczema measure (POEM) Scale from: 0 to 28 follow up: mean 12 weeks	The mean patient-reported atopic eczema severity was **-3.6** points	The mean patient-reported atopic eczema severity in the intervention group was 2.03 points lower (3.55 lower to 0.51 lower)	323 (1 RCT)[18]	⊕⊕⊕◯ MODERATE [c]	Water softeners probably reduce patient-reported atopic eczema severity slightly.
Atopic eczema disease control assessed with: Well-controlled weeks (WCW) Scale from: 0 to 12 follow up: mean 12 weeks	The mean atopic eczema disease control was **7.3** WCW	The mean atopic eczema disease control in the intervention group was 0.99 WCW higher (0.04 higher to 1.95 higher)	267 (1 RCT)[18]	⊕⊕⊕◯ MODERATE [c]	Water softeners probably improve atopic eczema disease control slightly.

This article is protected by copyright. All rights reserved

Accepted Article

Water softeners for the treatment of atopic eczema

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with water softeners**			
Atopic eczema disease control assessed with: Totally-controlled weeks (TCW) Scale from: 0 to 12 follow up: mean 12 weeks	The mean atopic eczema disease control was **1.7** TCW	The mean atopic eczema disease control in the intervention group was 1.19 TCW higher (0.43 higher to 1.95 higher)	265 (1 RCT)[18]	⨁⨁⨁◯ MODERATE [c]	Water softeners probably improve atopic eczema disease control.

Explanations

a. Rated down for imprecision due to wide confidence interval

b. Rated down for imprecision due to small study size

c. Rated down due to unclear risk of bias

d. Rated down for high risk of bias in patient-reported outcomes due to unblinded study design

TABLE 5 - GRADE Summary of findings table – water softeners for the treatment of atopic eczema in animals

Water softeners compared to hard water for animals

This article is protected by copyright. All rights reserved

Accepted Article

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Animal Eczema Severity assessed with: Canine Atopic Dermatitis Extent and Severity Index (CADESI) in dogs, Clinical skin severity score in mice follow up: range 22 days to 0	In dogs, CADESI score was measured pre- and post-treatment within each group (UPSW, tap water). Comparisons were not reported between UPSW and tap water. In the UPSW group there was a decrease from a mean score of 96.8 (+/- 21.0 SEM) to a mean score of 76.5 (+/- 20.7), P<0.05. In the tap water group the CADESI score changed from a mean of 87.7 (+/- 19.9) to 88.1 (+/- 18.9). In mice, Blinded assessment of clinical skin severity score of AD-type lesions in mice. Severity score reduced in the group of mice treated with UPSW compared to tap water, P<0.05, at 21 days after treatment.	39 (2 observational studies)[30,31]	⨁◯◯◯ VERY LOW [a,b]
Transepidermal water loss (TEWL) assessed with: Tewameter follow up: range 22 days to 0	In dogs, TEWL was measured pre- and post-treatment within each group (UPSW, tap water). Comparisons were not reported between UPSW and tap water. In the UPSW group there was a decrease from mean 12.5 g/m2/h (+/- 2.3 SEM) to 6.7 g/m2/h (+/- 0.8), P=0.0096. In the Tap water group, TEWL changed from a mean 16.85 g/m2/h (+/- 4.2) pre-treatment to a mean 17.8 g/m2/h (+/- 4.6) post-treatment. In mice, TEWL was measured at the dorsal area pre- and post-treatment within each group (UPSW, tap water, untreated). Comparisons were not reported between groups. In the UPSW group, there was a statistically significant reduction in TEWL at Day 22, P<0.05. No statistically significant difference was seen at Day 22 in the untreated mice or in those treated with tap water.	39 (2 observational studies)[30,31]	⨁◯◯◯ VERY LOW [a]

This article is protected by copyright. All rights reserved

Accepted Article

Water softeners compared to hard water for animals

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Pruritus (PVAS) assessed with: Owner pruritus visual analogue score (PVAS) in dogs, Scratching frequency/30 minutes in mice follow up: range 22 days to 0	In dogs, PVAS was measured pre- and post-treatment within each group (UPSW, tap water). Comparisons were not reported between UPSW and tap water. In the UPSW group, there was a decrease in PVAS from a mean score of 6.2 (+/- 0.7 SEM) to 4.7 (+/- 0.6). In the tap water group, PVAS changed from a mean score of 5.5 (+/- 0.6) to 5.3 (+/- 0.6). In mice, scratching behaviour was recorded by an automated system. Comparisons were made pre- and post-treatment within each group (UPSW, tap water, untreated). Scratching frequency per 30 minute interval increased in the untreated and tap water groups at Day 22, P<0.05. There was no statistically significant difference in scratching frequency in the UPSW group.	39 (2 observational studies)[30,31]	⊕◯◯◯ VERY LOW [a,b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed pooled risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

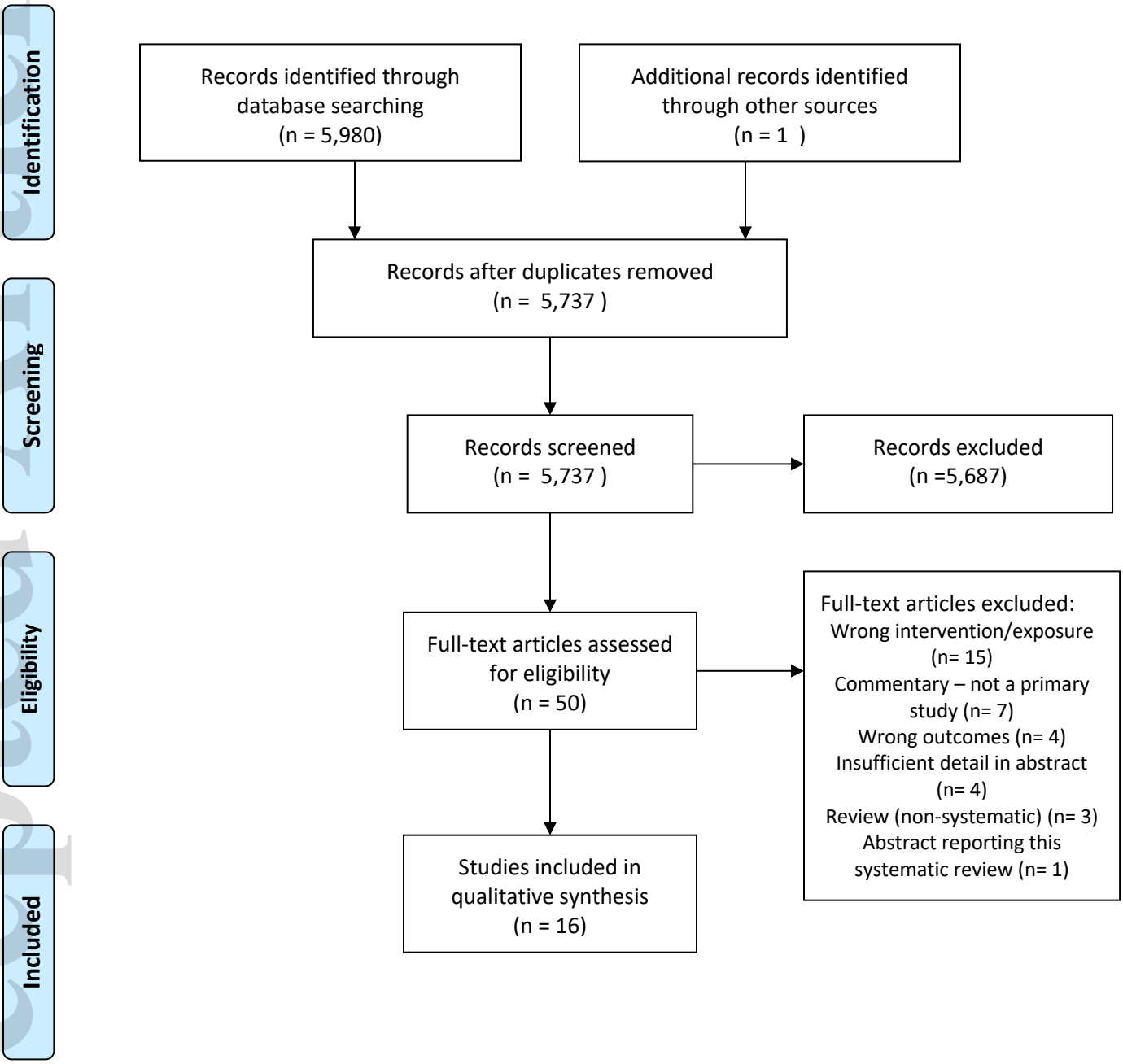
Explanations

a. Rated down for imprecision due to small study size

b. Rated down for indirectness due to differences in outcome assessment

This article is protected by copyright. All rights reserved

Accepted Article

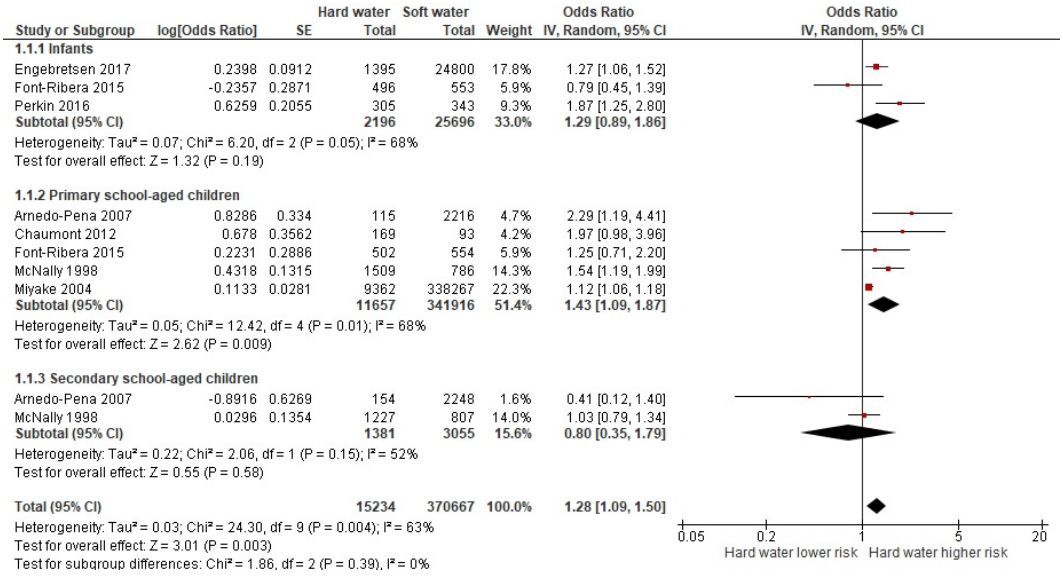


From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

This article is protected by copyright. All rights reserved

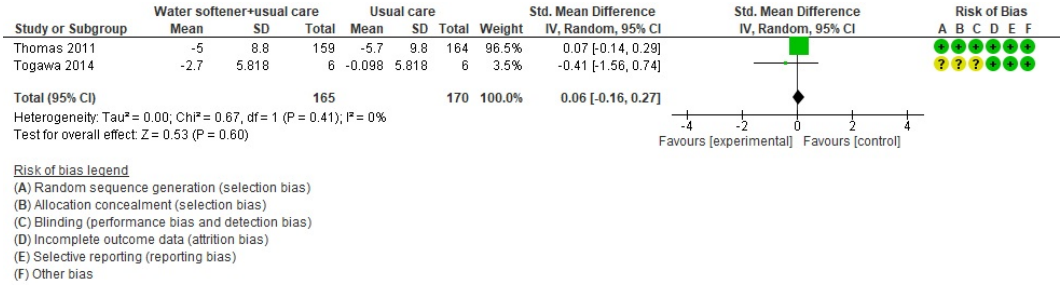
Accepted Article



cea_13797_f2.jpg

This article is protected by copyright. All rights reserved

Accepted Article



cea_13797_f3.jpg

This article is protected by copyright. All rights reserved

SUPPLEMENTARY APPENDIX

S1 – Supplementary Figure 1

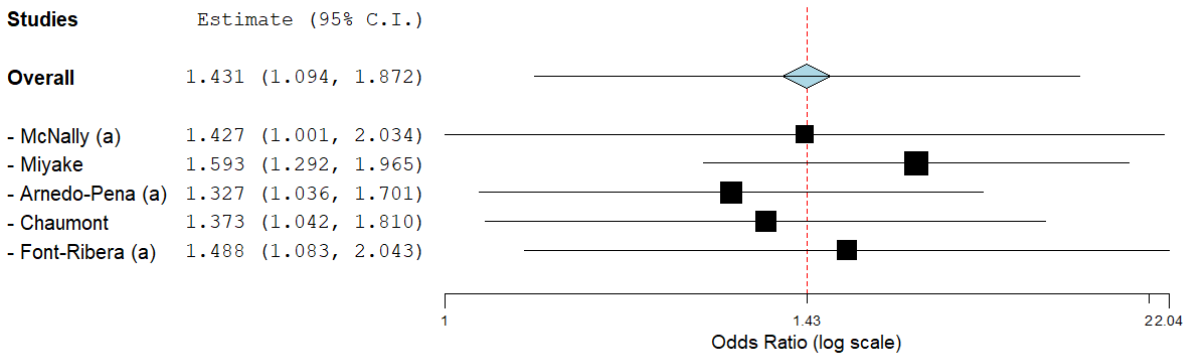
S2 – Search strategy

S3 – Excluded studies

S4 – Risk of bias assessments

S5 – Supplementary references

S1 – Supplementary Figure 1 – Leave-one-out meta-analysis of risk of atopic eczema in primary school-aged children exposed to harder versus softer water



S2 - Search strategy

Original search date 03/08/2018

MEDLINE (OVID) and EMBASE search strategies

1. exp Dermatitis, Atopic/ (MESH)
2. atopic dermatitis.mp.
3. atopic eczema.mp.
4. exp neurodermatitis/ (MESH)
5. neurodermatitis.mp.
6. infantile eczema.mp.
7. childhood eczema.mp.
8. Besnier's prurigo.mp.
9. exp Eczema/ (MESH)
10. cutaneous irritation.mp
11. cutaneous reaction.mp
12. skin dryness.mp
13. xerosis.mp
14. or/1-13
15. exp Water (MESH)
16. exp Water softening/ (MESH)
17. water hardness.mp.
18. exp Drinking water/ (MESH)
19. exp Calcium/ (MESH)
20. exp Magnesium/ (MESH)
21. Chlorine/ (MESH)
22. Chloramine.mp.
23. Stearate.mp or exp Stearic acid/ (MESH)
24. Alkalinity
25. Hydrogen ion concentration/ (MESH)

26. pH
27. transepidermal water loss.mp
28. or/16-27
29. 14 and 28

Indices:

Exp: indicates that the term was exploded

Mp: indicates a free text search for a term (title, abstract, original title, subject heading word, keyword heading word; MESH: Medical subject heading

GREAT

(water) OR (calcium) OR (hardness)

CENTRAL

#1
MeSH descriptor: [Dermatitis, Atopic] explode all trees
#2
MeSH descriptor: [Water] explode all trees
#3
MeSH descriptor: [Water Softening] explode all trees
#2 or #3
#1 and #4

Web of Science Core Collection search strategy

#26	#25 AND #12 *DocType=All document types; Language=All languages;*
#25	#24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 *DocType=All document types; Language=All languages;*
#24	ts=transepidermal water loss *DocType=All document types; Language=All languages;*
#23	ts=pH *DocType=All document types; Language=All languages;*
#22	ts=alkalinity *DocType=All document types; Language=All languages;*
#21	ts=stearate *DocType=All document types; Language=All languages;*
#20	ts=chloramine *DocType=All document types; Language=All languages;*
#19	ts=chlorine *DocType=All document types; Language=All languages;*
#18	ts=magnesium *DocType=All document types; Language=All languages;*
#17	ts=calcium *DocType=All document types; Language=All languages;*
#16	ts=drinking water *DocType=All document types; Language=All languages;*

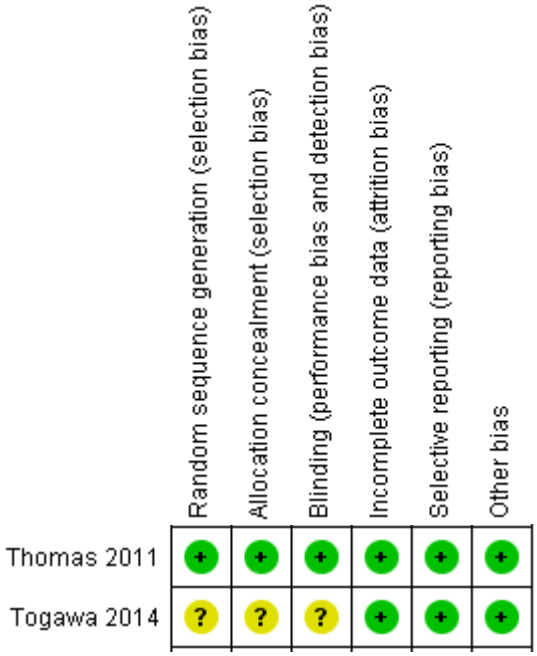
#15	ts=water hardness *DocType=All document types; Language=All languages;*
#14	ts=water softening *DocType=All document types; Language=All languages;*
#13	ts=water *DocType=All document types; Language=All languages;*
#12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *DocType=All document types; Language=All languages;*
#11	ts=xerosis *DocType=All document types; Language=All languages;*
#10	ts=skin dryness *DocType=All document types; Language=All languages;*
#9	ts=cutaneous reaction *DocType=All document types; Language=All languages;*
#8	ts=cutaneous irritation *DocType=All document types; Language=All languages;*
#7	ts=Eczema *DocType=All document types; Language=All languages;*
#6	ts=Besnier's prurigo *DocType=All document types; Language=All languages;*
#5	ts=childhood eczema *DocType=All document types; Language=All languages;*
#4	ts=infantile eczema *DocType=All document types; Language=All languages;*
#3	**TOPIC:** (neurodermatitis) *DocType=All document types; Language=All languages;*
#2	TS=atopic eczema *DocType=All document types; Language=All languages;*
#1	TS=Atopic dermatitis *DocType=All document types; Language=All languages;*

S3 – Excluded studies

Author, year	Reason excluded
Anonymous, 1998[1]	Commentary - not a primary study
Adachi, 1998[2]	Wrong intervention/exposure
Akimoto, 1990[3]	Wrong intervention/exposure
Anonymous, 2011[4]	Commentary - not a primary study
Anonymous, 2012[5]	Wrong outcomes
Anveden Berglind, 2009[6]	Wrong intervention/exposure
Anveden Berglind, 2012[7]	Wrong intervention/exposure
Barthel, 1994[8]	Wrong intervention/exposure
Choi, 2013[9]	Wrong intervention/exposure
Donato, 2003[10]	Commentary - not a primary study
Fernandez-Luna, 2016[11]	Wrong intervention/exposure
Font-Ribera, 2009[12]	Wrong outcomes
Gamble, 2011[13]	Commentary - not a primary study
Giannetti, 2005[14]	Wrong intervention/exposure
Gittler, 2017[15]	Not a systematic review
Jabbar-Lopez, 2017[16]	Abstract reporting this systematic review
Jungmayr, 1998[17]	Commentary - not a primary study
Kantor, 2016[18]	Not a systematic review
Kim, 2015[19]	Wrong intervention/exposure
Kim, 2012[20]	Wrong intervention/exposure
Lacour, 1999[21]	Commentary - not a primary study
Licu, 2002[22]	Wrong intervention/exposure
Lipkin, 1965[23]	Wrong intervention/exposure
Nardi, 2003[24]	Wrong intervention/exposure
Proksch, 2005[25]	Wrong intervention/exposure
Sengupta, 2013[26]	Wrong outcomes
Simmonds, 2009[27]	Commentary - not a primary study
Tanaka, 2008[28]	Insufficient detail presented in abstract
Tanaka, 2009[29]	Insufficient detail presented in abstract; wrong outcomes
Tanaka, 2012[30]	Insufficient detail presented in abstract
Tanaka, 2012[31]	Insufficient detail presented in abstract
Tsai, 1999[32]	Not a systematic review
Walters, 2016[33]	Wrong outcomes
Yoshizawa, 2003[34]	Wrong intervention/exposure

S4 – Risk of bias of included studies

a) Cochrane risk of bias assessment of RCTs



b) Newcastle-Ottawa Quality Assessment Scale – Cohort Studies

Study	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Font-Ribera et al., 2015	1	1	1	1	1	0	1	0
Engebretsen et al., 2017	1	1	1	1	2	0	1	0
Jabbar-Lopez et al., 2019	1	1	1	1	2	1	1	0

c) ToxTool quality assessment of Tanaka et al, 2015

Reliability assessment of in vivo toxicity studies	
Study under evaluation	
Authors:	
Tanaka et al.	
Titel:	
Ultra-pure soft water amerliorates atopic skin disease by preventing metallic soap deposition in NC/Tnd mice and reduces skin dryness in humans	
Testing facility, year, sponsor, study no. or bibliographic reference:	
2015	
Explanations are available for most criteria and show up, when the cursor is moved over the criteria field. Please read carefully! Red criteria: the maximum score is needed for these criteria to achieve reliability category 1 or 2 (see worksheet Explanations): Please evaluate with special care!	
Criteria	
No. Criteria Group I: Test substance identification	**Score**
1 Was the test substance identified?	1
2 Is the purity of the substance given?	1
3 Is information on the source/origin of the substance given?	0
4 Is all information on the nature and/or physico-chemical properties of the test item given, which you deem indispensable for judging the data (see explanation for examples)?	1
	3
Criteria Group II: Test organism characterisation	
5 Is the species given?	1
6 Is the sex of the test organism given?	0
7 Is information given on the strain of test animals plus, if considered necessary to judge the study, other specifications (see explanation for examples)?	1
8 Is age or body weight of the test organisms at the start of the study given?	0
9 For repeated dose toxicity studies only (give point for other study types): Is information given on the housing or feeding conditions?	1
	3
Criteria Group III: Study design description	
10 Is the administration route given?	1
11 Are doses administered or concentrations in application media given?	1
12 Are frequency and duration of exposure as well as time-points of observations explained?	1
13 Were negative (where required) and positive controls (where required) included (give point also, when absent but not required, see explanations for study types and their respective requirements on controls)?	1
14 Is the number of animals (in case of experimental human studies: number of test persons) per group given?	1
15 Are sufficient details of the administration scheme given to judge the study (see explanation for examples)?	1
16 For inhalation studies and repeated dose toxicity studies only (give point for other study types): Were achieved concentrations analytically verified or was stability of the test substance otherwise ensured or made plausible?	
	6
Criteria Group IV: Study results documentation	
17 Are the study endpoint(s) and their method(s) of determination clearly described?	1
18 Is the description of the study results for all endpoints investigated transparent and complete?	1
19 Are the statistical methods applied for data analysis given and applied in a transparent manner (give also point, if not necessary/applicable, see explanations)?	1
	3
Criteria Group V: Plausibility of study design and results	
20 Is the study design chosen appropriate for obtaining the substance-specific data aimed at (see explanations for details)?	1
21 Are the quantitative study results reliable (see explanations for arguments)?	1
	2
	17
A Numerical result leads to initial Category:	2
B Checking red scores leads to revised Category:	2
C Evaluator's proposal: Category:	
D Justification in case evaluator deviates from B:	

S5 – Supplementary references (excluded studies)

1 Eczema linked with hard water. *Chem. Br.* 1998; **34**: 12-.

2 Adachi J, Sumitsuzi H, Endo K *et al.* Evaluation of the effect of short-term application of deep sea water on atopic dermatitis. [Japanese]. *Arerugi = [Allergy]* 1998; **47 (1)**: 57-60.

3 Akimoto KI, Saito H, Kanemoto H *et al.* Sea water therapy for children with severe atopic dermatitis. *Jikeikai Medical Journal* 1990; **37**: 397-405.

4 Anonymous. Water softeners not found to improve childhood eczema. *Pakistan journal of biological sciences: PJBS* 2011; **14**: 312.

5 Anonymous. British Society for Paediatric Dermatology 26th Annual Symposium and AGM. *British Journal of Dermatology. Conference: 26th Annual Symposium and AGM of the British Society for Paediatric Dermatology. Nottingham United Kingdom. Conference Start* 2012; **166**.

6 Anveden Berglind I, Alderling M, Jarvholm B *et al.* Occupational skin exposure to water: A population-based study. *British Journal of Dermatology* 2009; **160**: 616-21.

7 Anveden Berglind I, Alderling M, Lindahl G *et al.* Is skin exposure to water mainly occupational or non-occupational? *Contact Dermatitis* 2012; **66**: 40-1.

8 Barthel HR, Stuhlmuller B. Improvement in atopic dermatitis with change to low-salt table water [8]. *Lancet* 1994; **344**: 1089.

9 Choi YJ, Lee HJ, Lee DH *et al.* Therapeutic effects and immunomodulation of suanbo mineral water therapy in a murine model of atopic dermatitis. *Ann* 2013; **25**: 462-70.

10 Donato F, Monarca S, Premi S *et al.* Drinking water hardness and chronic degenerative diseases. III. Tumors, urolithiasis, fetal malformations, deterioration of the cognitive function in the aged and atopic eczema. [Italian]. *Annali di igiene : medicina preventiva e di comunita* 2003; **15**: 57-70.

11 Fernandez-Luna A, Burillo P, Felipe JL *et al.* Perceived health problems in swimmers according to the chemical treatment of water in swimming pools. *Eur. J. Sport Sci.* 2016; **16**: 256-65.

12 Font-Ribera L, Kogevinas M, Zock JP *et al.* Swimming pool attendance and risk of asthma and allergic symptoms in children. *European Respiratory Journal* 2009; **34**: 1304-10.

13 Gamble RG, Dellavalle RP. Ion-exchange water softener use and eczema. *Archives of Dermatology* 2011; **147**: 1208-10.

14 Giannetti A. The hydrotherapy centre in Avene-les-bains. A controlled study in atopic dermatitis. [French]. *Annales de Dermatologie et de Venereologie* 2005; **132**: 6S12-6S5.

15 Gittler JK, Wang JF, Orlow SJ. Bathing and Associated Treatments in Atopic Dermatitis. *American Journal of Clinical Dermatology* 2017; **18**: 45-57.

16 Jabbar-Lopez Z, Phongphit V, Ung CY *et al.* The role of domestic water hardness in the development of skin barrier dysfunction and atopic eczema: A systematic review of the literature. *British Journal of Dermatology* 2017; **177**: 159.

17 Jungmayr P. Which role does domestic water hardness play in atopic eczema?. [German]. *Deutsche Apotheker Zeitung* 1998; **138**: 47.

18 Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. *Expert rev* 2016: 1-12.

19 Kim CG, Kang M, Lee YH *et al.* Bathing Effects of Various Seawaters on Allergic (Atopic) Dermatitis-Like Skin Lesions Induced by 2,4-Dinitrochlorobenzene in Hairless Mice. *Evidence-based Complementary and Alternative Medicine* 2015; **2015 (no pagination)**.

20 Kim HS, Yu DS, Lee HJ *et al.* Therapeutic effect and immunomodulation induced by Su-An-Bo mineral water on a model of atopic dermatitis in Nc/Nga mice. *Journal of the American Academy of Dermatology* 2012; **1)**: AB9.

21 Lacour JP. Atopic dermatitis and hard water. [French]. *Annales de Dermatologie et de Venereologie* 1999; **126**: 553-7.

22 Licu D, et al. Efficacy of a thermal spring water in the treatment of mild atopic dermatitis. Abstract. *20th World Congress of Dermatology Paris 1st to 5th July 2002* 2002: P0231.

23 Lipkin G. Some Observations on Minerals in Eczema. *Journal of Pediatrics* 1965; **66**: SUPPL:216-7.

24 Nardi G, Donato F, Monarca S *et al.* Drinking water hardness and chronic degenerative diseases. I. Analysis of epidemiological research. [Italian]. *Annali di igiene : medicina preventiva e di comunita* 2003; **15**: 35-40.

25 Proksch E, Nissen HP, Bremgartner M et al. Bathing in a magnesium-rich Dead Sea salt solution improves skin barrier function, enhances skin hydration, and reduces inflammation in atopic dry skin. Int J Dermatol 2005; 44: 151-7.25
26 Sengupta P. Potential health impacts of hard water. *International Journal of Preventive Medicine* 2013; **4**: 866-75.
27 Simmonds R, Dean T. The soft option. Interview by Louise Hunt. *Nursing standard (Royal College of Nursing (Great Britain) : 1987)* 2009; **23**: 24.
28 Tanaka A, Takai M, Yoshinari Y et al. Bathing in ultra-pure soft water improves skin barrier functions both in patients with atopic dermatitis and in atopic NC/Nga mice. Allergy 2008; 63: 206-.
29 Tanaka A, Takai M, Yoshinari Y et al. Ultrapure soft water reduces growth of Staphylococcus aureus adopted on skins of the barrier-disrupted animal model. Allergy: European Journal of Allergy and Clinical Immunology 2009; 64: 556.
30 Tanaka A, Matsuda A, Makita Y et al. Metallic soap aggravates skin conditions in patients with atopic dermatitis and a mouse model for human atopic dermatitis, NC/ TND mice. World Allergy Organization Journal 2012; 5: S33-S4.
31 Tanaka A, Matsuda A, Takai M *et al.* Topical metallic soap on the skin induces Th2-type immune responses in a model for human atopic dermatitis, NC/Tnd mice. Allergy: European Journal of Allergy and Clinical Immunology 2012; 67: 637.
32 Tsai TF, Maibach HI. How irritant is water? An overview. Contact Dermatitis 1999; 41: 311-4.
33 Walters RM, Anim-Danso E, Amato SM et al. Hard water softening effect of a baby cleanser. Clinical, Cosmetic and Investigational Dermatology 2016; **9**: 339-45.
34 Yoshizawa Y, Kitamura K, Kawana S *et al.* Water, salts and skin barrier of normal skin. *Skin Research and Technology* 2003; **9**: 31-3.