

Total and drinking water intake and risk of all-cause and cardiovascular mortality: a systematic review and dose-response meta-analysis of prospective cohort studies

Maryam Majdi¹, Fatemeh Hosseini¹, Sina Naghshi¹, kurosh djafarian¹, and Sakineh Shab-Bidar¹

¹Tehran University of Medical Sciences

November 12, 2020

Abstract

Background: Understanding the association between water consumption and mortality is important for guiding consumers and prioritizing dietary guidelines to reduce the risk. Therefore, in the current study, we conducted a systematic review and dose-response meta-analysis of prospective cohort studies to summarize the association between total water and drinking intake and risk of mortality from all causes and CVD. **Method:** A comprehensive search was performed on PubMed/Medline, Scopus, and ISI Web of Science up to February 2020. The random effects model was used to calculate pooled effect size (EFs) and 95% confidence interval. **Result:** Seven prospective cohort studies with a total of 116816 reporting 14754 cases of all-cause mortality and 7611 of CVD mortality, were included in the present meta-analysis. No significant association was found between drinking water intake and all-cause mortality (EFs: 0.82; 95% CI: 0.63-1.08, P=0.65) and CVD mortality (EFs: 0.82; 95% CI: 0.63-1.08, P= 0.16). Total water intake was not associated with all-cause mortality (EFs: 0.95; 95% CI: 0.83-1.09, P=0.47). However, indicating a significant inverse association between total water intake and risk of CVD mortality (EFs: 0.84; 95% CI: 0.77-0.93, P<0.001). Linear dose-response meta-analysis revealed a significant inverse association between total water intake and all-cause mortality by an additional one cup per day (Pooled ES: 0.98; 95% CI: 0.97-0.99, P= 0.001). Furthermore, each additional cup of total water intake per day was associated with a 3% lower risk of death from CVD (Pooled ES: 0.97; 95% CI: 0.96-0.98, P<0.001). **Conclusion:** High consumption of total water is associated with a lower risk of CVD mortality. However total water intake was not associated with an increased risk of all-cause mortality.

Total and drinking water intake and risk of all-cause and cardiovascular mortality: a systematic review and dose-response meta-analysis of prospective cohort studies

Maryam majdi^{1,2}, Fatemeh hosseini³, Sina Naghshi³, Kurosh Djafarian³, Sakineh Shab-Bidar²

¹Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran

²Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

³Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

Corresponding author:

Sakineh Shab-Bidar, Associate Professor

Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran

University of Medical Sciences (TUMS), Tehran, Iran. No 44, Hojjat-dost Alley, Naderi St.,

Keshavarz Blvd, Tehran, Iran. Tele:

E-mail address: s.shabbidar@tums.ac.ir

Short title: Total and drinking water intake and risk of all-cause and cardiovascular mortality

Author’s contribution: MM and FH contributed to literature search, data extraction, and, data analysis. SS-B contributed to study conception and data analysis. SN and MM contributed to study conception, manuscript drafting, and data analysis. SS-B critically revised the manuscript. All authors acknowledgment the full responsibility for the analyses and interpretation of the report.

Conflict of interest: The authors declare no conflict of interest.

Funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements: All authors acknowledgment the full responsibility for the analyses and interpretation of the report.

SUMMARY

Background: Understanding the association between water consumption and mortality is important for guiding consumers and prioritizing dietary guidelines to reduce the risk. Therefore, in the current study, we conducted a systematic review and dose-response meta-analysis of prospective cohort studies to summarize the association between total water and drinking intake and risk of mortality from all causes and CVD.

Method: A comprehensive search was performed on PubMed/Medline, Scopus, and ISI Web of Science up to February 2020. The random effects model was used to calculate pooled effect size (EFs) and 95% confidence interval.

Result: Seven prospective cohort studies with a total of 116816 reporting 14754 cases of all-cause mortality and 7611 of CVD mortality, were included in the present meta-analysis. No significant association was found between drinking water intake and all-cause mortality (EFs: 0.82; 95% CI: 0.63-1.08, P=0.65) and CVD mortality (EFs: 0.82; 95% CI: 0.63-1.08, P= 0.16). Total water intake was not associated with all-cause mortality (EFs: 0.95; 95% CI: 0.83-1.09, P=0.47). However, indicating a significant inverse association between total water intake and risk of CVD mortality (EFs: 0.84; 95% CI: 0.77-0.93, P<0.001). Linear dose-response meta-analysis revealed a significant inverse association between total water intake and all-cause mortality by an additional one cup per day (Pooled ES: 0.98; 95% CI: 0.97-0.99, P= 0.001). Furthermore, each additional cup of total water intake per day was associated with a 3% lower risk of death from CVD (Pooled ES: 0.97; 95% CI: 0.96-0.98, P<0.001).

Conclusion: High consumption of total water is associated with a lower risk of CVD mortality. However total water intake was not associated with an increased risk of all-cause mortality.

keywords: drinking water, total water, all-cause mortality, CVD mortality

INTRODUCTION

Several modifiable risk factors such as tobacco use, unhealthy diet, and excessive alcohol intake are linked to the greater risk of non-communicable diseases, some evidence suggests that adequate water intake may improve health outcomes^[1]. Adequate hydration and water intake are necessary for critical physiological and metabolic processes^[2]. Using this framework dietary guidelines recommended consumption of 2 and 2.5 L per day from water for females and males respectively^[3]. Low fluid consumption and inadequate water intake may provoke dehydration. This condition can lead to low-grade inflammation in the human body. It should be noted that the low-grade inflammation in long-term was associated with inanition and progression of some chronic diseases^[4], CVD^[5], and mortality^[6]. Previous meta-analysis on the association of specific beverages, such as tea^[7, 8], coffee^[9, 10], and alcohol^[11-13] with mortality reported inverse, positive or null associations. Findings on the link between water intake and longevity remain an unresolved question.

While total water intake from foods and beverages was associated with a lower risk of mortality in some investigations^[14] others failed to find such evidence^[15, 16]. No information is available about the strength and shape of dose-response relation between water intake and risk of mortality. On the other hand, understanding the association between water consumption and mortality is important for guiding consumers and prioritizing dietary guidelines to reduce the risk. Therefore, in the current study, we conducted a systematic review and dose-response meta-analysis of prospective cohort studies to summarize the association between total water intake from foods and beverages and drinking intake and risk of mortality from all causes and CVD.

METHODS

Findings from this systematic review and meta-analysis were reported based on Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline ^[17].

Search strategy: A systematic literature review was conducted by using the databases PubMed/Medline, Scopus, and ISI Web of Science up to February 2020 with no language or time restriction. Details of the search terms are provided in **Supplemental Table 1** . Furthermore, the reference list of the relevant articles was manually searched.

Inclusion criteria: Published studies that met the following criteria were included: 1) observational prospective studies conducted on adults; 2) reported effect sizes (ESs) including hazard ratios (HRs) or relative risks (RRs) or odds ratios (ORs) with corresponding 95% CIs for the association between intakes of total water from all foods and beverages as well as drinking water as the exposure of interest and mortality from all causes and CVD as the outcome of interest.

Exclusion criteria: We excluded letters, comments, reviews, meta-analyses, and ecologic studies. We also did not include studies that performed on children or adolescences, those conducted among chronic kidney disease or hemodialysis patients, critically ill patients, and those enrollment acute respiratory distress syndrome patients. All outcomes were classified based on the World Health Organization's international classification of disease criteria.

Data extraction: The selection and data extraction process were executed by 2 independent reviewers (MM and FH). We extracted the following data from each study: name of the first author, publication year, study design, location of the study conducted, gender, the sample size of the cohort, the age range at entry, duration of follow-up, exposure, method of assessment of exposure, incidence of death, comparison categories and relevant effect size along with 95% CIs and list of confounders adjusted in the statistical analysis.

Risk of bias assessment: We used the Risk Of Bias In Non-randomized Studies of Exposures (ROBINS-E) tool to assess the risk of bias. The ROBINS-E tool comprises 7 domains: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in the classification of exposures, (4) bias due to departure from intended exposures, (5) bias due to missing data, (6) bias in the measurement of outcomes, and (7) bias in the selection of reported results. Studies were categorized as low risk, moderate risk, serious risk, and critical risk of bias under each domain. The results of risk of bias assessment are presented in **Supplemental Table 2** .

Statistical analysis: ORs, RRs, and HRs (and 95% CIs) for comparison of the highest versus lowest categories of water intake were used to calculate log ORs, RRs, and HRs \pm SE. The analyses were performed with the use of a random-effects model, in which we calculated both Q-statistic and I^2 as indicators of heterogeneity. As random-effects model can account for variation between studies, it can provide more conservative results than a fixed-effects model. For studies that reported effect sizes separately for drinking water and other fluids, we first combined the estimates using the fixed-effects model to obtain an overall estimate, and then, the pooled effect size was included in the meta-analysis. In the study of Wu et al that reported effect size for CKD and non-CKD patients separately, we included only non-CKD patients in the meta-analysis. Studies that investigated only CVD mortality in relation to water intake were also considered in the meta-analysis of all-cause mortality because CVD mortality accounts for a very high proportion of the all-cause mortality. considered in the meta-analysis of all-cause mortality. We conducted a sensitivity

analysis, using a fixed-effects model, in which each prospective cohort study was excluded to examine the influence of that study on the overall estimate. In case of finding a significant between-study heterogeneity, we performed subgroup analysis to examine possible sources of heterogeneity. Between-subgroup heterogeneity was examined through the fixed-effects model. Publication bias was examined by visual inspection of funnel plots. Formal statistical assessment of funnel plot asymmetry was also done with the use of Egger's test. In case of significant publication bias, the trim-and-fill method was used to detect the effect of missing studies on the overall effect of meta-analysis.

A method suggested by Greenland and Orsini was used to compute the trend from the ORs/RRs/HRs estimates and their 95% CIs across categories of water intake^[18]. In this method, the distribution of cases and the ORs/RRs/HRs with the variance estimates for [?]3 quantitative categories of exposure were required. We considered the midpoint of water intake in each category. For studies that reported the water intake as range, we estimated the midpoint in each category by calculating the mean of the lower and upper bound. When the highest and lowest categories were open-ended, the length of these open-ended intervals was assumed to be the same as that of the adjacent intervals. A two-stage random-effects dose-response meta-analysis was applied to examine a possible non-linear association between water intake and mortality. This was done through modeling of water intake and restricted cubic splines with three knots at fixed percentiles of 10, 50, and 90% of the distribution. Based on the Orsini method^[18], we calculated restricted cubic spline models using generalized least-squares trend estimation method, which takes into account the correlation within each set of reported ORs/RRs/HRs. Then, all the study-specific estimates were combined with the use of the restricted maximum likelihood method in a multivariate random-effects meta-analysis. A probability value for non-linearity was estimated using null hypothesis testing in which the coefficient of the second spline was considered equal to 0. A linear dose-response association was investigated using the two-stage generalized least-squares trend estimation method. First, study-specific slope lines were estimated, and then, these lines were combined to obtain an overall average slope.³⁰ Study-specific slope lines were combined using a random-effects model. Statistical analyses were conducted using STATA version 14.0. $P < 0.05$ was considered as statistically significant for all tests, including Cochran's Q test.

RESULTS

Literature search: We identified 1327 articles in our initial search. After exclusion of duplicate papers and those that did not meet the inclusion criteria, we identified 11 full-text articles of potentially relevant studies. After full-text review, we excluded an additional 4 articles for the following reasons: studies that enrolled patients with chronic renal diseases or hemodialysis patients, papers that were conducted on critically ill patients, one document that was conducted on children. Finally, seven cohort studies were included in the current systematic review and meta-analysis^[5, 6, 14-16, 19, 20]. Four studies had reported effect sizes for all-cause mortality^[6, 15, 19, 20] and 6 studies for CVD mortality^[5, 6, 14-16, 20]. Of these publications, seven had reported effect sizes for total water^[5, 6, 14-16, 19, 20] and four for drinking water^[5, 16, 19, 20]. A flow diagram of study selection is shown in **Figure 1**.

Characteristics of included studies: Characteristics of included prospective cohort studies are presented in **Tables 1**. All included studies published between 2002 and 2018. Participants in these studies ranged from 1055 to 35362 people, with an age range between 18 and over 70 years. The duration of the follow up of the included cohort was between 6 and 19.1 years. In total 116816 participants were enrolled in the studies. Among the included studies, 3 studies were done in the USA^[5, 6, 19], 2 in Australia^[15, 20], and the rest in Japan^[14] and Netherland^[16]. In total 14754 patients died due to all-cause in the studies and 7611 deaths were due to CVD. One study was performed on women^[20] and 4 studies^[5, 14, 16, 19] were reported effect size for men and women separately. Out of the remaining studies, two^[6, 15] reported effect sizes for both genders in combination. To assay fluid/water intake, all studies had used a food frequency questionnaire and 24h recall. All included studies applied record linkage for assessment of mortality as the outcome. All studies adjusted the associations for age. Most cohorts controlled for some conventional risk factors, including body mass index (n=5), smoking (n=5), and energy intake (n=3). Some others had also adjusted for alcohol consumption (n=2) and other dietary variables (n=2). Based on the ROBINS-E tool, two studies had a

low-risk of bias in all components (**Supplemental Table 2**).

Findings from the meta-analysis on total water intake and all-cause mortality:

Six cohort studies investigated the association between total water intake and risk of all-cause mortality^[5, 6, 14-16, 19]. These studies included a total of 115815 participants, among them 14250 deaths occurred. The summary effect size for all-cause mortality comparing the highest and lowest intakes of total water was 0.95(95% CI: 0.83-1.09, P=0.47), indicating no clear significant association between total water intake and risk of all-cause mortality (**Figure 2**). However, significant between-study heterogeneity was seen ($I^2 = 66\%$; P=0.002).

Findings from the meta-analysis on water intake and all-cause mortality:

Examining the association between drinking water consumption and risk of all-cause mortality in three studies^[5, 16, 19], that involved a total of 51474 participants with 9279 deaths, we found no significant association (Pooled ES comparing the highest and lowest intakes: 0.82; 95% CI: 0.63-1.08, P=0.65), with high heterogeneity among the studies ($I^2 = 77.3\%$; P=0.001) (**Figure 3**).

Findings from the meta-analysis on total water intake and CVD mortality:

Five cohort studies examined the association between total water intake and risk of CVD mortality^[5, 6, 14-16]. These studies included a total of 91051 participants among them 7107 mortality cases were found. The summary effect size for CVD mortality, comparing the highest and lowest total water intakes, was 0.84(95% CI: 0.77-0.93, P<0.001), indicating a significant inverse association between total water intake and risk of CVD mortality (**Figure 4**). No significant heterogeneity among the studies was observed ($I^2 = 0\%$; P = 0.76).

Linear and non-linear dose-response analysis

Four of six studies on the association between total water intake and all-cause mortality were included in the dose-response analysis^[6, 14-16] (**Figure 5**). We found a significant non-linear association (P-nonlinearity=0.01). Furthermore, linear dose-response meta-analysis revealed a significant inverse association between total water intake and all-cause mortality by an additional one cup per day (Pooled ES: 0.98; 95% CI: 0.97-0.99, P= 0.001) (**Supplemental Figure 1**).

In the dose-response analysis of total water intake and CVD mortality, based on four studies, out of six studies, we found a significant non-linear association (P-nonlinearity=0.009) (**Figure 6**). Based on linear dose-response analysis, each additional cup of total water intake per day was associated with a 3% lower risk of death from CVD (Pooled ES: 0.97; 95% CI: 0.96-0.98, P<0.001) (**Supplemental Figure 2**).

Subgroup, sensitivity analyses, and publication bias:

To test the robustness of the results and investigate the between-study heterogeneity, we conducted subgroup analyses. **Supplemental Table 3** presents findings for the different subgroups. In terms of total water intake and risk of all-cause mortality, a significant inverse association was obtained in studies conducted in US countries. However, a significant positive association was seen in studies conducted in US countries and those that had applied food recall or record for total water intake assessment. In terms of total water intake and risk of CVD mortality a significant inverse association was seen in studies that conducted in US and non-US countries, those that performed in females and males, studies that had used FFQ for total water intake assessment, studies with a >10 years follow-up duration and those that controlled for BMI and energy intake in their analysis. In terms of drinking water intake and all-cause mortality, a significant inverse association was reached in studies that had applied FFQ for drinking water assessment.

Findings from the sensitivity analysis using a fixed-effects model revealed that the exclusion of any single study from the analysis did not appreciably alter the pooled effect sizes. There were no missing studies imputed in regions of the contour enhanced funnel plots. No publication bias was found based on Egger's

linear regression test. The application of the trim and fill method did not change the average effect size, further suggesting that results were not affected by publication.

DISCUSSION

This systematic review and meta-analysis support a significant inverse association between total water intake and risk of CVD mortality. Moreover, total water intake was inversely linked with all-cause and CVD mortality in a linear and non-linear dose-response manner.

Water affects numerous physiological processes and, therefore, its net effects on health outcomes is important. There is substantial evidence that mild dehydration may account for many morbidities. The previous meta-analyses have focused mainly on individual fluid intakes with risk of mortality and total water intake has received less attention^[21]. To the best of our knowledge, this is the first meta-analysis of prospective cohort studies that examined the association between water intake and risk of mortality. In the current study, total water intake was associated with a lower risk of CVD mortality. In line with our, a review revealed that good hydration reduces the risk of hypertension, fatal coronary heart disease, venous thromboembolism, and cerebral infarct. Further study indicated serum sodium as a risk factor for CVDs and give additional support to recommendations for dietary salt restriction and adequate water intake as preventives of CVD. Moreover, finding from earlier meta-analyses have documented that coffee and tea consumption as total fluid subtypes were associated with a lower risk of CVD mortality^[7, 8, 21, 22]. However, it must be kept in mind that tea and coffee are mild diuretics and thus may raise blood viscosity which could increase the risk of mortality. Therefore, these inverse associations might be attributed to biologically active factors in tea and coffee. The inverse association between total fluid intake and cardiovascular mortality might be explained by reduced risk of inflammation and coagulation which are considered as major risk factors for the development of cardiovascular diseases. In our study total and drinking water was not associated with all-cause mortality. This might be attributed to the consumption of fluids other than water such as caffeinated beverages or high energy drinks which can cause a rapid elevation in blood viscosity after consumption.

In the context of our findings, it must be kept in mind individual fluids contain diverse biologically active components that may also account for the association between water intake and mortality. Also, other conditions such as medications and higher salt intake should be taken into account which can affect the fluid balance and in result alter the risk of mortality.

Exact mechanisms underlying the relation between water intake and mortality risk are not completely understood. Concerns about recommendations for high water intake have been based on the assumption that low fluid intake is associated with dehydration which can induce inflammation and physiological dysfunction in the body. Evidence has shown that chronic dehydration is associated with a higher risk of certain diseases, such as cardiovascular disease^[5]. Besides, chronic dehydration may be related to increasing levels of hemorrhagic factors^[23, 24]. Elevation coagulation factors along with high blood viscosity, fibrinogen, and hematocrit levels are correlated with coronary heart disease^[25-29]. They respond to circadian changes in hydration, daily activity, and medication such as diuretics^[30-33]. Moreover, raising of serum sodium within the physiological range as a result of dehydration can lead to vascular changes by stimulating inflammatory signaling in endothelial cells and promote atherosclerosis. Another theory concerns arginine vasopressin (AVP), which regulates the water balance in the body. AVP also has vasoconstrictive effects, and there is evidence that elevated plasma levels have adverse effects on blood pressure and ventricular function^[34, 35]. Increased water intake, suppresses plasma AVP, and exert other hemodynamic effects^[36-38].

Strengths and weaknesses of the study: The present meta-analysis has several strengths. First, the relatively large number of participants and deaths included, allowed us to quantitatively assess the association of water intake and risk of mortality, thus making it more powerful than any single study. Second, a dose-response analysis was conducted to evaluate the linear and non-linear relations. Third, because all included studies had a prospective design, the influence of recall and selection bias is minimized that are common in case-control studies. Fourth, in the significant relations of our study low heterogeneity among studies was seen which further confirms our results. Finally, we evaluated the associations separately for total and

drinking water intake as the exposure of interest. These data provide the most comprehensive insight into the association between water intake and risk of mortality based on the current evidence. Our findings also need to be interpreted in the context of some limitations, most of them are common to observational studies and meta-analyses. Residual or unmeasured confounding factors may have affected the magnitude of the association between water intake and mortality. Although most studies had controlled for potential confounders, some did not control the analyses for dietary intake of other nutrients and some others did not consider total energy intake and BMI as covariates. Lack of control for such factors might affect the independent association of water intake with mortality. Also, some studies in this review did not report sufficient information to be included in the dose-response meta-analysis. Also, different methods were used for water intake assessment including FFQ and dietary recall in the included cohorts. Measurement errors in dietary assessment are inevitable and would have could alter the associations with water intake. As we considered studies on apparently healthy populations, our conclusions about water intake cannot be generalized to those with specific diseases such as hemodialysis, CKD, and ARDS patients, in which fluid imbalance is more prevalent in them.

Conclusion

This current systematic review and meta-analysis of prospective cohort studies provide evidence that higher total water intake is associated with a lower risk of CVD mortality. However total water intake was not associated with an increased risk of all-cause mortality. Further studies are needed to investigate the associations of water intake with all-cause and other causes of mortality as well.

Further studies with a prospective design are required to confirm these findings.

REFERENCES

1. Valtin H. "Drink at least eight glasses of water a day." Really? Is there scientific evidence for "8x 8"? *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 2002.
2. Electrolytes IoMPoDRIf, Water. DRI, dietary reference intakes for water, potassium, sodium, chloride, and sulfate: National Academy Press 2005.
3. Tetens I. European Food Safety Authority: EFSA: Panel on Dietetic Products, Nutrition, and Allergies (NDA); Scientific Opinion on Dietary reference values for water. *EFSA J* 2010; **8** : 1459.
4. Sontrop JM, Dixon SN, Garg AX et al. Association between water intake, chronic kidney disease, and cardiovascular disease: a cross-sectional analysis of NHANES data. *American journal of nephrology* 2013; **37** : 434-42.
5. Chan J, Knutsen SF, Blix GG et al. Water, other fluids, and fatal coronary heart disease: the Adventist Health Study. *American journal of epidemiology* 2002; **155** : 827-33.
6. Wu L-W, Chen W-L, Liaw F-Y et al. Association between fluid intake and kidney function, and survival outcomes analysis: a nationwide population-based study. *BMJ open* 2016; **6** .
7. Tang J, Zheng J-S, Fang L et al. Tea consumption and mortality of all cancers, CVD and all causes: a meta-analysis of eighteen prospective cohort studies. *British Journal of Nutrition* 2015; **114** : 673-83.
8. Zhang C, Qin Y-Y, Wei X et al. Tea consumption and risk of cardiovascular outcomes and total mortality: a systematic review and meta-analysis of prospective observational studies. Springer 2015.
9. Je Y, Giovannucci E. Coffee consumption and total mortality: a meta-analysis of twenty prospective cohort studies. *British Journal of Nutrition* 2014; **111** : 1162-73.
10. Nordestgaard AT, Nordestgaard BG. Coffee intake, cardiovascular disease and all-cause mortality: observational and Mendelian randomization analyses in 95 000–223 000 individuals. *International journal of epidemiology* 2016; **45** : 1938-52.

11. Horvat P, Stefler D, Murphy M et al. Alcohol, pattern of drinking and all-cause mortality in Russia, Belarus and Hungary: a retrospective indirect cohort study based on mortality of relatives. *Addiction* 2018; **113** : 1252-63.
12. Hernandez-Hernandez A, Gea A, Ruiz-Canela M et al. Mediterranean alcohol-drinking pattern and the incidence of cardiovascular disease and cardiovascular mortality: the SUN project. *Nutrients* 2015; **7** : 9116-26.
13. Jeong H-G, Kim TH, Lee JJ et al. Impact of alcohol use on mortality in the elderly: results from the Korean Longitudinal Study on Health and Aging. *Drug and alcohol dependence* 2012; **121** : 133-9.
14. Cui R, Iso H, Eshak ES et al. Water intake from foods and beverages and risk of mortality from CVD: the Japan Collaborative Cohort (JACC) Study. *Public health nutrition* 2018; **21** : 3011-7.
15. Palmer SC, Wong G, Iff S et al. Fluid intake and all-cause mortality, cardiovascular mortality and kidney function: a population-based longitudinal cohort study. *Nephrology Dialysis Transplantation* 2014; **29** : 1377-84.
16. Leurs LJ, Schouten LJ, Goldbohm RA, van den Brandt PA. Total fluid and specific beverage intake and mortality due to IHD and stroke in the Netherlands Cohort Study. *British journal of nutrition* 2010; **104** : 1212-21.
17. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology* 2009; **62** : e1-e34.
18. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *The stata journal* 2006; **6** : 40-57.
19. Kant AK, Graubard BI. A prospective study of water intake and subsequent risk of all-cause mortality in a national cohort. *The American journal of clinical nutrition* 2017; **105** : 212-20.
20. Lim WH, Wong G, Lewis JR et al. Total volume and composition of fluid intake and mortality in older women: a cohort study. *BMJ open* 2017; **7** : e011720.
21. Yi M, Wu X, Zhuang W et al. Tea Consumption and Health Outcomes: Umbrella Review of Meta-Analyses of Observational Studies in Humans. *Molecular nutrition & food research* 2019; **63** : 1900389.
22. Malerba S, Turati F, Galeone C et al. A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases. Springer 2013.
23. Dvilansky A, Bar-Am J, Nathan I et al. Hematologic values in healthy older people in the Negev area. *Israel journal of medical sciences* 1979; **15** : 821-5.
24. Kristal-Boneh E, Glusman J, Chaemovitz C, Cassuto Y. Improved thermoregulation caused by forced water intake in human desert dwellers. *European journal of applied physiology and occupational physiology* 1988; **57** : 220-4.
25. Lowe G, Lee A, Rumley A et al. Blood viscosity and risk of cardiovascular events: the Edinburgh Artery Study. *British journal of haematology* 1997; **96** : 168-73.
26. Koenig W, Sund M, Filipiak B et al. Plasma viscosity and the risk of coronary heart disease: results from the MONICA-Augsburg Cohort Study, 1984 to 1992. *Arteriosclerosis, thrombosis, and vascular biology* 1998; **18** : 768-72.
27. Ernst E. Haematocrit and cardiovascular risk. *Journal of internal medicine* 1995; **237** : 527-8.
28. De Simone G, Devereux RB, Chien S et al. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. *Circulation* 1990; **81** : 107-17.

29. ERIKSEN G, THAULOW E, SANDVIK L et al. Haematocrit: A Predictor of Cardiovascular Mortality? *Survey of Anesthesiology* 1994;**38** : 275.
30. Kurabayashi H, Kubota K, Tamura Ji, Shirakura T. A glass of water at midnight for possible prevention of cerebral infarction. *Stroke*1991; **22** : 1326-7.
31. Seaman G, Engel R, Swank RL, HISEN W. Circadian periodicity in some physicochemical parameters of circulating blood. *Nature* 1965;**207** : 833-5.
32. Vandewalle H, Lacombe C, Lelievre J, Poirot C. Blood viscosity after a 1-h submaximal exercise with and without drinking. *International journal of sports medicine* 1988; **9** : 104-7.
33. Yasaka M, Yamaguchi T, Oita J et al. Clinical features of recurrent embolization in acute cardioembolic stroke. *Stroke* 1993;**24** : 1681-5.
34. Torres VE. Vasopressin in chronic kidney disease: an elephant in the room? *Kidney international* 2009; **76** : 925-8.
35. Goldsmith SR. Is there a cardiovascular rationale for the use of combined vasopressin V1a/V2 receptor antagonists? *The American journal of medicine* 2006; **119** : S93-S6.
36. Shore AC, Markandu ND, Sagnella GA et al. Endocrine and renal response to water loading and water restriction in normal man. *Clinical Science* 1988; **75** : 171-7.
37. Bouby N, Bachmann S, Bichet D, Bankir L. Effect of water intake on the progression of chronic renal failure in the 5/6 nephrectomized rat. *American Journal of Physiology-Renal Physiology* 1990;**258** : F973-F9.
38. May M, Jordan J. The osmopressor response to water drinking. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 2011; **300** : R40-R6.

Legend to figure(s)

Figure 1: Flow diagram of study selection

Figure 2 : Forest plot for the association between total water intake and risk of all-cause mortality in adults aged >18 years, expressed as the comparison between the highest and lowest categories of total water intake. Horizontal lines represent 95% CIs. Diamonds represent the pooled estimates from the random-effects analysis. ES: effect size, CI: confidence interval

Figure 3: Forest plot for the association between drinking water intake and risk of all-cause mortality in adults aged >18 years, expressed as the comparison between the highest and lowest categories of total water intake. Horizontal lines represent 95% CIs. Diamonds represent the pooled estimates from the random-effects analysis. ES: effect size, CI: confidence interval

Figure 4 : Forest plot for the association between total water intake and risk of CVD mortality in adults aged >18 years, expressed as the comparison between the highest and lowest categories of total water intake. Horizontal lines represent 95% CIs. Diamonds represent the pooled estimates from the random-effects analysis. CVD: cardiovascular disease, ES: effect size, CI: confidence interval

Figure 5: Non-linear dose-response association of total water intake (based on cup/day) with risk of mortality from all-cause in adults aged [?]18 years. Total water intake was modeled with restricted cubic splines in a multivariate random-effects dose-response model. Dotted line indicates the linear model. Solid line indicates the spline model. Dashed line presents the 95% CI. CVD: cardiovascular disease, ES: effect size, CI: confidence interval

Figure 6: Non-linear dose-response association of total water intake (based on cup/day) with risk of mortality from CVD mortality in adults aged [?]18 years. Total water intake was modeled with restricted cubic splines in a multivariate random-effects dose-response model. Dotted line indicates the linear model. Solid

line indicates the spline model. Dashed line presents the 95% CI. CVD: cardiovascular disease, ES: effect size, CI: confidence interval

Table 1: Characteristics of included cohort studies on the association between fluid intake and mortality in adults aged >18 years

Author	Country	Age*	n	Follow up (year)	Cases	Exposure	Exposure assessment	Outcome	Comparison	ES (95% CI)**
Lim et al. 2017	Australia	>70	F: 1055	10	142	Total fluid Plain water	beverage intake questionnaire	CVD mortality	Per one cup	HR: 0.98 (0.93-1.03) HR: 1.02 (0.95-1.10)
Lim et al. 2017	Australia	>70	F: 1055	10	362	Total fluid Plain water	life style questionnaire	All-cause mortality	Per one cup	HR: 0.98 (0.95-1.01) HR: 0.99 (0.95-1.04)
Chan et al. 2002	USA	>38	F: 12017	6	118	Plain water Fluids other than water	life style questionnaire	CVD mortality	T3 vs. T1	RR: 0.52 (0.27-1.03) RR: 3.32 (1.18-9.30)
Chan et al. 2002	USA	38	M: 8280	6	128	Plain water Fluids other than water	life style questionnaire	CVD mortality	T3 vs. T1	RR: 0.39 (0.22-0.67) RR: 1.34 (0.59-3.04)
Cui et al. 2018	Japan	40-79	F: 35362	19.1	1707	Total water	FFQ, self-reported	CVD mortality	Q5 vs. Q1	HR: 0.79 (0.66-0.95)
Cui et al. 2018	Japan	40-79	M: 22939	19.1	1637	Total water	FFQ, self-reported	CVD mortality	Q5 vs. Q1	HR: 0.88 (0.72-1.07)
Palmer et al. 2014	Australia	>49	M/F: 3858	13.1	547	Total fluid	FFQ, self-reported	CVD mortality	Q4 vs. Q1	HR: 0.91 (0.70-1.19)

Author	Country	Age*	n	Follow up (year)	Cases	Exposure	Exposure assessment	Outcome	Comparison	ES (95% CI)**
Palmer et al. 2014	Australia	>49	M/F: 3858	13.1	547	Total fluid	FFQ, self- reported	All- cause mortality	Q4 vs. Q1	HR: 0.91 (0.68- 1.21)
Wu et al. 2016	USA	>20	2128	15.4	473	Total fluid	24-h recall, interview	CVD mor- tality (non- CKD)	Q4 vs. Q1	HR: 0.98 (0.75- 1.28)
Wu et al. 2016	USA	>20	2182	15.4	473	Total fluid	24-h recall	CVD mortal- ity (non CKD)	Q4 vs. Q1	HR: 1.00 (0.76- 1.30)
Leurs et al. 2010	Netherlands	55-69	F: 2958	10	537	Total fluid Plain water	FFQ, self- reported	IHD mortality	Q4 vs. Q1	HR: 1.04 (0.67- 1.61) HR: 0.70 (0.37- 1.34)
Leurs et al. 2010	Netherlands	55-69	M: 3509	10	1252	Total fluid Plain water	FFQ, self- reported	IHD mortality	Q4 vs. Q1	HR: 1.03 (0.73- 1.47) HR: 1.33 (0.76- 2.36)
Leurs et al. 2010	Netherlands	55-69	F: 2958	10	291	Total fluid Plain water	FFQ, self- reported	Stroke mortality	Q4 vs. Q1	HR: 0.60 (0.31- 1.15) HR: 0.49 (0.19- 1.24)
Leurs et al. 2010	Netherlands	55-69	M: 3509	10	417	Total fluid. Plain water	FFQ, self- reported	Stroke mortality	Q4 vs. Q1	HR: 0.77 (0.45- 1.30) HR: 0.85 (0.31- 2.29)

Author	Country	Age*	n	Follow up (year)	Cases	Exposure	Exposure assessment	Outcome	Comparison	ES (95% CI)**
Kant et al. 2017	USA	>25	F: 12660	10	3032	Total water Plain water	24-h recall- interview	All- cause mortality	Q4 vs. Q1	HR: 1.15 (0.96- 1.39) HR: 0.98 (0.83, 1.14)
Kant et al. 2017	USA	>25	M: 12050	10	3504	Total water Plain water	24-h recall- interview	All- cause mortality	Q4 vs. Q1	HR: 1.24 (1.09- 1.42) HR: 1.15 (1.00, 1.33)

Abbreviation: HR: hazard ratio- RR: risk ratio- CI: confidence interval- M: male- F: female- FFQ: food frequency questionnaire- US: United States-

*Presented as mean or range

**Effect size

+ Adjustments: age (1), gender (2), race (3), ethnicity (4), BMI (5), Fluid intake (6), total energy (7), alcohol consumption (8), education (9), family history of CVD (10), smoking (11), physical activity (12), hypertension (13)

Hosted file

Table.pdf available at <https://authorea.com/users/375397/articles/492649-total-and-drinking-water-intake-and-risk-of-all-cause-and-cardiovascular-mortality-a-systematic-review-and-dose-response-meta-analysis-of-prospective-cohort-studies>

Hosted file

Figures.pdf available at <https://authorea.com/users/375397/articles/492649-total-and-drinking-water-intake-and-risk-of-all-cause-and-cardiovascular-mortality-a-systematic-review-and-dose-response-meta-analysis-of-prospective-cohort-studies>