Supplementary Text 1. Details of the statistical analysis

To examine the association between osmolarity and all-cause mortality, we initially fit an unadjusted Cox regression model. We then imputed the missing data using the multiple imputation method [17]. Any missing data of osmolarity, Kt/V, serum albumin CRP, IWDG, serum phosphorous, hemoglobin, vascular access, modality, dialysate sodium concentration, and history of CAD, CHD, CVD, PAD, and diabetes that were needed to perform the analysis were imputed from the covariates using data with no missing values (age, dialysis vintage, gender, patient ID, and patient round number). We generated 20 imputed datasets using chained equations.

We assumed IWDG and Kt/V at time t were affected by the osmolarity at time t, and that osmolarity affected IWDG and Kt/V at time t+1. Therefore, we considered IDWG and Kt/V would be time-varying confounders affected by past osmolarity[1]. Moreover, the osmolarity itself would be a time-varying variable, and it might be affected by the prior osmolarity as well. On the other hand, we assumed hemoglobin, serum albumin, serum phosphorus, and serum CRP would be time-varying confounders but would not be affected by past osmolarity.

We used a marginal structural model (MSM) with inverse probability weight (IPW) to estimate exposure effects in the presence of time-dependent confounders affected by prior exposure [2-5]. We treated osmolarity as a continuous variable and followed the approach proposed by Hernan et al[4]. First, for each imputed dataset, we estimated each subject's probability of osmolarity using a multiple regression analysis with the following covariates: age, sex, dialysis vintage, diabetes, CAD, CHF, CVD, PAD, access type (fistula, graft, or catheter), dialysis modality (hemodialysis or

hemodiafiltration), sodium concentration of dialysate (≤140 mmol/L or >140 mmol/L), Kt/V, IDWG, hemoglobin, serum albumin, serum phosphorus, serum CRP, and follow-up variable. We then calculated the IPW using the estimated probability. Secondly, we estimated censoring weights using logistic regression with the same covariates above. Third, we generated overall weights calculated by multiplying IPWs and censoring weights. Subsequently, we estimated the association between osmolarity and all-cause mortality using the pooled logistic regression model that was weighted using the overall weights.

Our dataset was discretized into one observation per subject per 4 months. We could model the probability of being exposed at time t by a Cox proportional hazards model. However, because of the discretized dataset, we used a pooled logistic regression model in which we modelled the probability that each individual was exposed in each 4-month period. This was equivalent to a Cox model because the hazard of exposure in any single period was small [6].

We estimated the coefficient and the standard error of the coefficient of the association of osmolarity and all-cause mortality using the pooled logistic regression with IPW for each imputed dataset. Subsequently, we combined the 20 sets of estimates and standard errors using Rubin's rule [7].

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3. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550-60.

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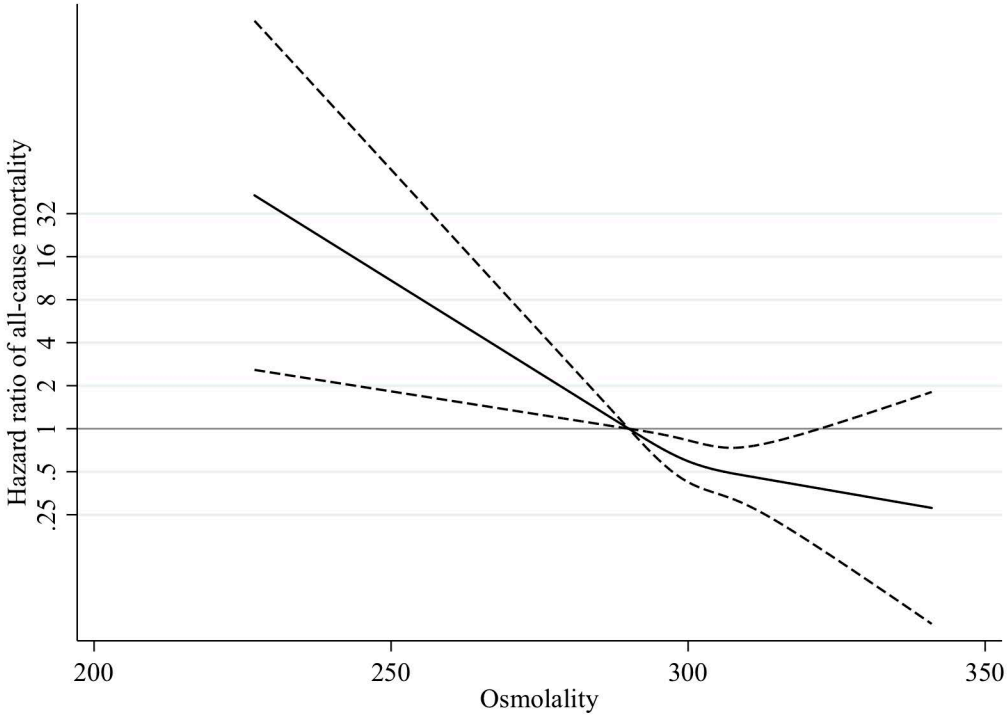
Supplementary Figure 1. Cubic splines based on three knots (290, 300, and 310 mOsm/kg of calculated osmolality) to allow for non-linear associations between calculated osmolality and all-cause mortality.


Hazard ratio of all-cause mortality
.25
.5
1
2
4
8
16
32
200
250
300
350
Osmolality