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Ultrafiltration rate thresholds and the risk of mortality, cardiovascular events, and intradialytic hemodynamic instability in adults on maintenance hemodialysis: protocol for a systematic review with dose-response meta-analysis

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ADMINISTRATIVE INFORMATION**Support** - None. This review received no specific funding.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100048

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 October 2026 and was last updated on 10 October 2026.

INTRODUCTION

Review question / Objective Primary objective: In adults receiving maintenance hemodialysis (Population), to quantify the association between intradialytic ultrafiltration rate (UFR) (Exposure), compared with a lower, study-defined reference UFR category or per unit increment in UFR (Comparator), and all-cause mortality (Outcome), and to characterize the shape of that dose-response relationship, including any threshold or inflection point.

Secondary objectives: (1) To estimate the association of UFR with cardiovascular mortality, cardiovascular events, and intradialytic hypotension (IDH). (2) To examine effect modification by heart failure, age, diabetes, body size, and UFR scaling method (weight-normalized vs absolute vs weight-indexed). (3) To appraise the risk of bias and residual confounding, and to grade the certainty of evidence.

Rationale No dedicated systematic review with meta-analysis has pooled ultrafiltration rate (UFR) thresholds against patient outcomes in chronic maintenance hemodialysis, despite explicit calls from the KDOQI 2015 Hemodialysis Adequacy guideline and the NKF-KDOQI Controversies Report to consolidate this evidence (Slinin et al., Seminars in Dialysis 2018; Kramer et al., AJKD 2016; Assimon & Flythe, Current Opinion in Nephrology & Hypertension 2015). The existing evidence comprises large individual observational cohorts (HEMO post-hoc, Fresenius, DOPPS, and others) that use inconsistent exposure definitions and reference categories and have never been quantitatively synthesized. Commonly cited thresholds (10 or less, 10 to 13, and more than 13 mL/h/kg) derive from single cohorts and have been described by authorities as partly arbitrary.

A rigorous dose-response synthesis could (1) identify a pooled inflection point for risk across cohorts, (2) quantify how the threshold shifts with heart failure, age, and body size, and (3) formally appraise confounding and reconcile the

observational signal with the discordant null randomized contrast within the HEMO Study.

Condition being studied End-stage kidney disease treated with maintenance (chronic) hemodialysis or hemodiafiltration. Each session removes accumulated fluid by ultrafiltration, and the ultrafiltration rate (UFR) is the volume removed per unit of treatment time, commonly normalized to body weight (mL/h/kg). Large observational cohorts have reported associations between higher UFR and mortality, cardiovascular events, and intradialytic hemodynamic instability, but exposure definitions vary, proposed thresholds derive from single cohorts, and causality remains uncertain. This review addresses the association between UFR and these outcomes in adults on maintenance hemodialysis.

METHODS

Search strategy Databases: MEDLINE (Ovid), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, and Web of Science Core Collection, from inception with no date or language limits.

Draft MEDLINE strategy (three concept blocks, combined as Block 1 AND Block 2 AND Block 3):
Block 1 (population): hemodialysis OR haemodialysis OR "renal dialysis" OR hemodiafiltration OR "maintenance dialysis" OR ESRD OR "end-stage kidney disease"
Block 2 (exposure): "ultrafiltration rate" OR UFR OR "fluid removal rate" OR "fluid removal" OR "ultrafiltration volume" OR "weight-normalized ultrafiltration"
Block 3 (outcomes): mortality OR death OR survival OR cardiovascular OR "intradialytic hypotension" OR hemodynamic OR hospitalization

The MEDLINE strategy will be peer reviewed by an information specialist using PRESS and adapted to the syntax and controlled vocabulary of each database. The full line-by-line strategy for each database, with dates run and records retrieved, will be reported in a PRISMA 2020 appendix.

Participant or population Inclusion: adults (18 years or older) receiving maintenance (chronic) hemodialysis or hemodiafiltration for end-stage kidney disease.
Exclusion: acute kidney injury treated with continuous or intermittent kidney replacement therapy in the intensive care unit; pediatric populations; patients on peritoneal dialysis; extracorporeal ultrafiltration for decompensated heart failure.

Intervention Exposure: intradialytic ultrafiltration rate (UFR), however defined by the primary study (weight-normalized mL/h/kg, absolute mL/h, or weight-indexed), quantified continuously or in at least two categories and analyzed across its full reported range. Exposure-definition details (numerator, denominator, scaling, averaging window, category boundaries, and reference category) will be extracted to support harmonization for dose-response modeling. Studies reporting UFR only as a descriptive baseline covariate without an outcome association will be excluded.

Comparator Lower UFR category (study-defined reference category), or UFR modeled continuously (effect per unit increment in UFR).

Study designs to be included Primary synthesis: prospective or retrospective observational cohort studies reporting an adjusted association between UFR and at least one listed outcome. Secondary synthesis: randomized controlled trials reporting outcomes by UFR or by interventions that primarily alter UFR, analyzed separately. Excluded: case reports and narrative reviews.

Eligibility criteria Inclusion: adult maintenance hemodialysis population; UFR quantified as an exposure (continuous or at least two categories); at least one listed clinical outcome reported with an effect estimate and variance, or data permitting their computation.
Exclusion: AKI/ICU kidney replacement therapy populations; pediatric populations; peritoneal dialysis; heart-failure ultrafiltration; studies reporting UFR only as a descriptive baseline covariate; case reports; narrative reviews.
Conference abstracts without extractable estimates will be tabulated but not pooled. No language restriction will be applied at screening; translation will be obtained where feasible, otherwise the record will be flagged.

Information sources Electronic databases: MEDLINE (Ovid), Embase, CENTRAL, CINAHL, and Web of Science Core Collection.
Trial registers: ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), for completed and ongoing trials.
Grey literature: conference proceedings (ASN Kidney Week, ERA-EDTA).
Citation searching: backward and forward citation chasing of all included studies and of the KDOQI 2015 Hemodialysis Adequacy guideline and NKF-KDOQI Controversies Report.
Contact with authors: investigators of major cohorts (including Fresenius and DaVita datasets)

will be contacted regarding individual-patient data and missing dose-distribution or event-count data.

Main outcome(s) All-cause mortality, as ascertained by each primary study over its reported follow-up. Effect measure: adjusted hazard ratio or risk ratio with 95% confidence interval per UFR category versus the study-defined reference category, or per unit increment when UFR is modeled continuously. The most fully adjusted estimate reported will be used as primary; minimally adjusted estimates will be extracted where available for sensitivity analysis. The headline output is a pooled dose-response curve for UFR versus all-cause mortality.

Additional outcome(s) (1) Cardiovascular mortality.

(2) Cardiovascular events or hospitalizations (composite as defined by each study).

(3) Intradialytic hypotension, as defined by each study; heterogeneity in definitions will be tabulated.

Effect measures for (1) to (3): adjusted hazard ratio, risk ratio, or odds ratio with 95% CI per UFR category versus the reference, or per unit increment for continuous models; the most fully adjusted estimate will be primary.

(4) Surrogate cardiac-structure outcomes (left ventricular mass, left atrial volume index), summarized narratively only.

Data management Records will be de-duplicated and screened in Covidence (or Rayyan). Two reviewers will independently screen titles and abstracts and then full texts, resolving disagreements by discussion or a third reviewer; Cohen's kappa will be reported for full-text decisions, and selection will be summarized in a PRISMA 2020 flow diagram with reasons for full-text exclusion tabulated.

Two reviewers will extract data independently and in duplicate into a piloted standardized form: bibliographic and design data, country, data source (registry, single-center, dialysis organization), enrollment period, sample size, and follow-up duration; the exposure definition (numerator: interdialytic weight gain vs delivered ultrafiltration volume vs weight change; denominator: prescribed vs delivered time and target vs post-dialysis weight; scaling; averaging window; category boundaries and reference category); outcome definitions and ascertainment; effect estimates (HR, RR, OR) per category with 95% CIs, person-time or number at risk and events per category where available (required for GLST), and continuous per-unit estimates;

adjustment covariates and analytic method (standard Cox, time-dependent Cox, marginal structural model/G-estimation, splines); and data for effect modifiers (heart failure, age, diabetes, body size).

For dose-response modeling, each category will be assigned its reported median or mean UFR; where only ranges are given, category midpoints will be used, and open-ended extreme categories will be assigned a value using the half-width of the adjacent interval. Authors will be contacted for missing dose-distribution or event-count data.

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently and in duplicate using ROBINS-E (Risk Of Bias In Non-randomized Studies of Exposures) for observational cohorts, across the confounding, exposure measurement, selection, missing data, outcome measurement, and selective reporting domains, and Cochrane RoB 2 for any included randomized controlled trials.

A structured confounding appraisal is the centerpiece of the review. It will evaluate residual confounding and reverse causation, explicitly addressing lower residual kidney function, low body weight/frailty, interdialytic weight gain, treatment time, and nonadherence, as well as the mathematical collinearity between UFR and its components (e.g., the IDWG-UFR correlation of about 0.91 in the Raimann data). E-values will be computed for pooled estimates to quantify the strength of unmeasured confounding required to nullify them, interpreted cautiously given modest effect sizes. Whether each study used methods appropriate for time-varying confounding affected by prior exposure (marginal structural models/G-estimation vs standard time-dependent Cox) will be tabulated as a bias indicator.

Strategy of data synthesis Primary analysis (dose-response meta-analysis): a two-stage Greenland-Longnecker (GLST) approach will estimate study-specific trends across each study's own dose values, accounting for the within-study correlation among estimates sharing a common reference, and pool them in a DerSimonian-Laird/REML random-effects model. Nonlinearity will be tested with restricted cubic splines (3 knots at the 10th, 50th, and 90th percentiles) to identify any threshold or inflection point; a pooled dose-response curve for UFR versus all-cause mortality is the headline output.

Supplementary analysis: a one-stage Crippa-Orsini dose-response meta-analysis (dosresmeta in R)

will retain studies reporting only a dichotomy (e.g., more than 13 vs 13 mL/h/kg or less) that the two-stage method, which requires at least three categories, would exclude; studies reporting a continuous per-unit estimate will contribute directly to the linear slope.

Secondary categorical analysis: where dose-response is not estimable, a conventional random-effects meta-analysis of the most comparable categorical contrasts (e.g., more than 13 vs 13 mL/h/kg or less; more than 10 vs 10 mL/h/kg or less) will be reported separately, with explicit caveats about discarded dose information. Randomized controlled trials will be analyzed separately from observational cohorts.

Heterogeneity will be quantified with tau-squared and I-squared. Individual-patient data: a hybrid design is pre-specified, with IPD meta-analysis (standardized UFR definition, harmonized covariate adjustment, continuous modeling with weight scaling) where data are obtainable and aggregate-data dose-response meta-analysis otherwise. Publication bias will be assessed with contour-enhanced funnel plots and Egger's test when at least 10 studies contribute to an outcome. Software: R (dosresmeta, metafor), cross-checked in Stata (drmeta, glst).

Subgroup analysis Heterogeneity will be explored through pre-specified subgroup analyses and meta-regression by: (1) heart failure status, testing whether excess risk emerges at a lower UFR threshold (per the HEMO interaction); (2) age strata; (3) diabetes; (4) body size and UFR scaling method (weight-indexed vs weight-normalized vs absolute); (5) data source (dialysis-organization registry vs independent cohort); (6) region; and (7) adjustment method.

Sensitivity analysis (1) Leave-one-out analysis, which is essential because nonlinearity conclusions in dose-response meta-analysis are fragile to single large studies and the Fresenius and DaVita cohorts are expected to dominate. (2) Alternative knot placements and numbers for the restricted cubic splines. (3) Restriction to studies using fully adjusted models. (4) Restriction to studies with homogeneous exposure definitions. (5) Fixed-effect vs random-effects comparison. (6) Minimally adjusted vs most fully adjusted estimates where both are available.

Language restriction No language restriction; translation will be obtained where feasible, otherwise the record will be flagged.

Country(ies) involved United States.

Other relevant information Certainty of evidence: rated per outcome with GRADE for observational evidence (starting at low). Rating up one level for a dose-response gradient will be considered under GRADE Guidance 38; rating down will be considered for risk of bias (residual confounding, collinearity between UFR and its components, reverse causation), inconsistency, indirectness, imprecision, and publication bias, and for discordance with the null randomized contrast within the HEMO Study. Conclusions will be framed as an association of uncertain causality rather than a causal safe threshold, and a summary-of-findings table will be produced for each outcome.

Reporting: the protocol is reported per PRISMA-P 2015; the completed review will be reported per PRISMA 2020, with dose-response methods reported per recommendations for dose-response meta-analysis.

Anticipated limitations: predominantly observational evidence in which residual confounding and reverse causation cannot be excluded; heterogeneous exposure definitions; dominance of a few large US dialysis-organization cohorts; proprietary data that may preclude full IPD analysis; and variable definitions of intradialytic hypotension.

Keywords ultrafiltration rate; fluid removal; maintenance hemodialysis; hemodiafiltration; intradialytic hypotension; all-cause mortality; cardiovascular mortality; cardiovascular events; dose-response meta-analysis.

Dissemination plans Results will be submitted for publication in a peer-reviewed journal and presented at a nephrology scientific meeting. Data and analysis code will be deposited in an open repository where permitted.

Contributions of each author

Author 1 - Marco Ladino - Conceived and designed the review and drafted the protocol; will screen records, extract data, assess risk of bias, and draft and critically review the manuscript.

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