Haemodiafiltration versus high-flux haemodialysis - a Consensus Statement from the EuDial Working Group of the ERA

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Abstract

Haemodialysis (HD) is a life-saving therapy for individuals with kidney failure. Post-filter haemodiafiltration (HDF) and high-flux HD are the most widely used treatment modalities. To date, five randomised controlled trials (RCTs) have been performed that compare all-cause and cardiovascular (CV) mortality between HDF and low- or high-flux HD in adults receiving maintenance dialysis for at least one year. RCTs, meta-analyses and pooled individual patient data analyses have been published on this topic. However, all of them are limited by the heterogeneity of inclusion criteria and significant methodological shortcomings, including informative selection bias and the exclusion of poorly performing patients from the HDF arm after randomisation.

Given this background, the European Dialysis Working Group of the European Renal Association presents a Consensus Statement on HDF and high-flux HD, addressing three key outcomes: survival, health-related quality of life and biochemical endpoints. A separate section is dedicated to paediatric patients. We searched five large electronic databases to identify parallel or cross-over RCTs comparing HDF with high-flux HD on pre-defined outcome measures. Using a mini-Delphi method, we developed twenty-two key consensus points by combining meta-analyses, clinical experience and expert opinion. They aim to inform and assist in decision-making and are not intended to define a standard of care. The key summary point is that HDF appears to be associated with improved overall and CV survival, provided high convection volumes are achieved. The generalizability of these findings to the entire dialysis population depends on the patient's overall health and requires further study.

Keywords:

all-cause mortality, convection volume, haemodiafiltration, haemodialysis, kidney failure

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Introduction

Haemodialysis (HD) is the most widely used modality of kidney replacement therapy for individuals with kidney failure [1]. It is based on the diffusive transport of solutes across a semi-permeable membrane. It is highly effective at removing small solutes, such as urea, and correcting electrolyte, acid-base and fluid imbalances. HD can be performed with low- or high-flux membranes [2,3]. As the importance of larger uraemic toxins has been recognised, alternative therapies have been developed that provide greater clearance of larger middle molecules. Solute sieving coefficients are less dependent on the molecular size than diffusion coefficients. This knowledge led to the development of convective therapies, such as haemofiltration in the 1970s [4], later followed by haemodiafiltration (HDF), a combined convective and diffusive therapy [5].

The Consensus Conference on Biocompatibility, held in 1993, defined HDF as "a treatment designed to remove accumulated metabolic products from the blood by a combination of diffusive and convective transport through a semi-permeable membrane of high-flux type. Fluid is removed by ultrafiltration, and the volume of filtered fluid exceeding the desired weight loss is replaced by sterile, pyrogen-free infusion solution" [6], also known as online HDF. Based on the site of replacement fluid infusion, there are different methods of performing HDF: post-filter HDF, pre-filter HDF, mixed pre- and post-filter HDF, and mid-filter HDF [7]. Post-filter HDF is the most widely used of these modalities (Figure 1).

A consensus conference held by the European Dialysis (EuDial) Working Group of the European Renal Association - European Dialysis Transplant Association (ERA-EDTA) in October 2011 defined a lower limit for the convection volume equivalent to 20% of the total blood volume processed during post-filter HDF treatment, below which treatment would not qualify as HDF. This filtration fraction is achievable with post-filter HDF in most patients without inducing excessive haemoconcentration [8]. The EuDial Working Group also recognised the need for clear definitions of 'high-flux' membranes to permit optimal HDF. The traditional definition of 'high-flux' relied

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solely on hydraulic permeability, which does not necessarily correlate with high large solute permeability. Therefore, the EuDial Working Group added a characteristic related to middle molecule clearance to the definition, using that of the Membrane Permeability Outcome study, i.e., a sieving coefficient > 0.6 for β_2-microglobulin (β2M) [9]. These considerations led to a revised definition of HDF in 2013, stating that HDF is a blood purification therapy combining diffusive and convective solute transport using a high-flux membrane characterized by a device ultrafiltration coefficient > 20 mL/hour/mmHg/m^2 and a sieving coefficient for β2M > 0.6 [8].

The need for a Consensus Statement

Five randomised controlled trials (RCTs) in adults have compared all-cause and cardiovascular (CV) mortality between HDF and HD in patients receiving maintenance dialysis [10,11,12,13,14]. It is worth noting that different HD (low- vs high-flux) and HDF (low- vs high-volume) techniques were used in these RCTs, with different patient demographics, vascular access types, treatment times and differences between the targeted vs the actual delivered convection volume [15]. Indeed, significant limitations of the major RCTs must be recognised and acknowledged to interpret the results correctly. All the RCTs were unblinded to the physicians and patients, and this lack of concealment may have led to the misreporting of events in highly motivated physicians and patients who completed self-reported quality of life questionnaires.

Several meta-analyses have been published comparing RCTs of HDF vs HD [16,17,18]. There is significant heterogeneity in the inclusion of RCTs. Some meta-analyses included studies with low-flux HD as a comparator, cross-over trials, trials on acetate-free biofiltration, and studies that did not have survival as a primary outcome and were underpowered to detect this. While individual meta-analyses may not show statistical heterogeneity, combining these different studies is inappropriate; in a meta-analysis, correcting these technical differences and reducing their influence on the observed effect is difficult, and combining biased studies only amplify the bias.

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The potential superiority of HDF vs high-flux HD on crucial patient-level outcomes, such as hospital admissions, infections, and quality of life (QoL), as well as on psychological factors and nutritional parameters, awaits a definitive answer. Recognising the need for clinical practice suggestions for HDF and high-flux HD, the Board of the EuDial Working Group of the European Renal Association (ERA) has developed a consensus statement on both therapies with the approval of the Scientific Advisory Board of ERA and the ERA Council. A dedicated section comparing HDF with high-flux HD in children has also been included.

Methods

Developing the PICO questions

Given that clinical practice suggestions are most valuable when they provide specific, actionable advice on choosing alternative approaches in particular clinical situations, we developed clinical questions to be addressed and framed them in a searchable format, specifying the patient group (P) to whom the statement should be applied; the intervention (I) taken into consideration; the comparator (C); and the outcomes (O) affected by the intervention. Our PICO terms were as follows:

Population: Patients (children and adults) on maintenance dialysis

Intervention: online HDF (both low- and high-volume)

Comparator: high-flux HD

Outcomes: grouped under three PICO questions:

- PICO 1: all-cause mortality, CV mortality, sudden cardiac death, intradialytic hypotension, hospital admissions, and infection rates.
- PICO 2: QoL, sleep disturbances, physical activity, and uraemic pruritus.
- PICO 3: clearance of uraemic toxins and biomarkers of nutrition, inflammation, anaemia, and mineral bone disorders.

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Search strategy and selection criteria

Descriptive terms “high-flux HD” and “HDF” were used as search strategies and literature selection criteria. Two scientists, experts in the field of methodology, Y.B. and I.N., and three research fellows (F.B., F.C. and C.M.), conducted a systematic search based on the pre-defined PICO terms. Disagreements were resolved by consensus and a third methodologist expert, where needed (A.M.). The search was conducted in the CENTRAL, Medline, PubMed, Scopus, and Web of Science databases from their inception to July 31, 2024, to identify parallel or cross-over RCTs reporting the impact of HDF compared with high-flux HD on all the outcome measures listed above. Non-randomised prospective observational studies in paediatrics on chronic high-flux HD or HDF were also included for PICO 1, 2 and 3 outcome measures. References were reviewed from original papers and review articles to identify further eligible studies not covered by our original database searches. No language restriction was applied. Exclusion criteria were: 1) congress abstracts, case reports, reviews, practice guidelines, case-control or cross-sectional or longitudinal or non-randomised studies in adult patients; 2) RCTs that did not report any estimate for the outcomes of interest; 3) RCTs conducted in patients with acute kidney injury; 4) RCTs on haemofiltration alone; 5) RCTs on “expanded haemodialysis”, a technique combining diffusive and convective transport inside a medium cut-off dialyzer (Table S1); 6) RCTs assessing HD or HDF with treatment regimens exceeding three sessions per week. The updated Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement was followed to perform this systematic review and the meta-analysis of PICO outcome data [19].

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Framing advice

This consensus presents "key consensus points", concisely summarising available evidence crafted with clinical practice experience and expert opinion. The suggestions of this Consensus Statement aim to inform and assist in decision-making to reduce uncertainty and improve patient outcomes. They are not intended to define a standard of care and should not be interpreted as an exclusive management path. Therefore, formal grading evidence was not applied since all key consensus points have similar relevance in clinical practice. Using the Estimate-Talk-Estimate (ETE) method, or "mini-Delphi" [20,21], through an iterative process, the EuDial team drafted key consensus points with their relative rationale, reaching a strong level of agreement among its members for each of them (Figure S1).

Fragility Index, Fragility Quotient, Survival-Inferred Fragility Index and Number Needed to Treat

Four indices were calculated for the RCTs with statistically significant results for outcomes of interest: the Fragility Index (FI), the Fragility Quotient (FQ), the Survival-Inferred Fragility Index (SIFI) and the Number Needed to Treat (NNT) (Table 1). The FI is an ancillary tool that quantifies the fragility (or robustness) of findings reporting statistically significant P values [22]. This intuitive index is primarily employed to assess the robustness of research findings for dichotomous outcomes. It represents the minimum number of participants whose status would need to change from an 'event' to a 'non-event' (or vice versa) to change the results from statistically significant to non-significant. Although no established cut-off exists, a higher FI score can indicate more robust results [23]. To mitigate the potential effect of the sample size on the FI, the FQ has been proposed. It is calculated as follows: FQ = FI/sample size [23]. There is no consensus on a cut-off value of FQ. However, empiric observation suggests that an FQ $\leq$ 0.03 raises a concern about the robustness of the findings [23].

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SIFI is defined as the minimum number of reassignments of the best survivors (defined as the patients with the longest follow-up time, regardless of having an event or being censored; the worst survivors were defined as the patients with the earliest event) from the experimental group to the control group, resulting in a loss of significance (in this specific case, defined as $\alpha = 0.05$ using the log-rank test) [23]. Thus, SIFI can provide a measure that accounts for events over time and retains all the advantages of the original FI. NNT is the number of patients needed to be treated to prevent one additional adverse outcome (e.g., death or stroke).

Results

RCTs comparing HDF with high-flux HD

Figures 2-4 summarize the results of the literature search and study selection (PRISMA flow diagrams). The main characteristics of the 37 unique RCTs [11, 12, 13, 14, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56] identified are reported in Supplementary Tables S2-S4, divided according to PICO outcomes. Primary and secondary outcomes of the RCTs were analysed; some were included in multiple PICO outcomes. The most up-to-date RCT or comprehensive data were included for RCTs with multiple publications. Only one RCT [11] was selected, with very few patients using low-flux filters (8%) in the HD group. The forest plot and pooled estimates of HDF vs high-flux HD on PICO outcomes are reported in Figures 6-12 and Figures S2-S6.

Paediatric Section

Figure 5 summarises the results of the literature research and study selection (PRISMA flow diagram) in paediatrics. Table S5 lists the main characteristics of the five selected paediatric studies [57,58,59,60,61], four of which [58,59,60,61] include a mix of low- and high-flux HD. Currently, no RCTs compare outcomes on HDF vs high-flux HD in children, and only prospective observational studies are described in Table S6. Since hard endpoints of survival or CV mortality are rare in paediatric patients, surrogate measures of CV disease, blood pressure (BP), biomarkers, and QoL measures have been analysed.

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Robustness of the RCT data

Testing robustness of the results using the FI statistics described above, it is clear that both the ESHOL [11] and CONVINCE trials [14] lack robustness (Table 1) [23]: just three participants of the CONVINCE trial, i.e., 0.2% of the study population, would be required to change the primary outcome of the study, all-cause mortality, from statistically significant to non-significant [14]. Similarly, the SIFI in the CONVINCE [14] and ESHOL [11] trials were 18 and 81, respectively, implying that the statistical significance for survival outcome in the CONVINCE trial [14] might be lost with a change in the assignment of 18 patients (1.3% of the CONVINCE cohort) (Table 1) [23]. Finally, using the time-to-event data in the CONVINCE trial [14], one would need to treat 22 patients with high-dose HDF rather than high-flux HD for 3 years to prevent one death (from any cause) per year (95% confidence interval 14 – 68) (Table 1).

Convection volume: the critical determinant of outcomes

Key consensus points

- **A high convection volume is associated with reduced overall and CV mortality in patients receiving HDF compared to those on high-flux HD. The effect size depends on both the convection volume delivered (target greater than 23 L/session) and the patient's overall health.**
- **Achieving a high convection volume requires optimal vascular access, and this is usually more likely to be reached in patients dialysed through an arteriovenous fistula (AVF) rather than a central venous catheter (CVC) or graft.**

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Rationale

All the 13 RCTs identified [12;13;14;24;26;27;28;29;30;31;32;33;34] in PICO 1 outcomes included a selected patient population, and no RCT has pragmatically randomised the entire HD population to HDF or high-flux HD. Importantly, it should be remembered that the selection criteria, which ensure that a high convection volume (the sum of the substitution volume and ultrafiltration volume) is possible and tolerated, also influence survival and other significant endpoints. The CONVINCE trial, for example, selected HD patients who were likely to achieve high-volume (≥ 23 L/session) HDF – this pre-selection bias meant that younger and fitter patients were included; the median age of the CONVINCE cohort was 62.5 years, and 82% of patients were dialysed through an AVF [14]. In comparison, approximately 35% of incident HD patients in the ERA registry are under 62, and approximately 60% have an AVF [62]. The generalisability of the RCT findings to the broader HD population remains to be investigated.

The Turkish HDF study was one of the first to assess the impact of substitution volume on clinical outcomes [12]. In a *post-hoc* analysis, a comparative analysis of all-cause and CV mortality was made between post-filter HDF with a substitution volume of more than 17.4 L, post-filter HDF with a substitution volume of less than 17.4 L, and high-flux HD. All-cause ($p = 0.03$) and CV ($p = 0.002$) mortality were lower in those treated by post-filter HDF with a substitution volume of more than 17.4L compared to those on maintenance HD [12]. The achieved convection volume was higher in ESHOL (23.4 L) [11] and CONVINCE (25.3 L) [14], demonstrating a lower risk of all-cause mortality in the HDF arm than in studies not showing a benefit of HDF.

The association between weekly convection volume, considered a continuous variable, and unadjusted relative survival rate at 2 years was analysed by Canaud et al. and presented as cubic spline curves [63]. The relative survival rate increased at around 55 L/week (also expressed as 18 L per 4-hour HD session) or 30 L/week/m^2 when convection volume was corrected for body surface area. Notably, the available data do not indicate a saturation effect nor a benefit reversal with higher convection volumes. Patients who are unable to tolerate and/ or achieve a convection volume

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greater than 18 L per session (standardised for body surface area) despite best efforts may not benefit significantly from HDF. They may, therefore, not be suitable candidates for the maintenance of high-volume HDF.

A key determinant of high convection volume (≥ 23 L/session) is a high blood flow rate (Qb), which requires optimal vascular access; AVFs are usually superior to CVCs or grafts, and younger, fitter patients are more likely to have optimal vascular access than older or multi-morbid patients. Some RCTs are subject to selection bias, in which only patients with well-functioning vascular access, permitting sufficiently high Qb, were recruited. The lowest mean Qb among 13 RCTs was reported by Kang et al. (300 ± 18 mL/min for high-flux HD and 304 ± 19 mL/min for HDF) [31]; in CONVINCE, the mean Qb was 367 ± 56 mL/min for high-flux HD and 369 ± 54 mL/min for HDF [14]. These observations highlight that patients included in the RCTs primarily had AVFs, with the highest percentage (above 80%) in CONVINCE [14]. This is also reflected in the ESHOL study, where the HD arm had significantly older patients with a higher prevalence of diabetes and higher CVC use than the HDF cohort [11].

Furthermore, ESHOL [11] and the Turkish HDF study [12] excluded approximately 10% of patients from the HDF arm after randomisation as they could not achieve high-volume HDF because of low blood flows; importantly, patients with similarly poor blood flows were not removed from the high-flux HD arm. The RCTs are, therefore, subject to significant methodological shortcomings, including informative selection bias, as patients unable to achieve high-volume were not systematically studied. It is unclear whether such patients would benefit from HDF.

The feasibility of achieving a high convection volume (≥ 23 L/session) should be tested before making treatment decisions on maintenance HDF vs high-flux HD. A formal evaluation of the feasibility of high-volume HDF in patients treated by maintenance HD, including incident patients, should be performed. The feasibility test could follow a stepwise protocol by modifying key treatment-related determinants, such as Qb, needle size, and surface area of the dialyser membrane

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[64]. The timing and duration of feasibility testing depend on the individual patient's tolerance to dialysis. As shown in a *post-hoc* analysis of the CONTRAST trial, which compared HDF to the low-flux HD group, the treatment time and Qb rather than the vascular access type, dialyser characteristics or patient-related factors correlated with the achieved convection volume [65].

Patients unable to achieve a high convection volume should be evaluated to optimise vascular access, blood flow, and dialysis filter; the algorithm suggested by the CONVINCE trial investigators may be applied to work towards an optimal convection volume [14]. An individualised approach with the convection volume standardised for patient size (by body surface area) may be more appropriate.

All-cause mortality

Key consensus points

- **All-cause mortality appears to be lower in patients treated by HDF than in those treated by high-flux HD. However, this effect cannot be generalized to the entire dialysis population, as its size depends on both the patient's overall health (not simply on the age, diabetes or pre-existing cardiovascular disease) and the delivered convection volume (target greater than 23 L/session).**

Rationale

The mortality of individuals with kidney failure exceeds that of many cancers, with a 5-year survival rate of less than 40%, [66] with few RCTs demonstrating any reduction in mortality.

In our meta-analysis, five RCTs [11,12,13,14,31] compared HDF to high-flux HD with all-cause mortality as a primary outcome. Overall, all-cause mortality was lower in patients treated by HDF than in those treated by high-flux HD (Table 2, Figure 6). However, only two RCTs, CONVINCE [14] and ESHOL [11], demonstrated a reduction in all-cause mortality with HDF compared to high-

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flux HD. In contrast, the others did not show a survival benefit [12,13,31]. Therefore, the conclusion that HDF confers a survival advantage over high-flux HD is predominantly based on the ESHOL [11] and CONVINCE trials [14]. Furthermore, testing the robustness of the results using the FI described above, it is clear that both the ESHOL [11] and CONVINCE trials [14] lack robustness (Table 1) [23]. Finally, individual RCTs were underpowered to detect effects on all-cause mortality. Even in CONVINCE [14], the largest RCT, only 1,360 patients were recruited out of the targeted 1,800, and the actual event rate was about half that expected.

Of note, the lower risk of all-cause mortality was not distributed equally among all participants in the different RCTs. Patients allocated to the HDF groups in the ESHOL [11] and CONVINCE [14] trials were healthier, either by pre-selection as in CONVINCE [14] or by excluding patients from the HDF arm after randomisation as in ESHOL [11]. In addition, despite randomisation, in the CONVINCE [14] trial, a higher, albeit not significantly different, percentage of patients with diabetes (HDF 33.7% vs high-flux HD 37.1%), coronary heart disease (HDF 19% vs high-flux HD 21.7%) and smokers (HDF 14.3% vs high-flux HD 16.2%) were assigned to the high-flux HD group [14]. Similarly, in the ESHOL [11] trial, patients treated by HDF were younger (HDF 64.5±14.3 vs high-flux HD 66.3±14.3 years) with a lower percentage of diabetes (HDF 22.8% vs high-flux HD 27.1%), a higher Charlson comorbidity index (HDF mean 6.0 vs high-flux HD 7.0) and higher use of native AVFs (HDF 89.3% vs high-flux HD 82.7%). Additionally, patients in the HDF arm achieved higher Qb and dialysate flow rates (Qd) at 36 months follow-up (HDF mean Qb 389 mL/min; mean Qd 566 mL/min vs high-flux HD mean Qb 380 mL/min; mean Qd 537 mL/min) [11]. Age and several comorbidities, i.e., the presence of diabetes and pre-existing cardiovascular disease (CVD), are known modifiers of all-cause mortality. These RCTs suggest that several subgroups may obtain differential benefits from HDF.

(i) ***Age:*** The different RCTs included patients across a relatively wide age range. Relatively younger patients were included in the Turkish (age 56.5 ± [SD] 13.9] years) [12], ESHOL (age 65.4 ± 14.4 years) [11] and CONVINCE studies (age 62.4 ± 13.5 years) [14]. In contrast, the FRENCHIE trial (age 76.3 ± 6.3 years) included only patients older than 65 years [13]. Not all

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studies performed sub-group analyses based on age strata. Remarkably, in the exploratory analysis of the CONVINCE study, the age group showing a significant benefit was those aged 65 years or more [14]. The FRENCHIE study, however, suggests that this benefit may be lost in elderly patients [13]. As chronological age does not adequately reflect frailty, we argue against using an absolute age threshold for treatment decisions when selecting the dialysis modality.

(ii) ***Diabetes mellitus***: While all RCTs collected data on diabetes, only two studies reported data on all-cause mortality in subgroups of patients with and without diabetes [11,14]. In the ESHOL study [11], the hazard ratio (HR) for overall mortality was lower in non-diabetics (HR 0.68; 95% CI 0.48-0.95) and was not significant in patients with diabetes (HR 0.75; 95% CI 0.46 – 1.21). In the CONVINCE study [14], the HR for overall mortality was significantly lower in those without pre-existing diabetes (HR 0.65; 95% CI 0.48 – 0.87) and not significantly different for individuals with pre-existing diabetes (HR 0.97; 95% CI 0.72 – 1.31). Although HDF may offer greater survival benefits in patients without diabetes, further studies are required to confirm this effect.

(iii) ***Pre-existing CVD:*** In the CONVINCE study [14], a risk reduction with HDF was seen only in those without pre-existing CVD (HR 0.58; 95% CI 0.42 – 0.79), whereas those with pre-existing CVD had no survival benefit with HDF (HR 0.99; 95% CI 0.76 – 1.28). Similarly, in the Turkish study [12], among patients with CVD before the start of the study (n=182), no statically significant differences in survival were found between the two groups (51.9% in high-flux HD vs 64.9%; in HDF; p=0.67). Other studies [11,13,31] have not assessed the impact of CVD history on survival outcomes. Also, no study stratified patients with a CVD history based on the presence of diabetes, one of the most significant risk factors for CVD. The available data remain inconclusive for patients with pre-existing CVD.

(iv) ***Residual kidney function:*** Few data on residual urine output are reported in the RCTs. In the CONVINCE trial [14], all-cause mortality risk was the same between HDF and HD groups for patients with more (HR 1.59; 95% CI 0.56 – 4.45) or less (HR 0.76; 95% CI 0.37 – 1.59) than 1

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L/daily urine output. However, these results must be interpreted cautiously, as data on residual kidney function was available in only 11% of the cohort.

There is good agreement between studies regarding individual HR in different subgroups. However, none of the RCTs [11,14] was powered to examine survival outcomes in any subgroup of patients, but taken together, these univariate comorbidity analyses suggest that the effect size of all-cause mortality reduction is greater in individuals without significant comorbidities.

A conventional meta-analysis of independent studies comparing HDF with low- or high-flux HD was used to determine the consistency of treatment effects across studies. However, in addition to the quality and heterogeneity of studies with different designs, populations, and methodologies, meta-analyses are based on published data. Therefore, meta-analyses of the CONTRAST [10], Turkish [12], FRENCHIE [13] and ESHOL [11] studies were confounded by variable amounts of missing data, as mortality follow-up data were incomplete for 355 (39%) of patients in the ESHOL study [11], for 43 (11%) patients in the FRENCHIE study [13] and for 199 (25%) patients in the Turkish study [12], as these patients were censored as alive at the time they discontinued the study. Furthermore, different HD techniques (low- vs high-flux) were used in these RCTs: 392 patients, 356 from the CONTRAST [10] and 36 from the ESHOL [11] studies of the 1979-2046 patients (19-20%), were on low-flux HD.

To overcome the missing data problem, the HDF Pooling Project Investigators [67] conducted an individual patient data analysis, which included additional follow-up data on all-cause mortality and cause-specific mortality (ESHOL and French HDF studies only). Data were collected for 2,793 patients, comprising 906 from the ESHOL study [10], 391 from the FRENCHIE study [13], 782 from the Turkish study [12] and 714 from the CONTRAST study [10]. The pooled data analysis showed increased overall and cardiac survival for patients treated by HDF compared to those treated by HD (high- or low-flux), with the greatest survival benefit observed in patients receiving the highest delivered convection volume. These results remain consistent after adjustments for body surface area and total body water [68].

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More recently, this pooled data analysis has been updated by including patients of the CONVINCE study [69]. After analysing the outcomes of 4,153 patients randomised into these five RCTs, HDF was associated with reduced all-cause and CV mortality. This survival benefit applied equally to adults of both sexes, ages above and below 65 years, those with and without diabetes, those with a history of CVD, and those with reduced serum albumin or dialysis vintage. Again, these analyses suggest that a single clinical variable cannot be used to identify patients who are likely to benefit from HDF; instead, it depends on the patient's overall health.

The survival benefit with HDF appeared to be higher with increasing convection volumes above 23 L/session. However, it should be emphasized that although pooled data analysis overcomes some of the limitations of a meta-analysis, it cannot correct the selection bias inherent in the RCTs and that patients were not randomised based on convection volumes.

It remains to be determined whether this benefit applies only to achieving an absolute volume of convective clearance, adjusted to body surface area or another scaling parameter. This issue may be addressed by the ongoing H4RT trial in the UK, which compares outcomes of patients randomised to high-flux HD and high-volume HDF, with the convective target volume adjusted for body surface area [70].

In conclusion, overcoming the inherent bias due to selective patient inclusion remains a challenge, whether using conventional meta-analysis or pooled data analysis. A different study design would be needed to fully appreciate the benefits of high convection volume.

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Cardiovascular events

Key consensus points

- **CV mortality appears to occur less frequently in patients treated by HDF than in those undergoing high-flux HD. However, this effect cannot be generalized to the entire dialysis population, as its size depends on both the patient's overall health and the delivered convection volume (target greater than 23 L/session).**
- **There is no difference in the risk of sudden cardiac death between patients treated by HDF and those treated by high-flux HD.**
- **HDF does not reduce the frequency of intradialytic hypotensive episodes compared to high-flux HD.**

Rationale

I –Cardiovascular mortality

Four RCTs reported CV mortality data: the Turkish [12], ESHOL [11], CONVINCE [14] and FINESSE [31] trials. All RCTs performed post-dilution HDF, although one participating centre in the FINESSE study [31] delivered pre-dilution HDF for one year (involving 4% of participants). Of note, given the extensive difficulties in conducting RCTs during the COVID-19 pandemic, mis-adjudication of events may have led to an incorrect reporting of the causes of death in CONVINCE [14]. In addition, the assessment of pre-existing CVD needs to be clarified. Specifically, neither the ESHOL [11] nor FINESSE [31] trials analysed subgroups with and without prior CVD. Furthermore, the Turkish trial [12] enrolled a younger dialysis population (56.5±3.9 years), with consequently fewer patients with prior CVD (26.4%) or pre-existing diabetes (34.7%). Our meta-analysis of these four studies demonstrated higher CV mortality in patients undergoing high-flux HD compared to HDF (Figure 7). This was confirmed in the pooled data analysis using patient-level data, including data from patients with pre-existing CVD [70]. However, a potential bias in

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adjudication should be noted, as causes of death were determined by physician judgment rather than by an independent adjudication committee.

Additionally, it is worth noting that in the FINESSE study [31], CV outcomes included not only CV death but also a composite of events requiring or occurring during hospital admission, such as acute myocardial infarction, stroke, percutaneous coronary or cerebrovascular revascularization, or surgical coronary or cerebral revascularization.

The mechanism(s) by which HDF confers survival benefits over high-flux HD remains uncertain [71]. Numerous factors are likely to be involved, including the total convection volume.

II - Sudden cardiac death

The term "sudden cardiac death" (SCD) is defined as death occurring within one hour of symptom onset or 24 hours of the last evidence of life after excluding other potential causes [72]. Typically, SCD results from ventricular arrhythmias, such as tachycardia or fibrillation [66], but can also occur from bradycardia, such as asystole [72]. According to the US Renal Data System, SCD resulting from arrhythmia or cardiac arrest accounts for 40% of all deaths and nearly 78% of CV deaths among dialysis patients [73]. However, the accuracy of this register data should be interpreted with caution, as it may be limited by the lack of post-mortem examinations.

The number of reported SCD in the three RCTs [11,12,13] comparing high-flux HD and HDF is low, with an annual risk between 0.3 and 3% (our meta-analysis: Figure S2). However, this result should be interpreted with caution and may not be generalisable to the HD population. Potential explanations for the nearly tenfold difference between studies include adjudication and case mix differences. An important factor is the significant age difference in patients in the studies described above. Furthermore, the adjudication of SCD is highly heterogeneous among RCTs. While the CONVINCE study [14] reported only the total number of patients with SCD in the HDF and HD arms, the ESHOL study [11] included CV and non-CV causes. In contrast, the FRENCHIE study [13] reported SCD as a cause of hospitalisation.

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While no previous study on HDF has directly demonstrated a correlation between electrolyte imbalance and SCD [65], pre-dialysis serum potassium, calcium and bicarbonate concentrations, and rapid electrolyte shifts are considered possible causes of SCD. Dialysate electrolyte compositions varied among RCTs: potassium from 1.5 to 3.0 mmol/L, calcium from 1.25 to 1.5 mmol/L, and bicarbonate from 25 to 37 mmol/L. The average pre-dialysis blood potassium levels were comparable in the Turkish [12] and ESHOL [11] trials but slightly lower in the FRENCHIE trial [13]. Due to the low number of events in individual studies, differences in adjudication, age differences, lack of data on pre-existing CVD, and potential impact of electrolyte imbalance, no conclusion can be drawn about the effects of HDF vs high-flux HD on SCD.

III - Intradialytic hypotension

Intradialytic hypotension is defined variably by international groups [74,75], and most studies do not distinguish between symptomatic and asymptomatic cases. Five RCTs assessed symptomatic intradialytic hypotension [11,12,13,24,25]. However, only three studies [11,13, 24] were included in our meta-analysis (Figure S3), in which we did not observe any significant difference in intradialytic hypotension between the two treatment modalities. The ESHOL study [11] reported a significantly lower incidence of symptomatic hypotensive episodes in the HDF arm than in the high-flux HD arm (HR 0.72; 95% CI 0.68–0.77). However, no definition of symptomatic hypotension was given in the manuscript. This was based on a pooled data collection, with data collected for one month per three treatment months. The FRENCHIE trial [13] reported data for both symptomatic and asymptomatic hypotensive episodes, both at the patient and session levels. At variance with the K/DOQI definitions [74], they used a 20 mmHg drop in systolic blood pressure (SBP) as symptomatic and asymptomatic hypotension thresholds. Although there was a trend, no significant reduction in symptomatic hypotensive episodes was documented ($p= 0.2$ at patient level; $p = 0.13$ at session level) [13]. The Turkish study [12] found no significant difference between treatment arms ($p = 0.9$). In this study, a different definition was used: SBP drop (>30 mmHg) and the requirement of saline infusion. In a cross-over study, Smith et al. found a higher incidence of hypotensive episodes during HDF (HR 1.52; 95% CI 1.2-1.9) but defined intradialytic hypotension

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as a decrease in SBP of more than 20 mmHg and requiring reduction/cessation of ultrafiltration and/or need for intravenous fluid bolus or Trendelenburg position [24].

A different way of analysing the effect of HDF on changes in BP is to analyse asymptomatic hypotension separately. Whereas no significant difference in symptomatic hypotension was found in the FRENCHIE study [13], the odds of asymptomatic hypotension were significantly lower in those treated by HDF (HR 0.87; 95% CI 0.79-0.95). When combining symptomatic and asymptomatic hypotension, the risk of any hypotensive episode was 12.5% in the HD group vs 10.9% in the HDF group (p =0.001).

A third way of analysing the available data is to include all types of hypotension, irrespective of symptoms. The Italian cooperative dialysis group [26] analysed all types, i.e., symptomatic, asymptomatic, and complicated hypotensive episodes. No specific definitions were provided in the manuscript. Furthermore, in this study no statistically significant difference between high-flux HD and HDF was reported. It should be noted that the study by Locatelli et al. was published in 1996. Although convection volumes were not reported, these were likely substantially lower than what would today be considered HDF [26]. The study by Rootjes et al. [34] is a four-arm cross-over study using the definition of Flythe absolute nadir SBP (see above), HDF showed the lowest frequency of intradialytic hypotensive episodes and the best intradialytic haemodynamic stability.

Another relevant factor, such as cooler infusion fluid affecting cardiac output, may indirectly influence the frequency of hypotensive episodes in the two treatment modalities [76]. However, the benefit of cooled dialysate remains uncertain [77], and most studies did not report data on dialysate temperature. In a cross-over RCT, 12 patients were randomly assigned to HDF or high-flux HD with cooled dialysate (unspecified temperature) at comparable pre- and post-dialysis temperatures. Despite a significant reduction in cardiac output, contractility and cardiac perfusion in high-flux HD and HDF patients, no statistically significant differences were found between the two groups [30]. In contrast, using echocardiography, Li et al. observed a significant reduction in intradialytic left ventricular systolic function in pre-dilution HDF (61.3 ± 9.9 to 59.0 ± 10.4%; p = 0.016), while a non-significant increase was observed in high-flux HD (61.7 ± 11.1 to 62.7 ± 11.2%; p = 0.19).

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However, the pre–and post-change differences between the two modalities did not reach statistical significance [33]. The disparate outcome may be attributed to the exclusive utilisation of pre-dilution HDF in the Li et al. study [33]. In contrast, in the Buchanan et al. study [30], the mode of HDF was not described but likely included both post- and pre-dilution.

None of the studies investigated HDF as a treatment modality to reduce intradialytic hypotensive episodes in hypotension-prone patients. While the beneficial effects of HDF may be mediated by a reduction in hypotensive episodes, treatment modality choices should not be based solely on the putative effects of HDF on intradialytic hypotension.

Infections and hospitalisations

Key consensus points

- **HDF is associated with a similar risk of all-cause and infection-related hospitalisations as high-flux HD.**
- **HDF may be associated with a lower risk of infection-related mortality compared to high-flux HD.**

Rationale

According to the Dialysis Outcomes and Practice Pattern Study (DOPPS), the leading causes of hospitalisation among people receiving dialysis are CVD, vascular access-related infections, and non-vascular access-related infections [78,79]. Hospitalisation was assessed in the ESHOL [11], FRENCHIE [13], and CONVINCE [14] trials. In our meta-analyses, there was no significant difference between the dialysis modalities in the number of hospitalisations from any cause (Figure S4) or infection-related hospitalisations (Figure S5).

In both the ESHOL [11] and FRENCHIE [13] trials, vascular access dysfunction was the primary cause of hospitalisation, particularly among patients undergoing high-flux HD (number of events in ESHOL 98/450 in high-flux HD vs 56/456 in HDF, and in FRENCHIE 67/191 in high-flux HD vs 36/190 in HDF). The CONVINCE trial [14] is the only study showing a weak preference for high-

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flux HD over HDF for hospitalisation outcomes. The reasons for these discrepancies remain unclear but may be attributed to difficulties in data collection during the COVID-19 pandemic or to the characteristics of the population, which was younger and had a longer period of dialysis compared to the ESHOL [11] and FRENCHIE [13] trials.

In the CONVINCE trial [14], infection-related deaths accounted for the higher all-cause mortality in the high-flux HD group; the HDF group had fewer deaths from sepsis (7 vs 14), cardiac infections (0 vs 2), respiratory infection (2 vs 5) and COVID-19 (15 vs 21) compared to the high-flux HD arm. There was no difference in the number of catheter-related infections and hospitalisations between dialysis modalities in the CONVINCE study [14], perhaps related to the high percentage of patients with AVFs. However, the ESHOL trial [11] had significantly more CVCs in the high-flux HD arm (13% in the high-flux HD vs 7.5% in the HDF arm) and significantly more hospitalisations for vascular access-related problems (98 in the high-flux HD arm vs 53 in the HDF arm), although it is not clear how many of the hospital admissions were related to catheter infections [11]. Like the CONVINCE study [14], the ESHOL trial [11] also reported significantly fewer deaths from infectious causes in the HDF cohort (our meta-analysis: Figure 8). Although the mechanisms are unclear, HDF may have a beneficial effect on immunological function. Several cytokines and inflammatory mediators, which are middle molecular weight substances, are removed by HDF. Furthermore, greater haemodynamic stability in HDF may reduce intestinal ischaemia and bacterial translocation.

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QoL

Key consensus points

- **HDF may better preserve self-reported physical symptoms and cognitive function of Health-related Quality of Life than high-flux HD.**
- **Improved physical activity levels may be achieved in patients receiving HDF than in those undergoing high-flux HD.**
- **Sleep quality appears similar in patients receiving HDF and high-flux HD.**
- **Neither HDF nor high-flux HD have shown superior outcomes in controlling uraemic pruritus.**

Rationale

I - Health-related Quality of Life

Numerous studies have shown that HD patients have significantly worse Health-related Quality of Life (HrQoL) compared to the general population [80,81,82]. Low HrQoL is correlated with adverse clinical outcomes, including higher hospitalisation and mortality rates [83,84,85]. Eight RCTs investigated the effect of HDF compared to high-flux HD on HrQoL [38,39,13,27,25,24,44,55]. The results among these RCTs are often different due to high heterogeneity in the patient-reported outcome measures (PROMs) administered, versions of PROMs used, scales used to calculate scores, population characteristics (e.g. ethnicity, religion and culture), and lack of blinding (Tables S6 and S7). Caution is needed when interpreting these data as some tools may not be sufficiently specific or sensitive enough to assess the effects of dialysis modality on patient perception accurately. Furthermore, results are presented as differences between cumulative scores rather than as ratios of individuals remaining within specific categories over time. Furthermore, the potential bias of a healthy caregiver who helped a dependent patient to complete the questionnaire cannot be excluded.

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The CONVINCE consortium [55] documented a deterioration in overall HrQoL over time, including physical and mental health scores, in both HDF and high-flux HD patients. However, this was less pronounced in the HDF group compared to the high-flux HD arm ($p = 0.006$) at 30 months of follow-up. The most prominent change in scores was noted in the physical health domains. The HDF group experienced a slower decline in cognitive function ($p = 0.049$), physical function ($p = 0.047$), pain interference ($p = 0.027$), and social participation ($p= 0.023$) compared to the high-flux HD group. On the other hand, mental health scores did not differ between the two modalities. Notably, these findings are based on only one of the PROMs, the PROMIS®-29 v2.0, used in the CONVINCE study [14]. Indeed, when analysing data from the Kidney Disease Quality of Life-36 (KDQOL-36), no difference was observed between the two groups [55]. Furthermore, although PROMIS®-29 v2.0 is strongly recommended, its results are calibrated to a T-score metric using the mean of a representative US general population, with no established threshold [55,86].

Among the four RCTs [13,27,24,44] that did not find any statistical difference between the two modalities in Mental Composite Score (MCS) and Physical Composite Score (PCS), Morena et al. reported that MCS tended to be higher in the high-flux HD group at 24 months ($p = 0.06$) [13]. Similarly, one RCT demonstrated a benefit of high-flux HD over HDF through an improvement in the MCS score of 12-item short-form (SF-12) within 12 weeks ($p < 0.05$) [38].

Conversely, two RCTs [25,39] identified HDF as more efficient in improving HrQoL. Schiffl et al. showed a sustained improvement in physical symptoms in patients treated by HDF compared to high-flux HD using the Kidney Disease Questionnaire (KDQ) [25]. However, the results are limited by the lack of data regarding the other four dimensions that KDQ explore - fatigue, depression, relationships with others and frustration.

Similarly, Karkar et al. found that post-dilution HDF improved social, physical, and occupational activities, energy levels, adherence to dialysis, sexual function, mood, taste perception, and appetite at 24 months follow-up. These benefits correlated with significantly reducing hypotension, cramps, itching, fatigue during and after dialysis, and joint discomfort. However, baseline HrQoL data are

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lacking; compared to other RCTs, the population was younger and came from different geographic regions (Saudi Arabia and Europe) [39].

II - Physical Activity

Individuals with kidney failure perform less physical activity than healthy individuals [87]. Lower levels of physical activity in this population have been associated with higher morbidity and mortality [88, 89,90].

Our systematic search identified one RCT that evaluated the effect of dialysis modality on physical activity levels, measured as the change in 24-hour steps taken on dialysis days from baseline to 6-month follow-up. Although a slight increase in step count was noted in the HDF arm, no statistically significant difference between dialysis modalities was found at six months, with a decrease in the step count over time in both arms [27]. Five RCTs [13,25,37,39,44] examined physical symptoms affecting physical activity levels (Table S6). Three RCTs suggested that HDF may improve subjective physical symptoms compared with high-flux HD. However, the results differ and are not comparable because different questionnaires were used (Table S7).

Karkar et al. assessed patient satisfaction with each dialysis modality using the KDQOL-SF questionnaire. Patients on high-efficiency post-dilution HDF after 24 months had a better perception of the level of sports activities (physical fitness including walking) than those treated by high-flux HD. Additionally, HDF was associated with better control of cramps, joint pain and stiffness, post-dialysis fatigue, and higher overall mood and body energy, which may motivate dialysis patients to increase their activity [39]. Similarly, Morena et al. found a significantly lower incidence of sessions with muscle cramps ($p=0.03$) in patients undergoing HDF [13].

Analogously, Schiffl et al. reported sustained improvement in physical symptoms, measured by the KDQ questionnaire, during HDF ($p<0.05$), but no change in this dimension with high-flux HD [25].

Further studies are needed to evaluate the impact of HDF vs high-flux HD on patient fitness levels, including simple (e.g., six-minute walk test) and more complex functional tests (e.g., the cardiopulmonary exercise tests).

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III - Sleep Quality

Patients undergoing chronic HD have a high prevalence of sleep disorders [91,92,93,94], which can negatively impact sleep quality and are associated with a higher risk of death [95]. The high chronic inflammatory burden typically observed in dialysis patients has been hypothesised to cause reduced sleep quality [96], and HDF may indirectly promote sleep quality by reducing inflammation through the removal of middle molecules [97].

Two RCTs [36,38] have been conducted in this field (Table S5). Although Han et al., in a *post-hoc* analysis of the HDFIT study [27], found no statistical differences in sleep time between HDF and high-flux HD, sleep time was slightly higher in the HDF arm [36]. In contrast, Jiang et al., using the Pittsburgh quality index, found an improvement in sleep quality within 12 weeks for the high-flux HD group compared to the HDF group. This improvement in sleep quality was closely associated with lower levels of pruritus in the high-flux HD group [38]. However, sleep quality depends on multiple physical and environmental factors, and this data is confusing.

IV - Uraemic Pruritus

CKD-associated pruritus (CKD-aP) is a common and debilitating complication for dialysis patients [98]. CKD-aP also carries a 17% higher mortality risk, attributed to poor sleep quality [99].

Only two RCTs evaluated the effect of the dialysis modality on the reduction of pruritus [38,39] (Table S5). A 12-week randomised and parallel-group clinical study demonstrated that high-flux HD was more effective in treating CKD-aP than HDF**.** This study also reported better HrQoL and sleep scores [38]. In contrast, Karkar et al. reported fewer episodes of pruritus in HDF patients. This improvement had a significant positive impact on patient satisfaction and HrQoL. However, the modified KDQOL-SF version 1.3 survey, a tool not specific for detecting CKD-aP, was used [39].

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Biochemical outcomes

Key consensus points

- **HDF allows for greater clearance of middle molecular weight uraemic toxins than high-flux HD.**
- **Pre-dialysis serum β_2-microglobulin concentrations may not differ between HDF and high-flux HD.**
- **Pre-dialysis serum phosphate concentrations are lower in HDF than in high-flux HD.**
- **Markers of nutritional and inflammatory status do not differ between HDF and high-flux HD.**
- **Anaemia control is similar in patients treated by HDF and high-flux HD.**

Rationale

***I* - Clearances of middle molecules and pre-dialysis serum β2M levels.**

HDF provides higher clearances of larger middle molecules associated with inflammation and metabolic disorders. β2M, a protein expressed on the surfaces of nucleated cells, is categorised as a "middle molecule" (molecular weight of 11.8 kDa) [44,100]. Disorders associated with β2M accumulation include dialysis-related amyloidosis and may contribute to the high prevalence of infection and CVD in kidney failure patients [101,102]. A previous meta-analysis has shown that convective therapies significantly reduced pre-dialysis serum β2M (12 studies, 1,813 participants; mean difference: -5.55 mg/L; 95% CI -9.11 to -1.98; I^2 = 94%) compared to diffusive therapy. The results between studies were very heterogeneous. Sensitivity analyses limited to studies comparing HDF with HD (high- or low-flux) showed similar results [103].

Our systematic search identified 23 studies [11,12,14,24,25,26,29,31,32,33,38,39,44,45,46,47, 48,49,50,51,52,53,56] that compared β2M removal between HDF and high-flux HD: 7 of them were included in our meta-analysis [11,12,25,26,29,32,52]. We observed no significant differences in pre-dialysis serum β2M levels between the two treatment modalities (Figure 9).

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A potential explanation could be differences in case mix among RCTs. β2M levels are directly associated with the patient's inflammation burden and removal by residual kidney function. Notably, in the Turkish study, which recruited only anuric patients, no difference in time-averaged pre-dialysis β2M levels between high-flux HD and HDF was found [12].

Information on other relevant parameters, such as Qb, Qd and replacement fluid rates, are not systematically reported. In the three RTCs [11,32,52] that reported achieved convection volumes, no additional benefits on β2M removal were observed with HDF compared to high-flux HD, even though a high mean convection volume (over 22 L) was achieved. Similarly, no adjunctive effect on β2M removal can be attributed to the different types of high-flux membrane, as all RCTS, except the Turkish study [12] and the study by Tammathiwat et al. [51], used the same filters for both modalities. Of note, data on β2M reduction ratio or dialyser β2M clearance were not systematically reported.

These findings seem to be at odds with experimental data showing that HDF results in higher β2M clearance than high-flux HD (80 mL/min vs 50 mL/min) [104]. However, β2M levels result from the balance between generation and removal. Recently, Ward and Daugirdas explored a kinetic model of HD and HDF with modelled β2M generation and removal, validated using data from the HEMO study [105]. Based on their kinetic model, residual kidney function has a more profound impact on reducing either pre-dialysis or time-averaged serum β2M levels than switching from high-flux HD to HDF. Modelling predicted that post-dilution HDF using 25 L of replacement fluid in 4 hours, similar to what has been achieved in the CONVINCE [14] study, would result in a reduction ratio of 63% for high-flux HD and 80% for HDF. However, at a constant generation rate of 240 mg/day, the differences between the two modalities with the model-predicted pre-dialysis serum β2M levels in non-anuric patients (27.2 vs 25.3 mg/L) were less than in anuric patients (31.7 vs 28.8 mg/L) [100]. Unfortunately, the CONVINCE study [14] did not report β2M concentrations or clearances. In addition, data on residual kidney function are lacking in a significant fraction of study participants.

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II - Phosphate removal

Our systematic review found 20 RCTs that measured phosphate. However, only data from eleven RCTs [12,11,14,25,24,27,28,30,39,42,52] were adequate for our meta-analysis (Figure 10). Pre-dialytic phosphate levels are lower in HDF than they are in high-flux HD. A high heterogeneity was found among the different studies. HDF was more effective than high-flux HD in four studies [25,28,39,52], limited by small sample sizes (fewer than 40 patients in each arm of the two modalities). The difference between pre-dialysis serum phosphate levels was approximately 1 mg/dL (0.32 mmol/L) between the two modalities.

Pecoits-Filho et al. reported a pre-dialysis phosphate level of 0.4 mg/dL lower with HDF compared to high-flux HD at 3 months ($p = 0.02$). However, no differences were observed at 6 months [27]. Interestingly, in the Thammathiwat et al. study, after 12-week treatment, the mean values of pre-dialysis serum phosphate in the high-flux HD group were not only significantly higher than those in the HDF group but also higher than baseline in the high-flux HD group only (from 4.16 ± 1.15 to 4.87 ± 1.47 mg/dL in high-flux HD and from 4.95 ± 1.35 to 4.37 ± 1.21 mg/dL in HDF; $p=0.003$). These conflicting results could be due to improved appetite in the high-flux-HD group, as indicated by significantly enhanced nPCR and serum albumin levels [51].

Of note, none of the studies mentioned above directly measured phosphorus clearance. Pre-dialysis serum phosphate level is not an exact measure of phosphorus removal. In addition to dialytic clearance, serum phosphate levels are influenced by diet, residual kidney function, and drugs, such as calcimimetics, vitamin D analogues, and phosphate binders. More detailed information in this regard is missing in most randomized studies. Data regarding changes in the dosage or type of phosphate binders and dietary protein intake should be included in future studies. Baseline pre-dialytic serum phosphate levels can affect phosphorus removal efficiency in several ways. For instance, in the Turkish study [12], since most patients had pre-dialysis serum phosphate levels below 5.5 mg/dL (72.2%), there was a lower probability of achieving the pre-specified risk reduction of 35% with HDF treatment. Furthermore, the mean serum phosphate level in HDF patients with higher infusion volumes was significantly lower than in high-flux HD [12]. Nearly all

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studies were not designed to assess phosphorus removal between the two modalities as the primary outcome. Therefore, RTCs were often underpowered, and sample sizes were inadequate.

A notable exception was the study by Francisco et al., who calculated phosphorus removal in mmol per session, considering the treatment time and the phosphorus concentrations in both dialysate and plasma. Greater phosphorus removal (1,099 ± 239 in HDF vs 864 ± 366 mmol/session in high-flux HD, p=0.05) was found in HDF, with lower pre-dialysis serum phosphate levels (3.4 ± 0.8 in HDF vs 4.5 ± 1.6 mg/dL in high-flux HD, p=0.05). However, this study was limited by the short follow-up of 3 months [28].

III - Nutritional and inflammatory status

Chronic inflammation can lead to decreased appetite, lower nutrient and calorie intakes, and hypercatabolism. There is a close correlation between malnutrition, inflammation, and atherosclerosis [106].

Our meta-analysis on pre-dialysis serum albumin levels, which included ten RCTs [11,12,25,27,28,29, 32,39,51,52], showed no clear benefit of HDF compared to high-flux HD (Figure 11). Despite the large number of patients (n=1,119), the results should be interpreted cautiously, given the high heterogeneity between the trials (I^2=87%). Schiffl et al. showed a 0.3-0.4 g/dL improvement in serum albumin for both modalities [25]. In comparison, Karkar et al. demonstrated higher pre-dialysis serum albumin levels with HDF compared to high-flux HD (3.6 ± 0.3 vs 3.3 ± 0.4 g/dL, p < 0.0001) [39]. In contrast, Maduell et al. found a reduction of 0.1-0.2 g/dL in serum albumin for both modalities [11], and Pecoits-Filho et al. reported a statistically significant reduction in serum albumin (0.1 g/dL) in the HDF group compared to the high-flux HD group [27].

Several factors can explain these conflicting data. Firstly, the potential HDF-related albumin loss can be masked by confounding variables, such as dialyser characteristics, which were not systematically reported. Indeed, albumin leakage in patients undergoing HDF varies with different convection volumes (20 vs 30 L), β2M clearance (20 vs 80 mL/min) or ultrafiltration coefficient (20 vs 40 mL/h/mmHg) of the dialysis membranes [107]. Secondly, serum albumin levels are not a

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reliable marker for albumin leakage in short-term follow-up studies, as albumin loss with high-flux membranes is negligible over a single dialysis session [108,109]. In addition, albumin redistribution between the intravascular and interstitial compartments and net fluid removal can alter the serum albumin level during dialysis. High-flux dialysers are generally associated with an initial increase in serum albumin [110]. Therefore, albumin losses in the dialysate may not always translate into post-dialysis serum albumin level reductions. Thirdly, parameters reflecting the inflammatory state should be considered when comparing serum albumin levels among studies. Since convection removes inflammatory cytokines more effectively than diffusion, the higher convection dose in HDF is expected to be associated with lower plasma levels of inflammatory markers like C-reactive protein (CRP), IL-6, and TNF-α compared to high-flux HD. This attenuation of the inflammatory status could reduce albumin catabolism. Data from the available RCTs are insufficient to determine whether HDF is associated with lower levels of inflammatory markers. Jiang et al. reported lower levels of inflammatory markers during HDF. Specifically, within 12-week follow-up, greater reductions in CRP and IL-6 levels were observed in the HDF group [38]. In contrast, other authors [12,13,24,29,45,51,56] found no difference between the two modalities. In our meta-analysis [11,14,38,50], neither treatment modality appears to have a differential effect on pre-dialysis CRP concentrations (Figure 12).

Normalised protein catabolic rate (nPCR) measurement [111] is also used to determine nutritional status, as it reflects daily dietary protein metabolism in dialysis patients [112]. Among the six RCTs that evaluated this parameter [11,13,26,27,42,51], four studies found no significant difference between the two modalities (Figure S6). However, a small prospective cross-over study found opposite changes in mean nPCR, with an increase in the high-flux HD group (1.22 ± 0.26 to 1.29 ± 0.23 g/kg/day) compared to a decrease in the HDF (from 1.30 ± 0.25 to 1.11 ± 0.29 g/kg/day) ($p = 0.012$) at 12 weeks [52]. In contrast, in the ESHOL study, patients treated by HDF had higher nPCR than those treated by high-flux HD [11].

Other parameters used to assess the nutritional status in RCTs include baseline subscapular skinfold, triceps skinfold, mid-arm circumference, and plasma cholesterol or triglyceride levels

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[26]. None of these factors were impacted by the dialysis membrane or convection volume. In Schiffl et al. study [25], mean dry body weight and upper arm muscle circumference were significantly higher in patients undergoing high-flux HD or HDF than patients undergoing low-flux HD after 12 months.

Another indirect method used to assess the nutritional status of HD patients is the plasma amino-acid profile, which tends to change quantitatively and qualitatively in dialysis. Amino acid loss can result from several factors, including inadequate nutritional intake [113], alteration in amino acid metabolism [114], reduction of kidney tissue [115], metabolic acidosis and hormonal imbalances [116].

Amino acids have relatively low molecular weights (ranging from 89 Da for alanine to 214 Da for tryptophan) and high sieving coefficients (between 0.8 and 1.0) [117]. Approximately 6–8 g of amino acids are lost in the dialysate, corresponding to a 20–40% reduction of plasma level [118], regardless of the type of membrane (low- or high-flux) [119].

Two RCTs by Murtas et al. assessed the impact of HDF on amino-acid profile compared to high-flux HD. In both [40], high exchange volume techniques, such as post-dilution HDF and particularly pre-dilution HDF, resulted in a significantly higher loss of amino acid into the dialysate than diffusive methods. As these studies have methodological biases, such as population selection, statistical analysis, and accuracy of measurement tools, we consider these findings inconclusive.

IV - Anaemia control

HDF may have benefits for anaemia management: patients treated by HDF require lower erythropoiesis-stimulating agents (ESAs) doses than those treated by conventional HD to maintain haemoglobin (Hb) levels within the recommended range [120,121,122,123]. Furthermore, a lower ESA resistance index was reported in patients treated by convective dialysis than those treated by conventional HD [124,125]. However, data in this context are conflicting, as other studies could not confirm these results [126,127,128], due to many factors, including the presence of residual kidney function.

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Our systematic search selected 12 RCTs focused on anaemia control [11,12,13,25, 27,30,31,32,33,39,44,51]. The results of these clinical trials are conflicting and vary substantially in terms of the treatment protocol, type of ESAs and their doses (Table S8). In the Turkish [12] study, a significantly lower dose of recombinant human erythropoietin (rHuEPO) was administrated in the HDF group (2,282 ± 2,121 IU/kg) than in the high-flux HD group (2,852 ± 2,706 IU/kg) (p=0.001). In the FRENCHIE study [13], ESA doses were reduced only in the HDF group (from 120.8 ± 134.3 to 110.7 ± 99.8 IU/kg/week; p=0.01).

In contrast, although a reduction of rHuEPO use was observed at 24 months by Schiffl et al., there were no significant differences between the groups (27% less in HDF and 24% less in high-flux HD) [25]. Furthermore, in the ESHOL study [11], doses of erythropoietin β, darbepoetin α and methoxy polyethylene glycol–epoetin β were not reduced over time and did not differ between the two modalities.

Paediatric section

Key consensus points

- **In children, HDF appears to be as safe and well tolerated as high-flux HD.**
- **In children, non-randomised studies suggest that HDF may attenuate CV damage progression and improve blood pressure, growth and QoL compared to high-flux HD.**

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Rationale

Children on dialysis have high mortality [129], a significant burden of comorbidities, and report poor HrQoL compared to their peers [130]. HDF was introduced in paediatric practice by Fischbach et al., who showed that growth retardation in children with CKD stage 5 could be reversed by daily HDF [131]. HDF can be performed in children above 10 – 15 kg in weight, depending on the dialysis machine specifications and circuit size available. As for adults, a high convection volume is crucial for effective HDF in children. In children, a target convection volume of 13-15 L/m²/session in post-dilution mode is derived from adult studies suggesting improved survival when convection volumes of 23 L/session are achieved in post-dilution HDF. It is possible to achieve and consistently maintain these high convection volumes in children, irrespective of access type [132].

While many studies in paediatric HDF have been small, single-centre and cross-sectional, much of our knowledge of paediatric HDF is based on the HDF, Hearts and Height (3H) study, a multi-centre, non-randomised parallel-arm intervention study that has prospectively studied nearly 40% of all children on extracorporeal dialysis across 10 countries in Europe and North America [133]. Both incident and prevalent patients between 5 - 20 years of age undergoing post-dilution HDF or HD (low- or high-flux) on a 4-hours per session 3-times per week schedule were included. Efforts to achieve the highest possible blood flow rate in both groups and a target convection volume of 12-15 L/m^2 of body surface area in the HDF cohort were aimed for. There was no difference in the change in residual kidney function between the HD and HDF treatment arms over the 1-year study period in the 3H study participants [58]. Key findings from all paediatric studies are described below and summarised [57,58,59,60,61] in Table S5. It must be noted that the paediatric data is derived from non-randomised studies and therefore interpreted with caution.

Children are uniquely suited to study the effects of dialysis treatment on the CV system due to the absence of secondary pathologies like pre-existing CVD, diabetes and smoking that are typically present in many adults on dialysis. Several studies have documented reduced inflammation,

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oxidative stress, and endothelial dysfunction in children treated by HDF [58,60,61,134,135,136], which are linked to improved CV health. Ağbaş et al. showed that within just 3 months of switching patients from high-flux HD to HDF, with all other dialysis-related parameters left unchanged, a decrease in inflammation and an increase in antioxidant capacity with an improved endothelial risk profile was achieved [57].

I - Cardiovascular mortality

Within one year of HD, the carotid intima-media thickness (cIMT) was higher by 0.41 standard deviation score (SDS), whereas there was no change in HDF patients [58]. Propensity score analysis showed that children treated by HD had a +0.47 greater increase in the annualised cIMT-SDS (95% CI 0.07-0.87; p = 0.02) than those treated by HDF. Clearance of middle molecular weight uraemic toxins, and improved fluid removal by HDF were correlated with improved cIMT [58]. The left ventricular mass index was higher in HD patients compared to HDF patients at 12 months, correlating with improved fluid control, lower PTH and higher Hb levels in HDF [58]. Similarly, Fadel et al. have shown that within six months of moving children from HD to HDF, systolic function improved, and diastolic dysfunction decreased, but left ventricular mass was unchanged [131].

II - Blood pressure control

The mean arterial pressure (MAP)-SDS measured by 24-hour ambulatory blood pressure recordings was higher in children treated by HD than in those treated by HDF [58]. Over a 1-year follow-up, the MAP increased by 0.98 SDS in the HD arm, whereas there was a non-significant increase of 0.15 SDS in children treated by HDF [59]. Also, uncontrolled hypertension was far more common in children treated by HD [61]. A further study showed that when children were moved from nocturnal in-centre HD to nocturnal in-centre HDF, BP, phosphate, and parathyroid hormone (PTH) control improved [137].

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III - Bone health and growth

Biomarkers of bone turnover, including bone formation marker bone-specific alkaline phosphatase (BAP) and bone resorption marker tartrate-resistant acid phosphatase 5b (TRAP5b), were studied. The ratio of the enzymatic activity of BAP/TRAP5b, implying net bone formation, was higher in HDF patients but remained unchanged in HD patients over 12 months [131]. HDF achieved excellent convective clearance of Fibroblast Growth Factor 23 (FGF23), a middle molecular weight toxin, showing a 25% reduction in patients treated by HDF. In contrast, levels increased by over 100% in children treated by HD [131]. FGF23 is known to have several "off-target" effects, and a reduction in levels may partially explain the lower left ventricular mass in the 3H study [58]. Some studies have also shown reduced serum phosphate and PTH levels with HDF vs HD [132].

In the 3H study, patients treated by HDF experienced a small but statistically significant increase in the annualised height SDS, whereas it remained static in patients treated by HD [58]. This effect was independent of growth hormone treatment. The increase in height-SDS correlated with serum β2M concentrations, suggesting that clearance of middle molecular weight compounds such as endogenous gonadotropin and somatomedin inhibitors, as well as inflammatory cytokines, may partly alleviate resistance to growth hormone (GH) in patients treated by HDF [58], with HDF suggested to be the perfect 'stimulus package' for growth [138]. These potential anabolic effects of HDF were confirmed by Ibrahim et al., who showed that children treated by HDF had significantly higher height-SDS and higher per cent changes in height-SDS and weight-SDS compared to the HD group [132].

IV - QoL

HDF promoted 'life participation' by improving post-dialysis recovery time, increasing physical activity and improving school attendance [58,61]. Children receiving HDF also had fewer incidences of headaches, dizziness and cramps compared to those treated by HD [58]. Lower ultrafiltration rates and better haemodynamic stability on HDF most likely led to improved vascular

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refilling during the dialysis session, reducing hypotensive episodes [58]. A significant reduction in post-dialysis fatigue and improvement in physical activity was shown in the short and long term for HDF patients [132,58].

Implications for clinicians, patients and policymakers

Key consensus points

- **HDF is as safe as high-flux HD for adults and children with proper protocols and monitoring.**
- **The environmental impact of HDF may be greater than that of high-flux HD. However, it could be comparable if managed through optimized machine controls, such as automated efficiency settings that minimize resource use while maintaining care standards.**
- **Limited availability of HDF compared to high-flux HD may compromise equal access to a personalised treatment approach. A cost-utility analysis is necessary to guide the decision-making process between these two modalities.**

Rationale

I - Safety

Safety and regulatory aspects must be followed when performing high-flux HD and HDF. This includes: (i) the use of approved and certified machines that allow for accurate ultrafiltration control and have dialysis fluid ultrafilters for the 'online' production of large volumes of 'ultrapure' substitution fluid; (ii) a water treatment system based upon standards published by the International Organization for Standardization (ISO) and local regulations to ensure water quality; and (iii) high-flux dialysers [7,139]. A detailed discussion of the technical requirements is beyond the scope of this document.

All RCTs have consistently shown that high-flux HD and HDF are safe treatments in children and adults, assuming that the technical requirements for sterile 'ultrapure' water are met. All reported

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studies on serum albumin levels show no difference between the HDF and high-flux HD groups [11,14,25,58].

II - Sustainability and environmental impact

The environmental impact of dialysis treatment is a significant concern and must be carefully considered by healthcare workers, professional organisations and the dialysis industry. Dialysis uses large volumes of water and electricity and generates considerable plastic waste. With a mean of 500 L of water/per patient/treatment three times a week, each dialysis patient uses nearly 80,000 L of water per year [140]. It is widely acknowledged that the environmental impact of HDF may be considerably higher than that of high-flux HD. However, a recent study that reports real-world data from more than 26,000 patients, as well as simulation modelling, has shown that by reducing the dialysate to blood flow ratios to 1.2 (rather than 1.4 or 1.5) and incorporating automated ultrafiltration and substitution control HDF delivers a higher dialysis dose for small- and middle-molecule uremic compounds with the same dialysis fluid consumption as standard HD [141,142]. The authors showed that post-dilution HDF at a reduced dialysis flow rate of 430 mL/min (reflecting a Qd/Qb ratio 1.2) achieved an adequate online clearance Kt/V of 1.70. Importantly, these results were achieved using dialysis machines that can automatically adjust the dialysate flow to match blood flow and substitution flow rates in response to changes in transmembrane pressure and dialyser viscosity [143]; these technical features are unavailable on most dialysis machines. Further real-world studies are essential to accurately assess the environmental impact of implementing these technical adaptations in post-dilution HDF. While specific adaptions (e.g., delivering saturated ultrafiltrate at lower dialysis flow) might reduce water usage, robust data are needed to validate these adjustments in clinical practice.

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III - Global availability

The utilisation of HDF and high-flux HD differ significantly worldwide, related, at least in part, to regulatory and technical issues, healthcare policy, reimbursement rates, clinical evidence, and perceived patient benefits. Also, in low- and middle-income countries, there is a substantial gap in the availability and access to appropriate technology, including ultra-pure water, machines with HDF capability, a trained nephrology workforce, and essential medications [144], as highlighted by Global Kidney Health Atlas project of the International Society of Nephrology. National and international registry data suggests that HDF therapy is increasing in Europe and Asia Pacific, where HDF is approved; the average growth rate is 12 to 24%, well above the total patient HD growth rate of 6.6% [145]. Clinicians must weigh the potential benefits of HDF when considering a personalised medicine approach. A cost–utility analysis to express efficiency in terms of costs per Quality Adjusted Life Year (QALY) has been undertaken in the CONVINCE trial [14], and results are awaited. A cost-utility analysis takes a societal perspective, implying that healthcare, patient, family, and productivity costs are all considered.

Conclusions

HDF therapy provides promise for the growing dialysis populations worldwide, who have amongst the highest mortality and the lowest quality of life reported in patients with chronic diseases [146]. However, further RCTs are required to overcome the significant bias in existing studies and better clarify the impact of high-volume HDF on survival, clinical and biochemical outcomes, HrQoL and cost-effectiveness. Most importantly, it must be reminded that the RCTs do not represent the 'real-world' situation seen in dialysis clinics; the RCTs generally include younger population [147,148], with a lower prevalence of diabetes [147,149], and CVD [147,149,150], and a higher prevalence of AVF use [147], which are therefore more likely to achieve higher blood flows and the desired convection volume that are associated with superior outcomes [146].

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This Consensus Statement on HDF and high-flux HD consists of twenty-two key consensus points, which concisely summarise the available evidence crafted with clinical practice experience and expert opinion. The suggestions of this Consensus Statement aim to inform and assist in decision-making to reduce uncertainty and improve patient outcomes. They are not intended to define a standard of care or serve as an exclusive management path but are intended to provide nephrologists with a critical overview of the literature and help them select the most appropriate dialysis modality for each patient.

Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

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Table 1. Indexes evaluating the robustness of three statistically significant outcomes of the ESHOL [11] and CONVINCE [14] trials.

Outcomes	Authors, years [ref]	Sample (events/population)	Duration (months)	FI	FQ	SIFI	NNT
All-cause mortality	Maduell et al., 2013 [11]	HD 122/450 HDF 85/456	36	13	0.014	81	12
	Blankestijn et al., 2023 [14]	HD 148/677 HDF 118/683	30	3	0.002	18	22
All-cause Hospitalisations	Maduell et al., 2013 [11]	HD 412/450 HDF 317/456	36	73	0.081	NA	5
Mortality due to infections	Maduell et al., 2013 [14]	HD 22/450 HDF 10/456	36	1	0.001	NA	38

FI: Fragility Index; FQ: Fragility Quotient; HD: Haemodialysis; HDF: Haemodiafiltration; NA: Not applicable; NNT: Number Needed to Treat; SIFI: Survival-Inferred Fragility Index.

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Table 2. Main characteristics of five RCTs comparing the impact of HDF and high-flux HD on all-cause mortality.

Authors, year, country, study design, duration (PMID) [Ref.]	Key enrolment criteria	Sample characteristics		Dialysis characteristics	
		high flux HD	HDF	high flux HD	HDF
Blankestijn et al., (CONVINCE) 2023, Europe RCT 30 months (37326323) [14]	Inclusion: - age ≥18 years - HD >3 months - convection volume: 23 L in post-filter Exclusion: - life expectancy <3 months - previous HDF treatment <90 days before screening - anticipated kidney transplantation from a living donor within 6 months after screening	n. 677 Age: 62.3±13.5 years Males: 62% Diabetes: 37.1% Active smokers: 16.2% Previous CVD: 46.7%	n. 683 Age: 62.5±13.5 years Males: 63.8% Diabetes: 33.7% Active smokers: 14.3% Previous CVD: 43.3%	Dialysis vintage: 30 (14-67) months Duration: 240 (240-245) min Vascular access: CVC 13.9%, AVF 82.3% Graft 3.8% Filter: NA	Dialysis vintage: 35 (16-78) months Duration: 240 (240-248) min Vascular access: CVC 13.2%, AVF 81.7% Graft 5.1% Filter: NA Infusate volume: 23±1 L/session Convection strategy: 23 L/session
Ok et al., (TURKISH) 2012, Turkey 39 months RCT (23229932) [12]	Inclusion: - age >18 years - bicarbonate HD 3 t/w for a total of 12 hours/week - mean single-pool Kt/V >1.2 Exclusion: - scheduled for living donor renal transplantation - serious life-limiting comorbid situations - active malignancy or infection - end-stage cardiac, pulmonary,	n. 391 Age: 56.5±14.9 years Males: 58.1% Diabetes: 33% Active smokers: 26% Previous CVD: 25.7%	Low efficiency HDF (RF ≤17.4 L): n. 196 Age: 56.9±11.6 years Males: 56% Diabetes: 43% Active smokers: 23.8% Previous CVD: 25%	Dialysis vintage: 58.7±43.2 months Duration: NA Vascular access: AVF 95.4% Filter: FX60 or FX80	Low efficiency HDF (RF ≤17.4 L): Dialysis vintage: 60.9±45.8 months Duration: NA Vascular access: AVF 95.4 % Filter: FX60 or FX80 Infusate volume:

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	or hepatic disease - temporary catheter as a vascular access - Qb 250 <mL/min - urine output >250 mL/day - pregnancy or nursing mothers - mental incompetence		High efficiency HDF (RF>17.4 L): n. 195 Age: 58.8±13.8 years Males: 62% Diabetes: 33% Active smokers: 23.8% Previous CVD: 29%		16.2±1.0 L/session Convection strategy: ≤17.4 L/session High efficiency HDF (RF>17.4 L/session): Dialysis vintage: 60.9±45.8 months Duration: NA Vascular access: AVF 97.5 % Filter: FX60 or FX80 Infusate volume: 18.1±0.68 L/session Convection strategy: >17.4 L/session
Morena et al., (FRENCHIE) 2017, France 24 months RCT (28318624) [13]	Inclusion: - age ≥65 years - diuresis <100 mL/24 h and/or residual kidney function <2 mL/min/1.73 m^2 - HD for ≥3 months - HD 3 t/w - haemoglobin 9 - 13 g/dL Exclusion: - severe malnutrition (serum albumin <20 g/L) - unstable clinical condition - unipuncture or failed vascular access flow - problems of coagulation	n. 152 Age: 76.41±6.79 years Males: 61.18% Diabetes: 38.42% Active smokers: NA Previous CVD: 51.05%	n. 151 Age: 76.61±5.86 years Males: 59.6% Diabetes: 39.36% Active smokers: NA Previous CVD: 52.66%	Dialysis vintage: 4.76±5.41 months Duration: 234.6±20.4 min Vascular access: AVF 68.06 % Filter: NA	Dialysis vintage: 4.93±6.2 months Duration: 238.8±36 min Vascular access: AVF 86.75 % Filter: NA Infusate volume: 22.53±6.76 L/session Convection strategy baseline: NA

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Kang et al., (FINESSE) 2021, Australia 48 months RCT (34233923) [31]	Inclusion: - adult patients on maintenance HD Exclusion: - life expectancy <6 months - definite plans to undergo kidney transplantation - transfer to home dialysis within 12 months - already receiving HDF	n. 61 Age: 65±16 years Males: 54% Diabetes: 30% Active smokers: NA Previous CVD: NA	n. 63 Age: 66±13 years Males: 57% Diabetes: 41% Active smokers: NA Previous CVD: NA	Dialysis vintage: 37.2 (14.4-72) months Duration achieved: NA Vascular access: AVF 74% Graft 12% CVC 15% Filter: NA	Dialysis vintage: 38.4 (22.8-62.4) months Duration achieved: NA Vascular access: AVF 81% Graft 8% CVC 11% Filter: NA Infusate volume: 24.7 (22.4-26.5) L/session Convention Strategy: >17.4 L/session
Maduell F et al., (ESHOL) 2013, Spain 36 months RCT (23411788) [11]	Inclusion: - age >18 years - 3 t/w standard HD for >3 months Exclusion: - active systemic diseases - liver cirrhosis, malignancy - immunosuppressive therapy - dialysis dose (Kt/V<1.3) - single needle dialysis - temporary non-tunnelized catheter	n. 450 Age: 66.3±14.3 years Males: 64.2% Diabetes: 27.1% Active smokers: NA Previous CVD: NA	n. 456 Age: 64.5±14.4 years Males: 69.5% Diabetes:22.8% Active smokers: NA Previous CVD: NA	Dialysis vintage: 27 (12-58) months Duration: 234.1 min (232.2-236.1) Vascular access: AVF: 82.7% Graft: 4.2% CVC: 13.1% Filter: high flux dialyzers (92%) and low flux dialyzers (8%)	Dialysis vintage:28.5 (12-60) months Duration: 235.8 min (234.2-237.3) Vascular access: AVF: 89.3% Graft: 3.3% CVC: 7.5% Filter: high flux dialyzers Infusate volume: 23.7 (23.3 - 24.1) L/session Convection strategy baseline: >18 L/session

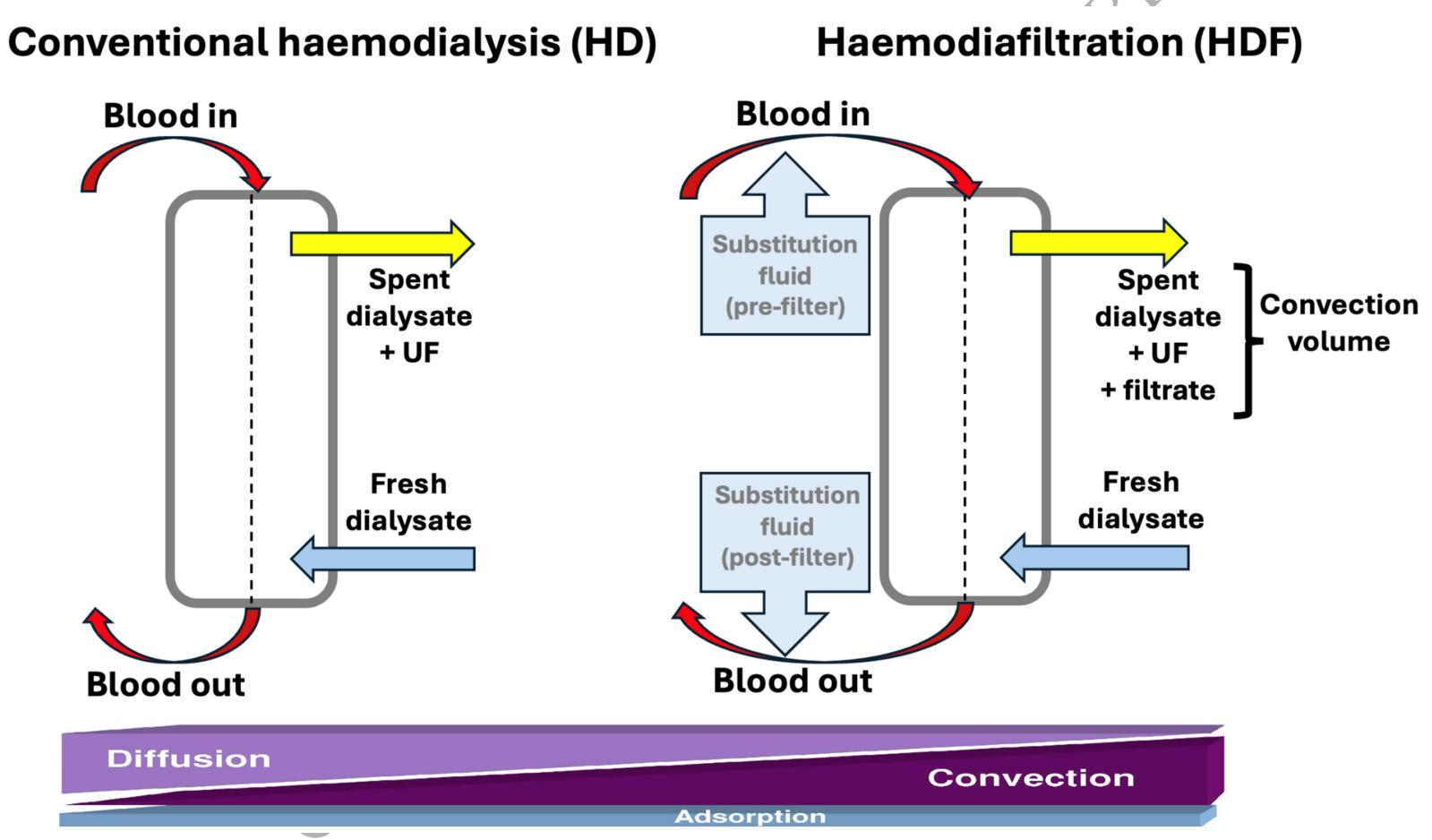
AVF: Arteriovenous Fistula; CVC: Central Venous Catheter; CVD: Cardiovascular Disease; HD: Haemodialysis; HDF: Haemodiafiltration;

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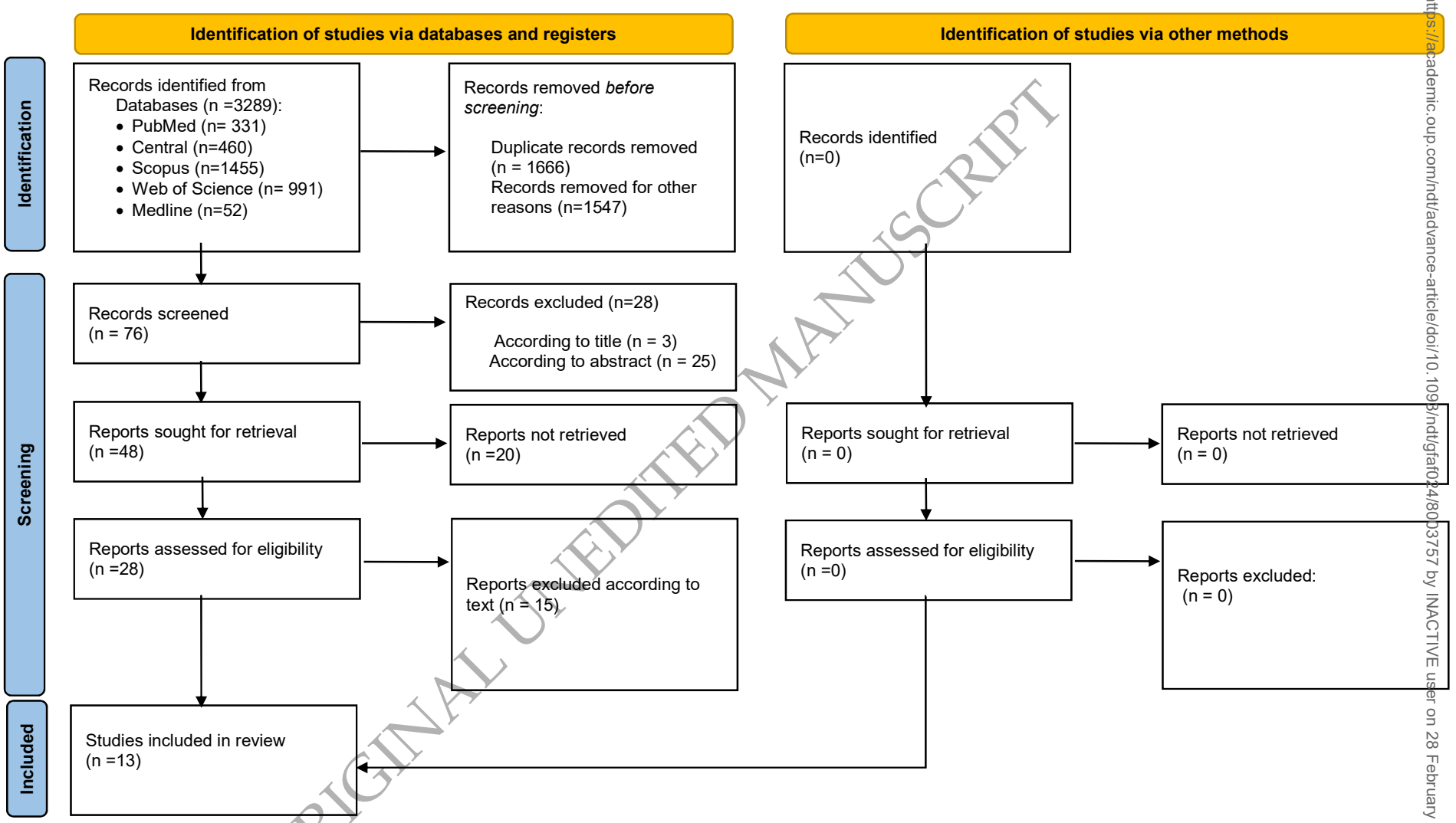
NA: Not available; Qb: Blood Flow Rate; RCT: Randomized Controlled Trial; RF: Replacement Fluid; t/w: Times per week.

Figure 1. Schematic representation of technical differences between haemodialysis and haemodiafiltration.



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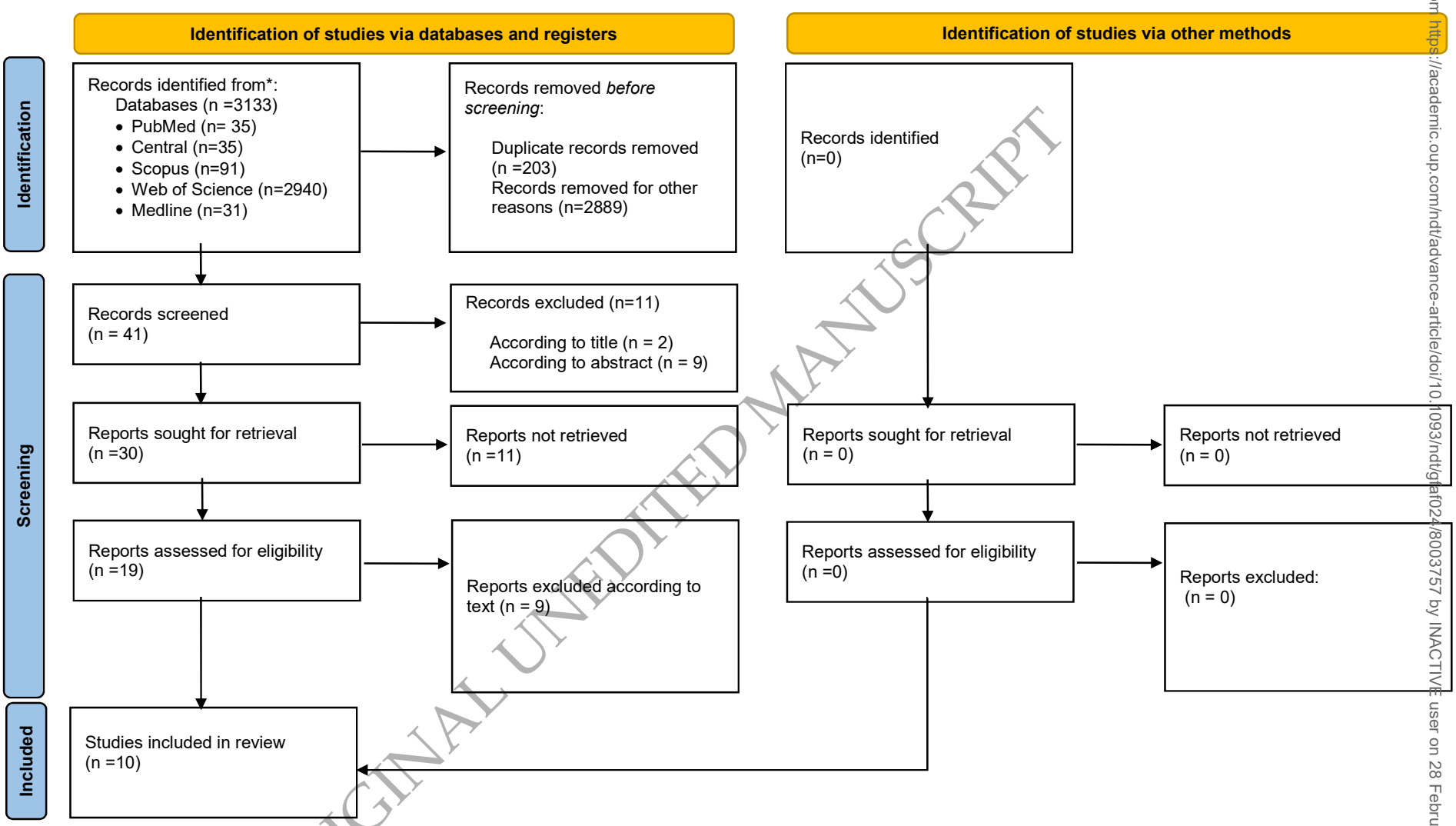
Figure 2. It summarises the results of the literature search and study selection (PRISMA Diagram) for the following outcomes: all-cause mortality, cardiovascular mortality, sudden cardiac death, intradialytic hypotension, hospitalisations, and infection rates.



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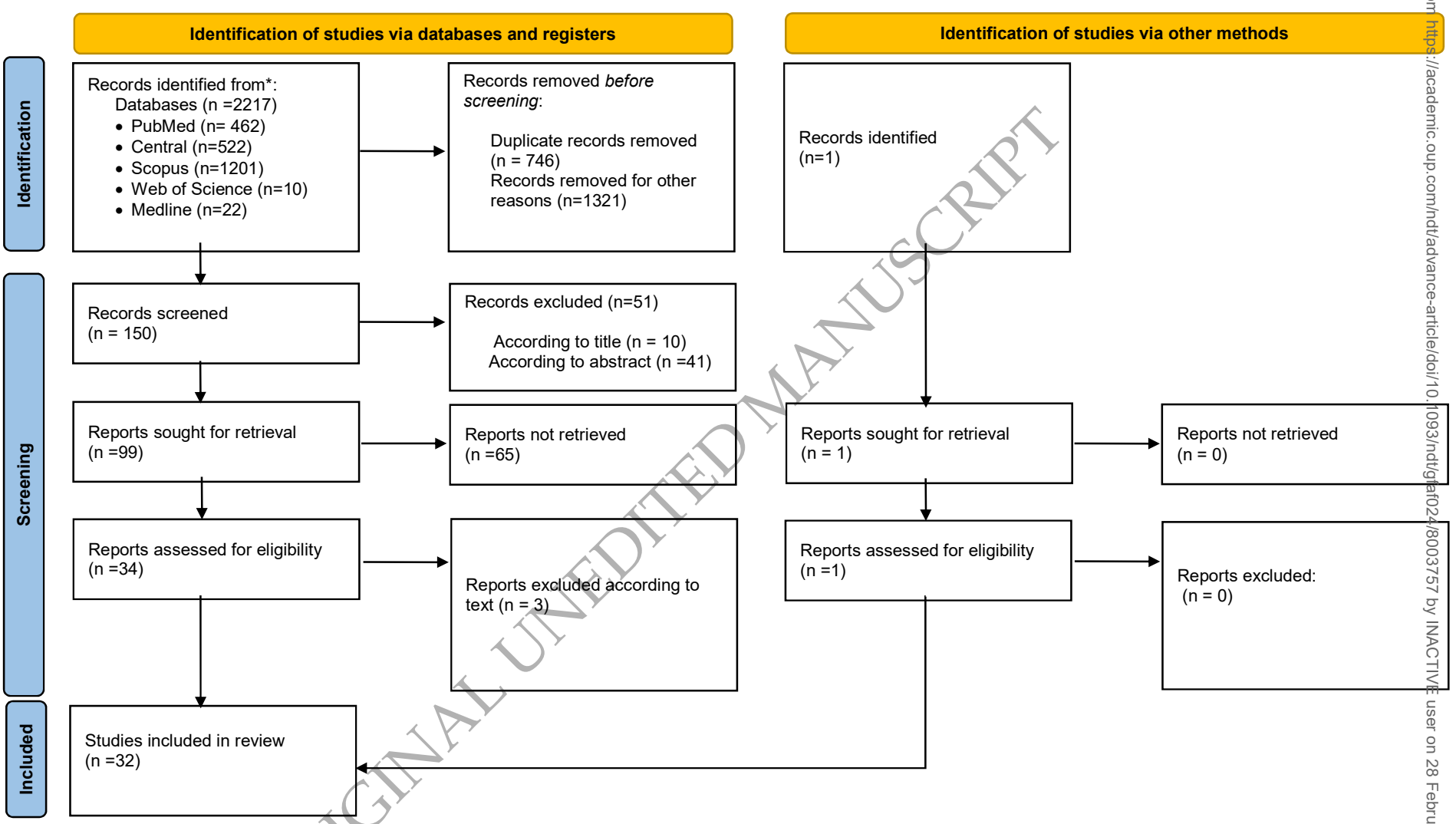
Figure 3. It summarises the results of the literature search and study selection (PRISMA Diagram) for health-related quality of life outcomes.



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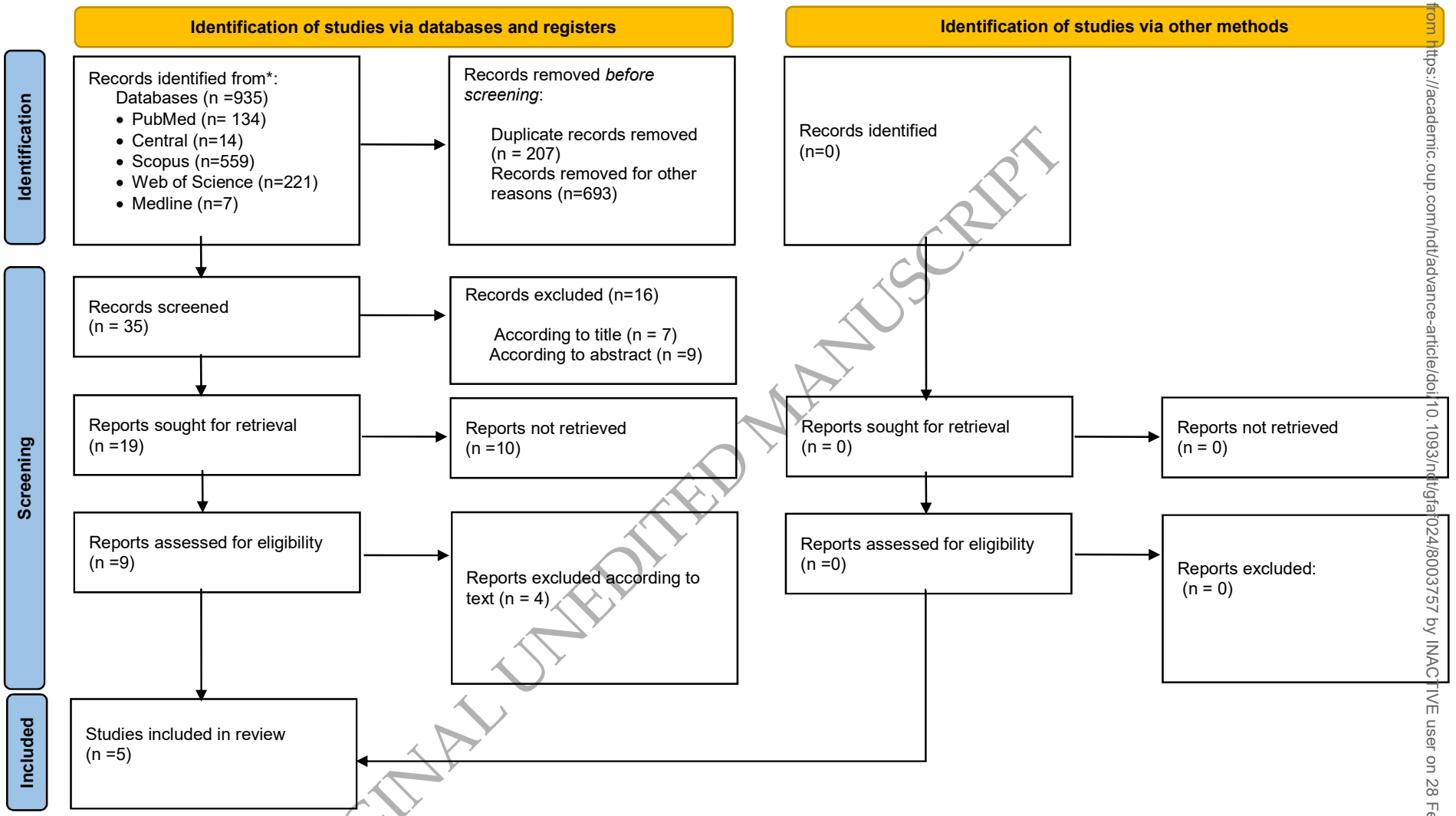
Figure 4. It summarizes the results of the literature search and study selection (PRISMA Diagram) for the following outcomes: biochemical data and clearance of uraemic toxins.



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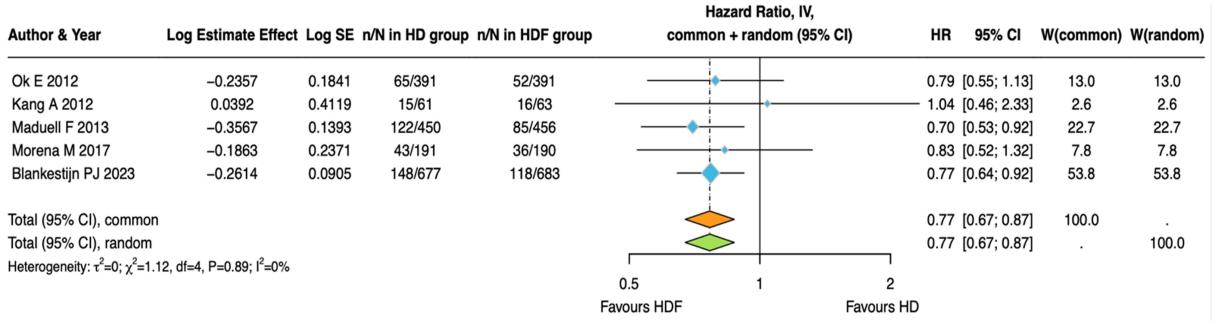
Figure 5. It summarizes the results of the literature search and study selection (PRISMA Diagram) for paediatric studies.



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Figure 6. Forest plot and pooled estimates of the effects of HDF vs high-flux HD on all-cause mortality.

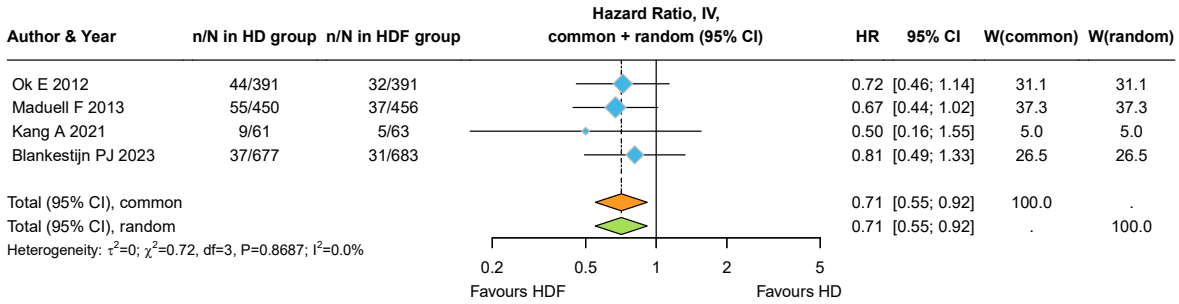


CI: confidence interval; HD: haemodialysis; HDF: haemodiafiltration; HR: Hazard Ratio; n/N: numbers of patients/population; SE: standard error; WMD: weighted mean differences; W: weight.

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Figure 7. Forest plot and pooled estimates of the effects of HDF vs high-flux HD on cardiovascular mortality.

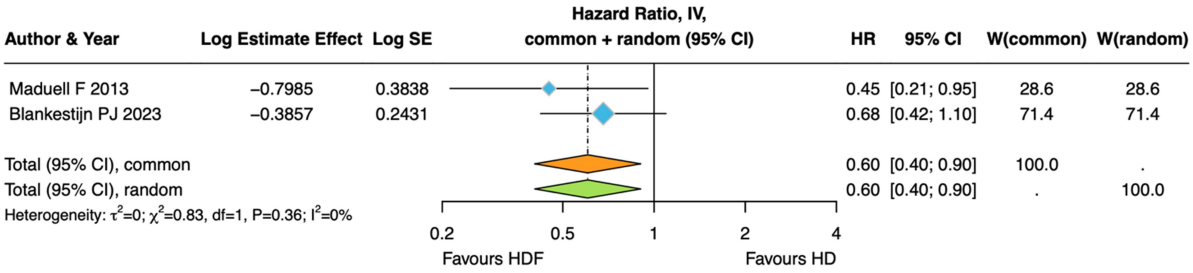


CI: confidence interval; HD: haemodialysis; HDF: haemodiafiltration; HR: Hazard Ratio; n/N: numbers of patients/population; SE: standard error; WMD: weighted mean differences; W: weight.

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Figure 8. Forest plot and pooled estimates of the effects of HDF vs high-flux HD on infection-related mortality.

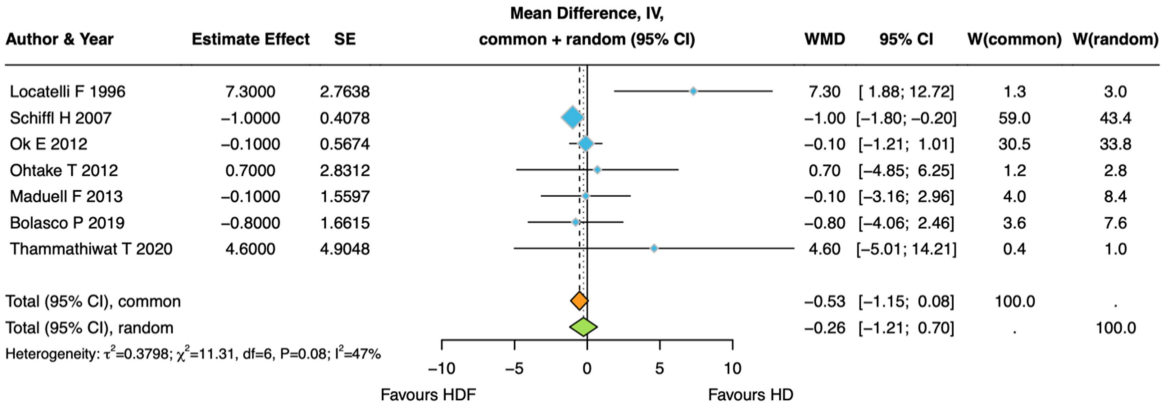


CI: confidence interval; HD: haemodialysis; HDF: haemodiafiltration; HR: Hazard Ratio; SE: standard error; W: weight.

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Figure 9. Forest plot and pooled estimates of the effects of HDF vs high-flux HD on pre-dialysis serum β_2-microglobulin (β2M) levels.

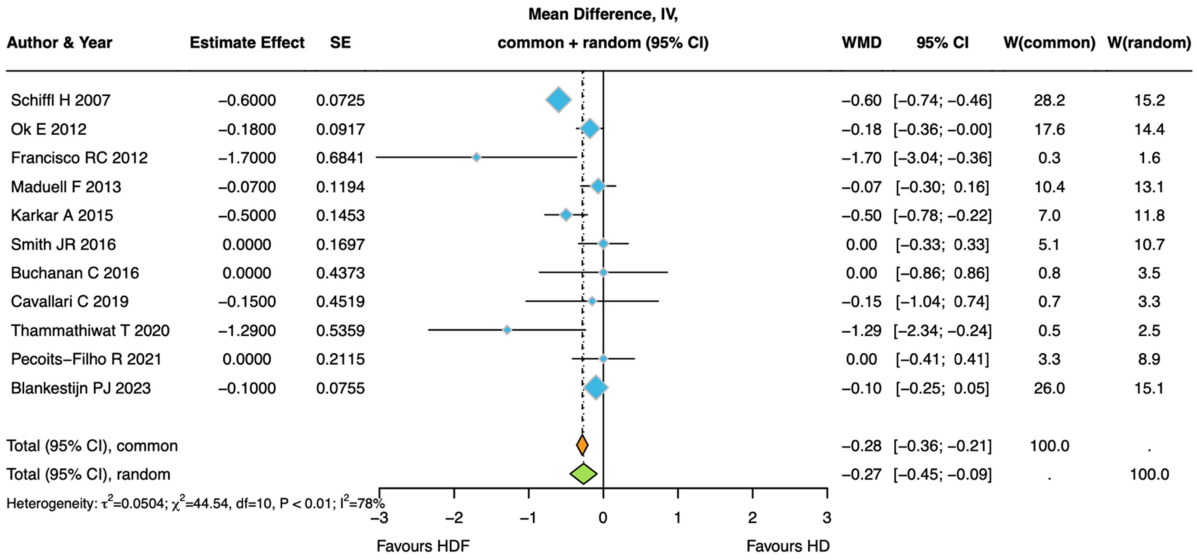


CI: confidence interval; HD: haemodialysis; HDF: haemodiafiltration; HR: Hazard Ratio; SE: standard error; WMD: weighted mean differences; W: weight.

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Figure 10. Forest plot and pooled estimates of the effects of HDF vs high-flux HD on pre-dialysis serum phosphate levels.

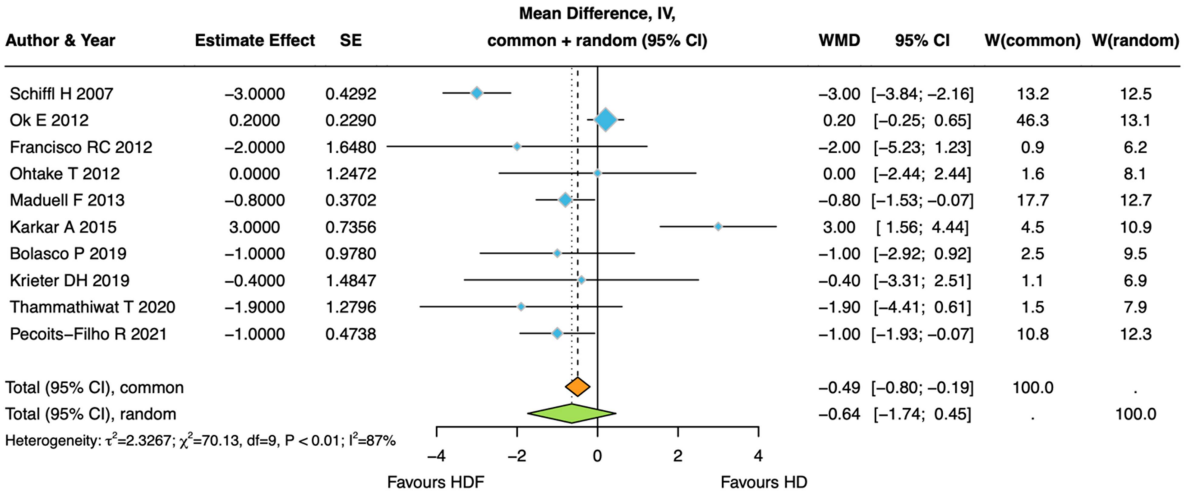


CI: confidence interval; HD: haemodialysis; HDF: haemodiafiltration; WMD: weighted mean differences; SE: standard error; W: weight.

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Figure 11. Forest plot and pooled estimates of the effects of HDF vs high-flux HD on pre-dialysis serum albumin levels.

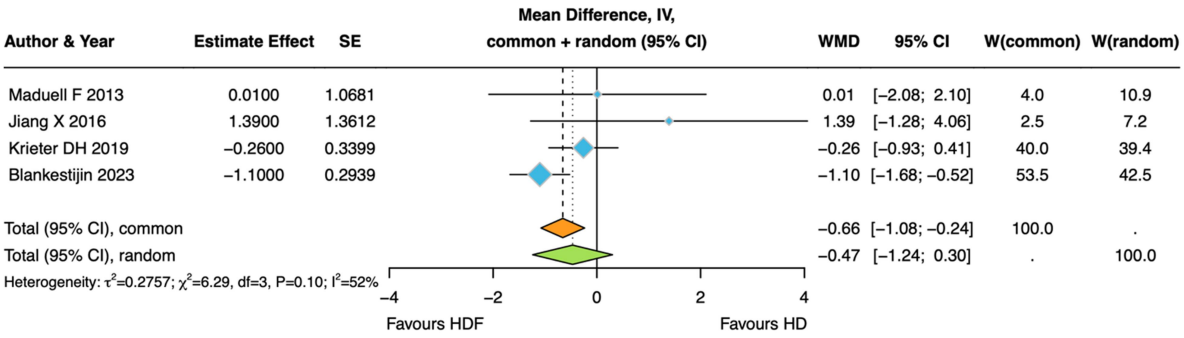


CI: confidence interval; HD: haemodialysis; HDF: haemodiafiltration; WMD: weighted mean differences; SE: standard error; W: weight.

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Figure 12. Forest plot and pooled estimates of the effects of HDF vs high-flux HD on pre-dialysis serum C-reactive protein (CRP) levels.



CI: confidence interval; HD: haemodialysis; HDF: haemodiafiltration; WMD: weighted mean differences; SE: standard error; W: weight.

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