Fibroblast Growth Factor-23 and Risks of Cardiovascular and Noncardiovascular Diseases: A Meta-Analysis

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ABSTRACT

Background Fibroblast growth factor-23 (FGF-23) has been hypothesized to play a role in the increased risk of cardiovascular disease in patients with CKD.

Methods We identified prospective studies reporting associations between FGF-23 concentration and risk of cardiovascular events. Maximally adjusted risk ratios (RRs) were extracted for each outcome and scaled to a comparison of the top versus bottom third of the baseline FGF-23 concentration, and the results aggregated.

Results Depending on the assay used, median FGF-23 concentrations were 43–74 RU/ml and 38–47 pg/ml in 17 general population cohorts; 102–392 RU/ml in nine cohorts of patients with CKD not requiring dialysis; and 79–4212 RU/ml and 2526–5555 pg/ml in eight cohorts of patients on dialysis. Overall, comparing participants in the top and bottom FGF-23 concentration thirds, the summary RRs (95% confidence intervals [95% CIs]) were 1.33 (1.12 to 1.58) for myocardial infarction, 1.26 (1.13 to 1.41) for stroke, 1.48 (1.29 to 1.69) for heart failure, 1.42 (1.27 to 1.60) for cardiovascular mortality, and 1.70 (1.52 to 1.91) for all-cause mortality. The summary RR for noncardiovascular mortality, calculated indirectly, was 1.52 (95% CI, 1.28 to 1.79). When studies were ordered by average differences in FGF-23 concentration between the top and bottom thirds, there was no trend in RRs across the studies.

Conclusions The similarly-sized associations between increased FGF-23 concentration and cardiovascular (atherosclerotic and nonatherosclerotic) and noncardiovascular outcomes, together with the absence of any exposure–response relationship, suggest that the relationship between FGF-23 and cardiovascular disease risk may be noncausal.

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Cardiovascular disease risk increases as kidney function declines and this elevated risk is apparent even in early CKD.[1–3] Cardiovascular disease in people with CKD is characterized particularly by arterial stiffening and left ventricular hypertrophy, which becomes increasingly marked as CKD progresses.[4–6] People with CKD are also at increased risk of atherosclerotic heart disease. It has been suggested that some of the excess cardiovascular risk in CKD may be mediated through disordered calcium-phosphate metabolism due to reduced kidney function.[7–9]

Blood fibroblast growth factor-23 (FGF-23) concentration rises early in CKD, and increases

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exponentially in relation to eGFR, functioning to maintain phosphate homeostasis as the capacity for urinary phosphate excretion declines.[10] FGF-23 possesses an atypical heparin-binding domain, which results in a low binding affinity to most FGF receptors.[11] Its physiologic actions may therefore be limited to the parathyroid glands and kidney, where the coreceptor Klotho is abundantly expressed. In the kidney, FGF-23 downregulates renal proximal tubular sodium-phosphate cotransport function, enhancing urinary phosphate excretion, and reduces vitamin D 1-α hydroxylation, leading to less intestinal calcium and phosphate absorption.[12] However, FGF-23 could have Klotho-independent actions in other tissues, including the heart,[13] and may contribute to the etiology of structural heart disease in patients with CKD.[14,15] If so, interventions targeting FGF-23 might hold therapeutic potential.

We conducted a systematic review and meta-analysis of the evidence from prospective studies for associations between FGF-23 and the risk of different cardiovascular diseases. We compared the evidence for associations among cohorts of people unselected for CKD (general population cohorts) with those in patients with CKD who were not receiving dialysis at the time of recruitment (nondialyzed CKD cohorts) and in patients on dialysis. We assessed for evidence of an exposure–response relationship both within and across each of these three separate populations.

Significance Statement

Fibroblast growth factor-23 (FGF-23) is positively associated with cardiovascular disease risk in patients with CKD, and suggested as a therapeutic target. This meta-analysis compared the associations in general, nondialyzed CKD and dialysis populations. The risk of myocardial infarction, stroke, and heart failure was consistently higher among participants in the top versus bottom third of the FGF-23 distributions. However, the size of association did not increase across these populations, despite absolute differences in FGF-23 concentration between the top and bottom thirds increasing by two orders of magnitude. Furthermore, associations were similar for cardiovascular and noncardiovascular mortality. Associations that are both nonspecific and do not exhibit an exposure–response relationship are inconsistent with cause and effect. These results do not support the hypothesis that targeting FGF-23 will reduce cardiovascular disease risk.

METHODS

Search Strategy/Selection Strategy

A systematic and comprehensive search for English language publications with mention of FGF-23 or equivalent terms was performed in MEDLINE (1948–April 2017) and EMBASE (1974–April 2017, see Supplemental Table 1 for terms). Abstracts were reviewed and cohort studies in adults were selected for inclusion in the meta-analysis if (*1*) FGF-23 was a key exposure of interest, (*2*) at least one clinical cardiovascular disease outcome was assessed, and (*3*) outcomes were ascertained prospectively. Cardiovascular outcomes of interest included myocardial infarction, stroke, heart failure, and peripheral arterial disease as well as mortality attributed to cardiovascular disease. Full texts of publications that appeared to meet inclusion criteria were reviewed. Duplicate studies and those that included <200 participants were excluded. The quality of remaining studies was assessed using the Newcastle–Ottawa scale,[16] and studies excluded if their results were at moderate-to-high risk of bias (score of <6/9). A study of terminal heart failure was excluded *post hoc* as the population was at exceedingly high risk.

Data Extraction

Three authors (A.M., K.D., and C.M.R.) extracted the following data from full-text articles: study and study population characteristics, FGF-23 assay type (C-terminal, reported in relative units per milliliter [RU/mL], or intact, reported in picograms per milliliter [pg/mL]), measures of FGF-23 distribution, details of statistical models, covariates used for multivariate adjustments, follow-up duration, and hazard ratios/risk ratios (RRs) for relevant cardiovascular outcomes for all reported models and, where reported, all-cause and cardiovascular mortality. Where necessary, further data were requested from study investigators.

Statistical Analyses

To assess the FGF-23 associations across the wide range of FGF-23 concentrations encountered in different populations, meta-analysis was prespecified to be performed overall and within three study population types: (*1*) general population (unselected individuals), (*2*) patients with nondialyzed CKD (defined as an eGFR<60 ml/min per 1.73 m^2), and (*3*) patients on dialysis.

For each study, we aimed to extract from the primary publication, for each outcome, the hazard ratio or RR yielded by the model that included the greatest number of covariates. These covariates included incrementally: basic demographics (+); cardiovascular risk factors including diabetes, body mass index, and smoking (++); kidney function (+++); and markers of CKD–mineral bone disorder (++++). Because of the usually skewed nature of FGF-23 distributions, studies reported associations for top versus bottom quintile, quartile, or third of the FGF-23 distribution, or less frequently, per SD or a unit increase in log-transformed FGF-23. To enable comparisons and synthesis of data across the studies, these associations were converted (where necessary) to a measure of association corresponding to the top versus bottom third of the baseline FGF-23 concentration using established methods (see Supplemental Methods, Supplemental Table 2 for more detail).[17,18] Where noncardiovascular mortality was not reported, RRs were derived indirectly from cardiovascular and all-cause mortality results assuming that on the natural logarithm scale, the RR for all-cause mortality is an inverse-variance weighted average of the RRs for cardiovascular and noncardiovascular mortality.

The heterogeneity between studies (both within each population and overall) was summarized. Random-effects meta-analytical methods[19] were used to combine the RRs for the top

versus bottom third of baseline FGF-23 concentration in each study, yielding a summary RR for all studies.

As the median baseline FGF-23 concentration correlated strongly with interquartile range, standard tests for linear trend (on a log scale) across studies ordered by median (or, if not reported, mean) baseline FGF-23 concentration (within each population and across all the individual studies) were used to assess whether larger absolute differences in FGF-23 concentration between top and bottom third were associated with larger RRs. Trend tests were also performed across population-specific summary RRs after meta-analysis of RRs from the contributing studies. In sensitivity analyses, to allow for a potentially different relationship in dialysis patients, the trend tests across individual studies were repeated after excluding dialysis population studies.

Primary analyses of disease associations did not take account of whether studies used C-terminal or intact assays, which is equivalent to the assumption that the results between the two assays are approximately comparable. However, this assumption may not necessarily hold as, for example, intraperson biologic variability of intact FGF-23 may be higher than C-terminal FGF-23.[20] To investigate the sensitivity of results to this assumption, analyses were performed repeating trend tests, firstly after converting intact FGF-23 concentration to an approximately equivalent C-terminal concentration using the formula intact FGF-23 = 0.110 × C-terminal FGF-23 + 32.2, developed from a small healthy general population,[21] and secondly, after excluding all studies that only reported intact FGF-23. To further assess whether associations in individual studies could have been affected by within-person FGF-23 variability, regression dilution ratios were calculated from individual studies that had repeat FGF-23 measurements,[22–24] using the McMahon nonparametric quintile method.[25] RRs for cardiovascular and noncardiovascular outcomes were compared by heterogeneity tests.[26] Analyses were performed using R version 3.2.1 (www.R-project.org) with the "metafor" package v1.

RESULTS

Our literature search (Supplemental Table 1) identified 2477 abstracts, of which 45 met the inclusion criteria (Figure 1). Three studies were excluded after a standard assessment for bias (Supplemental Table 3).[27–29] Eight studies reported associations that could not be extracted or reliably expressed as RRs comparing the top versus bottom third of baseline FGF-23 concentration (see Supplemental Table 4 for results from these and the other excluded studies).[30–37] Of 34 studies included in primary analyses, 17 were in predominantly general population cohorts,[22,38–53] nine were in patients with CKD not on dialysis,[23,54–61] and eight in patients on dialysis[24,62–68] (Figure 1). For patients on dialysis, a single large trial (EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events [EVOLVE], $n = 2985$) provided all the data on myocardial infarction, stroke, and heart failure (outcomes that were all confirmed by clinician adjudicators).[24]

Table 1 describes the characteristics of included studies. Most of the studies (26 out of 34) measured FGF-23 concentrations using a C-terminal assay, with the remainder (eight out of 34) using an intact assay. Measures (median or, if unavailable, mean) of FGF-23 concentration were lowest in general population cohorts (43–74 RU/ml and 38–47 pg/ml for the respective assays); higher in nondialyzed CKD cohorts (102–392 RU/ml), and substantially higher in dialysis cohorts (79–4212 RU/ml and 2526–5555 pg/ml; Table 1).

Across these three populations, the estimated absolute difference in mean FGF-23 concentrations between the top and the bottom third of the FGF-23 distributions ranged from 72 RU/ml in general population studies, to 433 RU/ml in nondialyzed CKD studies, to 8644 RU/ml in dialysis population studies (C-terminal studies only).

It was notable that the ten general population cohorts had a mean age of 65 years or above (Table 1). The estimated crude mortality rates were, on average, high in all populations, with evidence of higher mortality with reduced kidney function. For example, the average all-cause mortality ranged from 1.9% to 5.3% per annum (p.a.) across the general populations, 2.0% to 14.2% p.a. in nondialyzed CKD populations, and 2.0% to 21.0% p.a. in dialysis populations.

Association between FGF-23 and Risk of Cardiovascular Events

Six studies assessed the association between FGF-23 and risk of myocardial infarction (three in general populations,[22,44,49] two in patients with CKD not on dialysis,[44,56] and one in patients on dialysis[24]). Overall, comparing participants in the top versus bottom third of baseline FGF-23 concentration, there was a 33% increased risk of myocardial infarction (summary RR, 1.33; 95% confidence interval [95% CI], 1.12 to 1.58), but no evidence of linear trend across the different populations studied (trend $P = 0.32$; Figure 2).

For the studies reporting an interquartile range of baseline FGF-23 concentrations, there was good correlation between median baseline FGF-23 concentration and the interquartile range (correlation coefficient, 0.99), so ordering studies by increasing baseline FGF-23 concentration effectively orders the studies by increasing absolute difference between the means of FGF-23 concentrations in the top versus bottom third of each study's FGF-23 distribution. Tests for linear trend in the RRs for myocardial infarction across the ordered studies were nonsignificant both within the three separate populations and across all individual studies (trend across all individual studies $P = 0.22$; Supplemental Figure 1).

Associations between FGF-23 and risk of stroke of any type were reported in nine studies, including six in general populations,[22,44,45,48,49,52] two in nondialyzed CKD populations,[44,56] and one in dialysis populations.[24] Overall, comparing those in the top versus the bottom third of baseline FGF-23 concentration, there was a 26% increased risk of

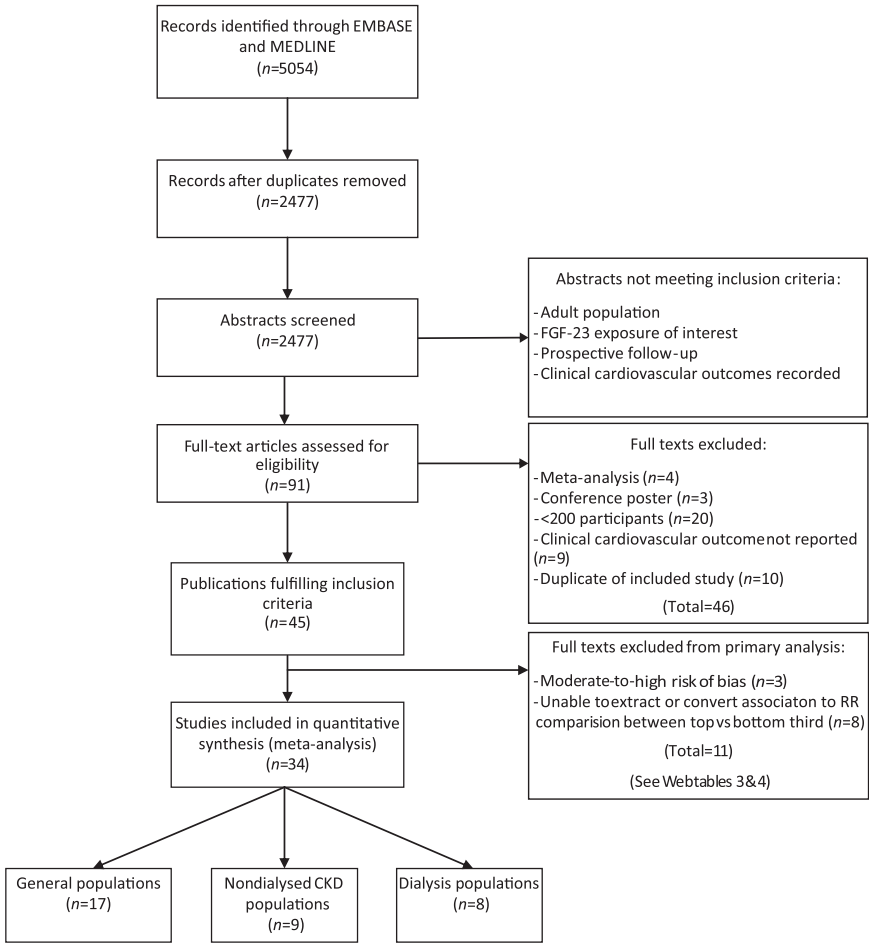

Figure 1. Study selection flowchart.

stroke (RR, 1.26; 95% CI, 1.13 to 1.41). This increase in risk was consistent between populations (trend $P=0.17$; Figure 2), and there was no significant trend toward larger RRs with higher median FGF-23 difference both within each population considered separately (where relevant) and across all studies (trend across all individual studies $P=0.95$; Supplemental Figure 2).

Four general population studies ($n=1251$ events)[22,45,48,52] and a small nondialyzed CKD study ($n=43$ events)[56] reported ischemic stroke events. Overall, no significant association between FGF-23 and risk of ischemic stroke was observed for the top versus the bottom third of baseline FGF concentration (RR, 1.08; 95% CI, 0.92 to 1.27; Supplemental Figure 3).

Associations between FGF-23 and risk of heart failure were reported in ten studies, including five in a general population,[42,44–46,49] four in patients with nondialyzed CKD,[23,44,58,59] and one in patients on dialysis.[24] Overall, comparing patients in the top versus the bottom third of baseline FGF-23 concentration, there was a 48% increased risk of heart failure (RR, 1.48; 95% CI, 1.29 to 1.69). There was no evidence of trend across populations (trend $P=0.89$; Figure 2) and no clear trend toward larger RRs with higher median FGF-23 difference both within each population considered separately and overall (trend across all individual studies $P=0.76$; Supplemental Figure 4). There was also no good evidence that FGF-23 was more strongly associated with heart failure than myocardial infarction or stroke, overall (heterogeneity $P=0.23$) or in any of the three separate populations (Figure 2).

Associations between FGF-23 and risk of peripheral artery disease and some other noted cardiovascular outcomes are provided in Supplemental Table 5.

Association between FGF-23 and Mortality

Twenty-three studies reported associations between FGF-23 and all-cause mortality: seven in a general population,[39,40,44,47,49,51,53] eight in a nondialyzed CKD population,[23,44,54,56,57,59–61] and eight in a dialysis population.[24,62–68]

Table 1. Study and participant characteristics by population type

Publication Author, Study Acronym	Study Location	No. of Participants; Follow-Up Duration	Baseline Demographics	Baseline Comorbidity Prevalences	FGF-23 Assay Type	Average FGF-23 Concentration
General population studies						
Ärnlöv *et al.*,[39] ULSAM	Uppsala, Sweden	727; Median: 9.7 yr (range, 0.3–12.9)	Age: 78 yr Men: 100%	DM: 13% eGFR: 74 (17) CVD: 27%	Intact	Median 44 pg/ml (range, 9–162)
Ärnlöv *et al.*,[38] PIVUS	Uppsala, Sweden	1003; Median: 5.1 yr (range, 4.8–5.8)	Age: 70 yr Men: 50% White: 100%	DM: 12% eGFR: 80 (14) CVD: 16%	Intact	Mean 47 pg/ml (SD 24)
Brandenburg *et al.*,[40] LURIC	Germany	2974; Median: 9.9 yr	Age: 63 (10) yr Men: 69% White: 100%	DM: 40% eGFR<60: 14% CAD: 78%	C-terminal	Median 54 RU/ml (IQR, 40–78)
Deo *et al.*,[41] CHS	USA	3244; Mean: 8.1 yr (SD 3.2)	Age: 78 (5) yr Men: 40% Black: 16%	DM: 15% eGFR: 71 (19) HF: 9% MI: 11%	C-terminal	Median 70 RU/ml (IQR, 53–99)
di Giuseppe *et al.*,[42] EPIC-Potsdam	Germany	1443; Mean 8 yr (SD 2.2)	Age: 52 Men: 44% White: NR	DM: 7% eGFR: NR CAD: 10.8%	C-terminal	Median 48 RU/ml (IQR, NR)
di Giuseppe *et al.*,[22] EPIC-Germany	Germany	2908; Mean: 8.2 yr	Age: 52 Men: 50% White: NR	DM: 6% eGFR: 108 Excluded MI and ST	C-terminal	Median 54 RU/ml (IQR, 38–72)[a]
Garimella *et al.*,[43] CHS	USA	3143; Median: 9.8 yr	Age: NR Men: NR White: NR	DM: NR eGFR: NR CVD: NR	C-terminal	Median 71 RU/ml (IQR, 54–100)
Ix *et al.*,[44] CHS	USA	3107; Median: 10.5 yr (IQR, 5.9–11.5)	Age: 78 (5) yr Men: 40% Black: 16%	DM: 15% eGFR: 71 (19) CVD: 29% HF: 9%	C-terminal	Median 70 RU/ml (IQR, 53–99)
Kestenbaum *et al.*,[45] MESA	USA	6547; Median: 8.5 yr (IQR, 7.7–8.6)	Age: 62 yr Men: 47% White: 39%	DM: 12% eGFR: 84 (eGFR<60: 16%) CVD: 0%	Intact	Median 38 pg/ml (IQR, 31–46) Mean: 40 pg/ml (SD 15)
Lutsey *et al.*,[46] ARIC	USA	11,638; Median: 18.6 yr (maximum, 20.9)	Age: 57 yr Men: 43% Black: 25%	DM: 13% eGFR: 92 (eGFR<60: 3%) CVD: 0%	Intact	Mean 44 pg/ml (SD 16)
Masson *et al.*,[47] PREDICTOR	Lazio, Italy	1835; Mean: 3.8 yr	Age: 73 (5) yr Men: 53% White: NR	DM: 17% Creatinine: 1.0 (0.3) mg/dl CVD: 29%	C-terminal	Median 74 RU/ml (IQR, 58–97)
Panwar *et al.*,[48] REGARDS	USA	1551 (615 cases); Follow-up: NR	Age: 65 yr Men: 45% Black: 40%	DM: 21% eGFR: 86.5 CVD: 16%	C-terminal	Median 70.5 RU/ml (IQR, 53–100)
Parker *et al.*,[49] HSS	San-Francisco, USA	833; Median: 6.0 yr	Age: 67 (11) yr Men: 81% White: 60%	DM: 27% eGFR<60: 22% CVD: 100%	C-terminal	Median 43 RU/ml (IQR, 29–72)

Table 1. Continued

Publication Author, Study Acronym	Study Location	No. of Participants; Follow-Up Duration	Baseline Demographics	Baseline Comorbidity Prevalences	FGF-23 Assay Type	Average FGF-23 Concentration
Souma *et al.*,[53] NOMAS	USA	2525; Median: 14 yr	Age: 69 (10) yr Men: 36% White: 21%	DM: 21% eGFR: 80 (22) CVD: NR (no STs)	C-terminal	Median 57 RU/ml (IQR, 44–81)
Speer *et al.*[50]	Saarland, Germany	859; Median: 2.3 yr (IQR, 0.98–2.93)	Age: 64 yr Men: 69% White: NR	DM: 25% Creatinine: 1.2 mg/dl (SD 0.8) CAD: 43% HF: 86%	C-terminal	Median 65 RU/ml (IQR, 45–115)
Westerberg *et al.*,[51] MrOS	Sweden	2838; Mean: 4.5 yr	Age: 75.5 (3) yr Men: 100% White: NR	DM: 9% eGFR: 72 (20) CVD: 19%	Intact	Median 44 pg/ml (IQR, 32–58)
Wright *et al.*,[52] NOMAS	USA	2525; Mean: 12 yr (SD 5)	Age: 69 (10) yr Men: 36% White: 21%	On glycemic agents: 15% eGFR: 80 (22) CVD: NR (no STs)	C-terminal	Median 57 RU/ml (IQR, 44–81)
Nondialyzed CKD population studies						
Alderson *et al.*,[60] CRISIS	Salford, UK	463; Median: 3.8 yr (IQR, 1.8–5.8)	Age: 64 (14) yr Men: 62% White: 96%	DM: 31% eGFR: 29 (15) CVD: 29% HF: 18%	C-terminal	Median 209 RU/ml (IQR, 128–470)
Baia *et al.*[54]	Groningen, The Netherlands	593; Median: 7.0 yr (IQR, 6.2–7.5)	Age: 52 (12) yr Men: 54% White: 95%	DM: 18% eGFR: 47 (16) CVD: NR	C-terminal	Median 140 RU/ml (IQR, 95–219)
Bouma-de Krijger *et al.*,[23] MASTERPLAN	The Netherlands	439; Follow-up: 2 yr	Age: 62 (12) yr Men: 71% White: 93%	DM: 23% eGFR: 36 (15) CVD: 27%	C-terminal	Median 149 RU/ml (IQR, 87–241)
Isakova *et al.*,[55] CRIC	USA	3879; 3.5 yr (IQR, 2.5–4.4)	Age: 58 (11) yr Men: 55% Black: 42%	DM: 48% eGFR: 43 (14) CAD: 22% HF: 10%	C-terminal	Median 146 RU/ml (IQR, 96–239)
Kendrick *et al.*,[56] HOST	USA	1099; Median: 2.9 yr Mean: 2.8 yr (SD 1.1)	Age: 69 (11) yr Men: 98% Black: 26%	DM: 55% eGFR: 18 (6) CVD: 57%	C-terminal	Median 392 RU/ml (IQR, 216–945)
Levin *et al.*,[57] CanPREDDICT	Canada	2402; Median: 1 yr	Age: 68 (13) yr Men: 63% White: 89%	DM: 48% eGFR: 28 (9) CVD: NR	C-terminal	Median 237 RU/ml (IQR, 150–432)
Munoz-Mendoza *et al.*,[61] CRIC	USA	3875; Median: 6.9 yr (IQR, 4.2–8.2)	Age: 58 yr Men: 55% Black: 42%	DM: 48% eGFR: 44 (15) CAD: 22% HF: 10%	C-terminal	Median 146 RU/ml (IQR, 96–239)
Scialla *et al.*,[58] CRIC	USA	3860; Median: 3.7 yr (IQR, 2.5–4.7)	Age: 58 (11) yr Men: 55% White: 42% Black: 41%	DM: 49% eGFR: 44 (15) CVD: 31%	C-terminal	Median 146 RU/ml (IQR, 96–239)

Table 1. Continued

Publication Author, Study Acronym	Study Location	No. of Participants; Follow-Up Duration	Baseline Demographics	Baseline Comorbidity Prevalences	FGF-23 Assay Type	Average FGF-23 Concentration
Seiler *et al.*,[59] CARE FOR HOME	Hamburg, Germany	444; Median: 2.6 yr (IQR, 1.4–3.6)	Age: 65 (12) yr Men: 60% White: NR	DM: 38% eGFR: 45 (16) Prevalent CVD: 30%	C-terminal	Median 102 RU/ml (IQR, 64–164)
Dialysis population studies						
Chonchol *et al.*,[62] HEMO	USA	1340; Mean: 2.8 yr (SD 1.7)	Age: 57 (14) yr Men: 45% Black: 64%	Hemodialysis: 100% DM: 44% CVD: 79%	Intact	Median 3118 pg/ml (IQR, 726–12,928)
Jean *et al.*[63]	France	219; Median: 1.9 yr	Age: 67 (14) yr Men: 57% White: NR	Hemodialysis: 100% DM: 35% CAD: 19%	C-terminal	Median 2740 RU/ml (IQR, 1192–8667) Mean: 7060 (SD 13,500)
Kim *et al.*[64]	South Korea	205; Mean: 3.5 yr	Age: 47 (14) yr Men: 60% White: NR	PD: 100% DM: 31% CAD: 7% HF: 8%	C-terminal	Median 79 RU/ml (IQR, 34–155)
Moe *et al.*,[24] EVOLVE	International	2985; Median: 4.2 yr (IQR, 1.0–5.0)	Age: 54 yr Men: 59% White: 58%	Hemodialysis: 100% DM: 32% CVD: 95% HF: 23%	Intact (Millipore)	Median 5555 pg/ml (Q10–Q90, 580–19540)
Montford *et al.*,[65] HOST	USA	654; Median: 2.9 yr	Age: 60 (11) yr Men: 98% White: 38%	Hemodialysis: 100% DM: 41% CVD: 52%	C-terminal	Median 4212 RU/ml (IQR, 1411–13,816)
Nowak *et al.*[66]	Germany	239; Median: 2.5 yr (IQR, 2.0–2.7)	Age: 68 (14) yr Men: 64% White: NR	Hemodialysis: 100% DM: 38% CAD: 31%	C-terminal	Mean 883 RU/ml (SD 1940)
Olauson *et al.*[67]	Sweden	229; Median: 1.9 yr (range, 0.1–5)	Age: 55 yr (IQR, 33–68) Men: 65% White: NR	Hemodialysis: 41% PD: 54% DM: 34% (as cause of ESRD) CVD: 41%	Intact	Median 2526 pg/ml (Q10–Q90, 431–19,495)
Scialla *et al.*,[68] CHOICE	USA	466; Median 3.4 yr (IQR, 1.8–5.9)	Age: 58 (15) yr Men: 55% Black: 36%	Hemodialysis: 100% DM: 57% CVD: 56%	C-terminal	Median 1577 RU/ml (IQR, 818–4946)

Age and eGFR are mean (SD). ULSAM, Uppsala Longitudinal Study of Adult Men; DM, diabetes mellitus; CVD, cardiovascular disease; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors study; LURIC, Ludwigshafen Risk and Cardiovascular Health study; IQR, interquartile range; CAD, coronary artery disease; CHS, The Cardiovascular Health Study; HF, heart failure; MI, myocardial infarction; EPIC, European Prospective Investigation into Cancer and Nutrition; NR, not reported; ST, stroke; MESA, Multi-Ethnic Study of Atherosclerosis; ARIC, Atherosclerosis Risk in Communities Study; PREDICTOR, Valutazionedella PREvalenza di DIsfunzione CardiacaasinTOmatica e di scompensocaRdiaco; REGARDS, Reasons for Geographic and Racial Differences in Stroke; HSS, Heart and Soul Study; NOMAS, Stroke-free North Manhattan Study; MrOS, multicenter prospective Osteoporotic Fractures in Men study; CRISIS, Chronic Renal Insufficiency Standards Implementation Study; MASTERPLAN, Multifactorial approach and superior treatment efficacy in renal patients with the aid of nurse practitioners; CRIC, Chronic Renal Insufficiency Cohort; HOST, Homocysteine in Kidney and End Stage Renal Disease study; CanPREDDICT, Canadian study of prediction of death, dialysis and interim cardiovascular events; CARE FOR HOME, Cardiovascular And REnal outcome in CKD stage 2–4 patients—The FOuRth HOMburg evaluation; HEMO, The Hemodialysis Study; PD, peritoneal dialysis; EVOLVE, Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events; Q10, 10th percentile; Q90, 90th percentile; CHOICE, Choices for Healthy Outcomes in Caring for ESRD.

[a]Approximated from median (IQR) of two mid quartiles.

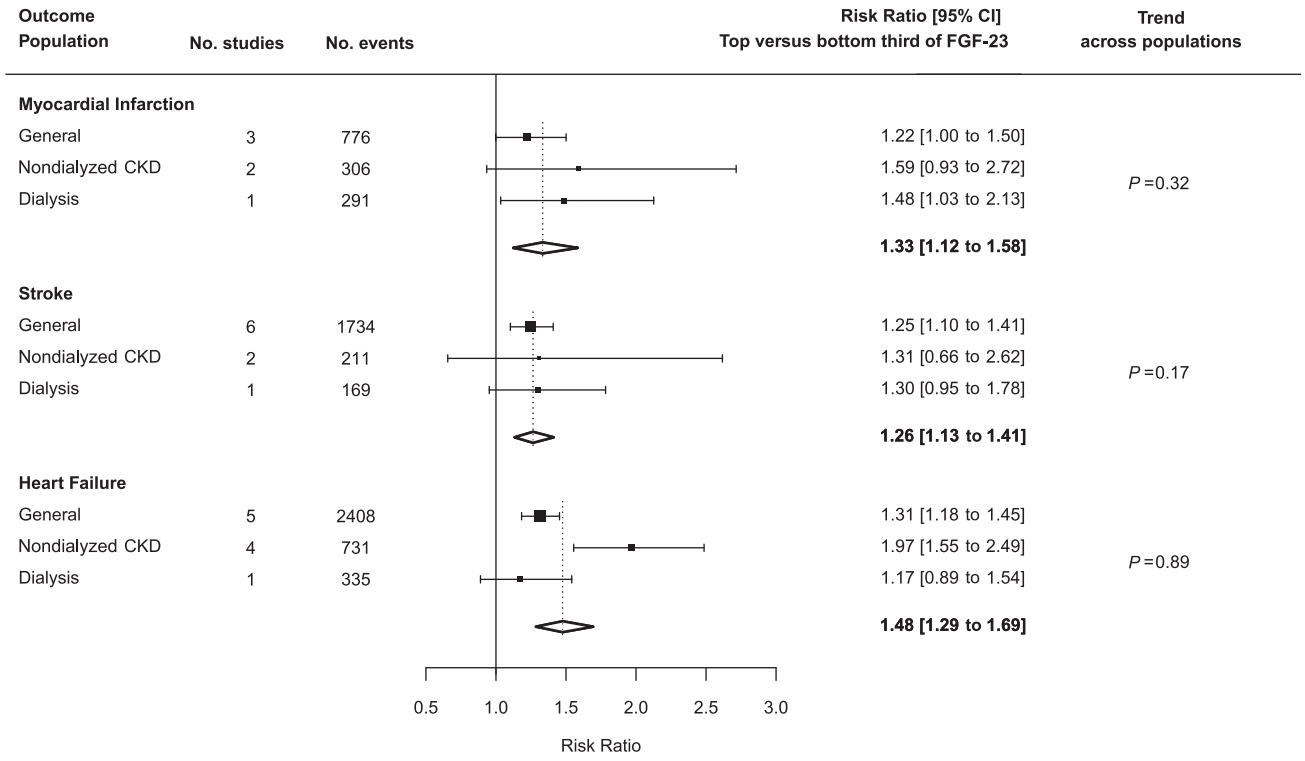

Figure 2. Association between FGF-23 and risk of cardiovascular disease event by population type. Heterogeneity tests across the summary RRs for the three outcomes: all populations combined, $P=0.23$; general populations, $P=0.59$; nondialyzed CKD populations, $P=0.75$; and dialysis populations, $P=0.47$.

Overall, comparing participants in the top versus bottom third of baseline FGF-23 concentration, there was an increased risk of death from all causes (RR, 1.70; 95% CI, 1.52 to 1.91). There was no good evidence of a trend across the three populations (trend $P=0.76$; Figure 3) or toward larger RRs with higher median FGF-23 at baseline (trend across all individual studies $P=0.97$; Supplemental Figure 5).

Eleven studies reported associations between FGF-23 level and cardiovascular mortality (seven studies in general populations,[39,40,44,46,47,51,53] two in nondialyzed CKD populations,[44,54] and two in dialysis populations[24,68]). Overall, comparing patients in the top versus bottom third of the baseline FGF-23 concentration, there was a 42% increased risk of cardiovascular mortality (RR, 1.42; 95% CI, 1.27 to 1.60) with no evidence of trend across populations (trend $P=0.53$; Figure 3) and no trend toward larger RRs with higher median FGF-23 (trend across all individual studies $P=0.49$; Supplemental Figure 6).

Among patients on dialysis in the EVOLVE trial,[24] comparing patients in the top versus the bottom third of the baseline FGF-23 concentration, there was a 27% (RR, 1.27; 95% CI, 1.02 to 1.58) increased risk of noncardiovascular mortality ($n=514$ deaths), which was similar to the RR for cardiovascular mortality (RR, 1.26; 95% CI, 1.00 to 1.57; $n=607$ deaths). Only one of the other nine studies (a general population cohort) reported RRs for cardiovascular mortality (RR, 1.76; 95% CI, 1.34 to 2.32; $n=474$) as well as for noncardiovascular mortality (RR, 1.47; 95% CI, 1.17 to 1.85; $n=612$ deaths).[53] For the remaining eight studies, RRs for noncardiovascular mortality were derived indirectly, using associations for cardiovascular and all-cause mortality.[39,40,44,46,47,51,54,68] The overall combined RR for all studies for noncardiovascular mortality for the top versus the bottom third of the baseline FGF-23 concentration was 1.52 (95% CI, 1.28 to 1.79), with results suggesting that for each of the separate populations, the RRs for cardiovascular and noncardiovascular mortality were comparable (Figure 4).

Sensitivity Analyses and Assessment for Publication Bias

The results of trend tests remained nonsignificant after exclusion of studies on patients on dialysis (Supplemental Figures 1, 2, and 4–6), after exclusion of studies that only reported intact FGF-23 concentrations, and after using a formula for interassay conversion.[21] Repeat measurements within groups of FGF-23 were highly correlated in all three types of populations studied (regression dilution ratios all >0.8, Supplemental Table 6),[22–24] so adjustment for regression-dilution bias was not performed. All-cause and cardiovascular mortality associations were not substantially affected by adjustment for other markers of CKD–mineral bone disorder (Supplemental Figure 7).[40,46,49,54,55,59,66]

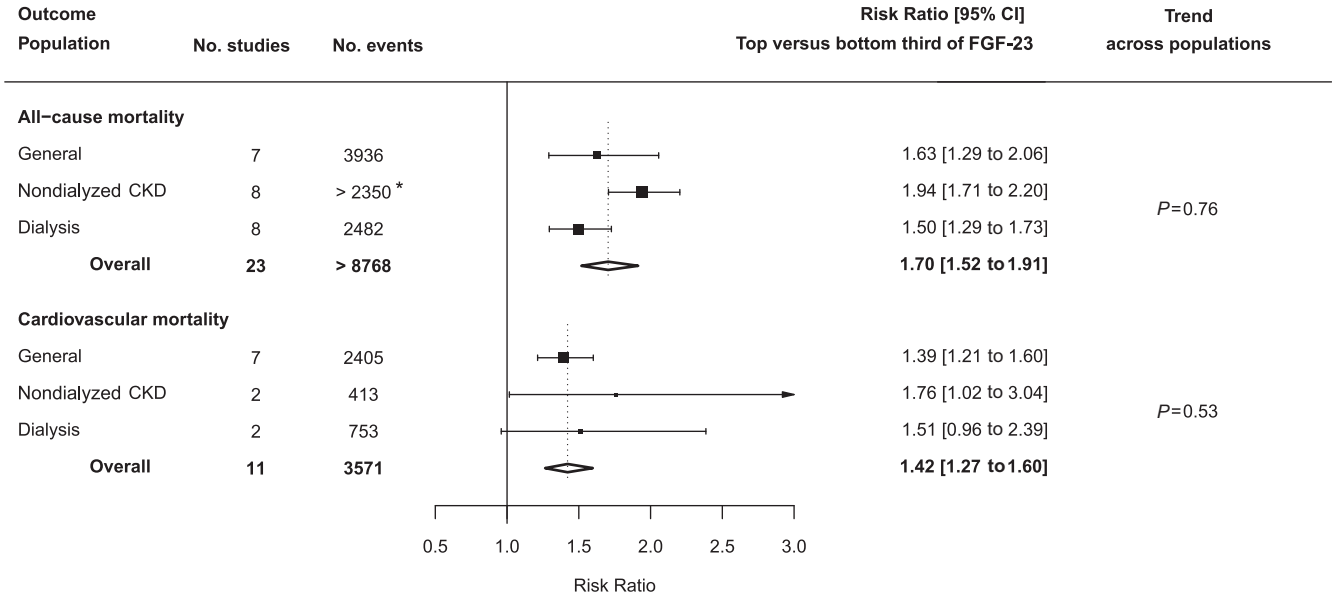

Figure 3. Association between FGF-23 and risk of all-cause and cardiovascular mortality by population type. *Number of events not reported for one study.

Funnel plots of associations between FGF-23 and all-cause mortality by type of population suggested evidence for publication bias for the general population cohorts (Egger regression test $P=0.005$) and that RRs for all-cause mortality may be slight overestimates (Supplemental Figures 5 and 8). There was no important heterogeneity between studies with respect to other outcomes (Supplemental Figures 1– 4 and 6).

DISCUSSION

This systematic review and meta-analysis assessed the epidemiologic associations between FGF-23 concentration and cardiovascular outcomes, as well as associations with cardiovascular and all-cause mortality in populations with and without known kidney disease. Overall, we found that, irrespective of a population's level of kidney function, a difference in FGF-23 concentration corresponding to that between top and bottom thirds of baseline FGF-23 concentration was associated with about 30% increased risk of myocardial infarction and stroke, 40% increased risk of cardiovascular mortality, and 50% increased risk of heart failure. In the studies where it was possible to estimated effects on both cardiovascular and noncardiovascular mortality, we found that the strength of the association between FGF-23 and these categories of deaths was approximately similar.

The Bradford Hill criteria for causality of a disease risk factor includes the presence of epidemiologic associations that are both consistent and specific for that disease, evidence of a biologic gradient (*i.e.*, greater exposure leads to increased effect, which we refer to as exposure-response), temporality (*i.e.*, the cause precedes the effect), and biologic plausibility.[69]

In support of raised FGF-23 concentration being a cause of cardiovascular disease, our study found consistent moderate associations between FGF-23 and disease risks. FGF-23 concentration also rises before any other marker of CKD–mineral bone disorder,[10] so it temporally mirrors the rise in cardiovascular risk as CKD progresses.[1] In addition, there is biologic plausibility because cardiac myocytes exposed to FGF-23 become hypertrophied and develop electrophysiologic disturbances (sometimes referred to as "off-target" effects as they appear to be Klotho-independent).[13–15]

We also observed that FGF-23 was strongly associated with noncardiovascular causes of death, reflecting a lack of specificity of the associations between raised FGF-23 concentration and disease risk. This observation could reflect the pleiotropy of FGF-23 in disease causation. It has previously been reported that raised FGF-23 concentration is associated with a higher risk of ESRD,[55] AKI (RR for top versus bottom quartile, 1.99; 95% CI, 1.04 to 3.80),[70] fractures (RR, 1.56; 95% CI, 1.11 to 2.20),[71] and serious infection (RR, 1.59; 95% CI, 1.14 to 2.22).[62] There is emerging evidence that FGF-23 may promote inflammation through direct effects on hepatocytes,[72] and predispose to infection through downregulation of monocytic expression of 1,25 dihydroxycholecalciferol[73] or other effects.[74] A mechanistic study has also suggested that FGF-23 may promote progression of prostate cancer.[75]

An alternative, more plausible explanation for the observed nonspecificity of associations across a range of disease outcomes is residual confounding. This may arise because of imprecise or incomplete measurement of baseline prognostic factors other than FGF-23. Examples of such factors include level of kidney function (which is measured with greater error at high eGFR), duration of CKD, and risk factors that correlate with low kidney function.

Furthermore, we found no evidence for a log-linear exposure-response relationship such as that which is commonly

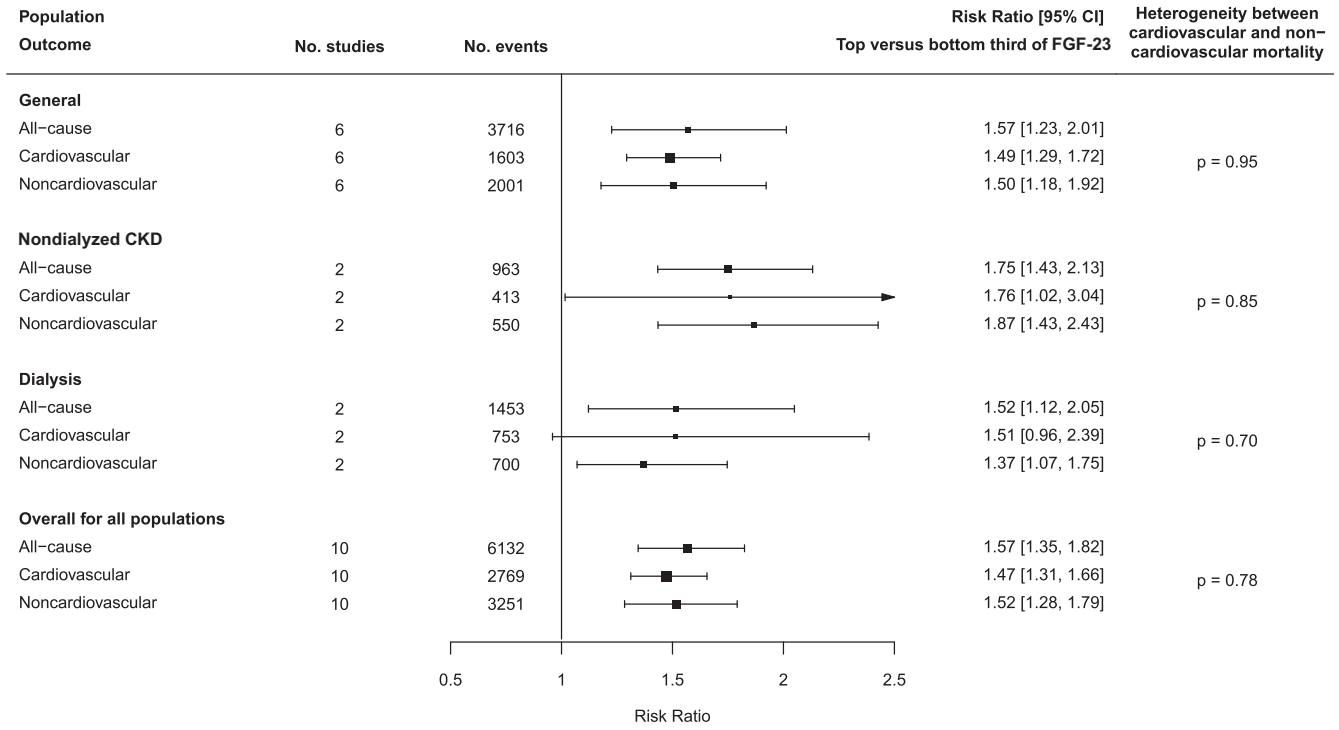

Figure 4. Association between FGF-23 concentration and risk of cause-specific mortality overall and by population type.

observed for known causes of cardiovascular disease (*e.g.*, LDL cholesterol[76,77] and BP[78]). Indeed, the RRs corresponding to a difference between top and bottom thirds of FGF-23 distribution were of similar magnitude in each of the three populations despite the absolute difference in FGF-23 varying by two orders of magnitude across these populations. Such a pattern could potentially be explained by a "log-log" relationship with flattening of the exposure-response curve at high FGF-23 concentration. But this shape of association would imply that, if FGF-23 is a cause of cardiovascular disease, therapeutic agents designed to reduce FGF-23 would need to achieve large absolute reductions in FGF-23 in those with high levels to achieve worthwhile risk reductions.

A limitation of this meta-analysis is that we were, for the most part, restricted to published summary data. The availability of individual participant-level data from all eligible studies could allow for more granular estimation of associations and perhaps a more sensitive analysis of any exposure-response relationship using a standardized method with fewer assumptions. It would also allow for the inclusion of the studies that could not be reliably converted onto a top versus bottom third scale. However, the studies excluded because of inability to convert associations showed positive associations between FGF-23 and disease risks that were similar in size to those observed by the included studies (Supplemental Table 4).[30–37] Furthermore, given the lack of trends across the three population types despite a two-fold increase in the absolute difference in FGF-23 concentration, it is unlikely that individual participant data would identify an important log-linear trend missed by our tabular meta-analysis. Individual participant-level data would also not overcome residual confounding, which is the main limitation of this meta-analysis. Finally, not all relevant studies reported associations for all outcomes of interest (which may have introduced bias) and there was a lack of detailed data on noncardiovascular causes of death, so it was not possible to examine whether there were deaths (*e.g.*, from cancer) that were particularly strongly associated with FGF-23.

In summary, this systematic review and meta-analysis has demonstrated that across a wide range of levels of kidney function, higher FGF-23 concentration was consistently associated with modest increased risks of myocardial infarction, heart failure, stroke, and cardiovascular death. However, higher FGF-23 was also associated with an increased risk of noncardiovascular causes of death. Our findings suggest that associations between FGF-23 and particular diseases, both in populations with CKD and those without known disease, may not signify cause and effect.

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DISCLOSURES

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