# Fibroblast growth factor 23 and risk of all-cause mortality and cardiovascular events: A meta-analysis of prospective cohort studies

Yunjun Xiao [*,1], Xianru Luo [1], Wei Huang, Jinzhou Zhang, Chaoqiong Peng

*Department of Nutrition and Food Hygiene, Shenzhen Center for Disease Control and Prevention, Shenzhen, China*

Fibroblast growth factor 23 (FGF23), a hormone that is secreted by osteoblasts, is an important regulator of phosphorus and vitamin D metabolism [1]. The past few years have seen a rapidly growing interest in testing the hypothesis that increased FGF23 level is an independent risk factor of mortality and cardiovascular disease (CVD). Cross-sectional studies have found higher circulating FGF23 concentrations were associated with severity of coronary artery disease (CAD) [2], prevalent CVD [3], left ventricular hypertrophy [4], total body atherosclerosis [5], endothelial dysfunction [6], and metabolic syndrome [7]. However, the reports from two nest case–control studies have been inconsistent; one concluded a positive association between FGF23 and mortality in hemodialysis patients [8], whereas the other concluded no association between FGF23 and risk of coronary heart disease (CHD) [9]. Recently, epidemiologic prospective cohort studies have investigated the link between FGF23 and risk of mortality and CVD events in different populations including kidney disease [10–17], diabetes [18], CAD patients [19], and community-based adults [20–23]. Some studies found a positive association, but the magnitudes of the association varied between these studies, and others reported no association. The inconsistent results of cohort studies prompted us to conduct a meta-analysis of prospective cohort studies to evaluate the association between FGF23 and risk of all-cause mortality and CVD events.

We followed a standardized protocol and conducted and reported this analysis according to the guidelines of the Meta-analysis of Observation Studies in Epidemiology group [24]. We conducted a systematic literature search of PubMed database through November 2013 for relevant articles that reported the association between FGF23 and risk of all-cause mortality and CVD events. To avoid missing any relevant study, we also searched the bibliographies of retrieved papers and recent reviews in the field. We did our search by using the following medical subject headings and keywords, such as Fibroblast Growth Factor-23, FGF23, and cardiovascular diseases, coronary disease, myocardial infarction, myocardial ischemia, coronary stenosis, coronary restenosis, cerebrovascular disorders, stroke, heart failure, death, mortality, all-cause mortality, cardiovascular mortality, and cohort studies, prospective studies, and follow-up studies. No restrictions were imposed. Two reviewers (Y.X. and X.L.) independently screened the abstracts and titles of the search results and eliminated articles only if they did not meet pre-stated inclusion criteria. The same 2 reviewers independently evaluated the remaining full-text articles for eligibility on the basis of a predefined set of eligibility criteria. Disagreements were resolved by discussion. Studies were considered eligible if they met the following criteria: 1) the study was a full-text, published prospective cohort study; 2) the exposure of interest was plasma or serum FGF23 concentrations; 3) the outcome of interest was all-cause or cardiovascular mortality or CVD events, myocardial infarction, stroke, or heart failure; and 4) relative risk (RR) and the corresponding 95% confidence interval (CI) or sufficient data to calculate them were provided. In addition, studies were excluded if they met the exclusion criteria that the sample size of a study was less than 200 and the duration of follow-up was less than one year.

Two reviewers independently abstracted data on participant characteristics and study results with adjustment factors by using a standardized data collection form. Discrepancies in data extraction between reviewers were resolved by consensus. We extracted any reported RRs, HRs, or incidence density ratios of outcomes and study characteristics for each trial. We also systematically assessed key indicators of study quality: methods of outcome adjudication and ascertainment that account for confounders and completeness of follow-up ascertainment. To calculate summary estimates and 95% CIs of the risk for FGF23, we pooled both RRs and HRs by using either fixed-effects models or, in the presence of heterogeneity, random-effects models [25]. The presence of heterogeneity across studies was evaluated by using the Q statistic with a conservative $p$ value of 0.10. Potential publication bias was evaluated by Begg and Egger tests at the $p < 0.10$ level of significance. All analyses were performed using STATA version 11.0 (StataCorp LP, College Station, Texas). A $p$ value $< 0.05$ was considered statistically significant, except where otherwise specified.
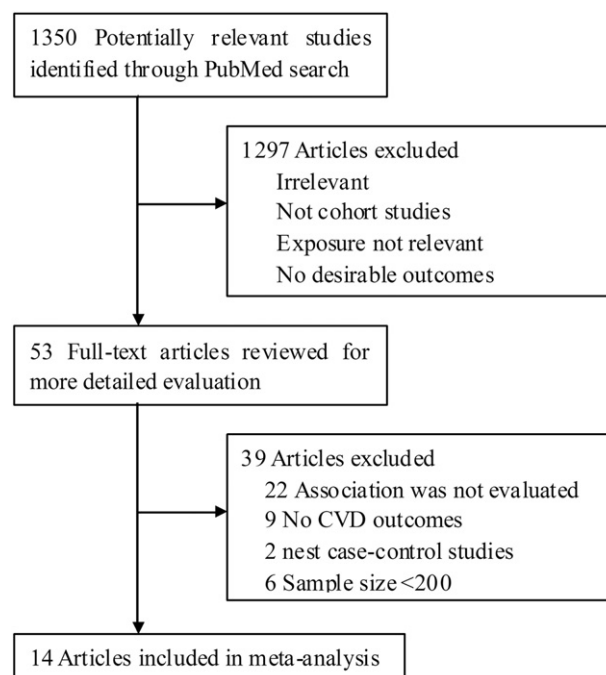


**Fig. 1.** Flow chart of study selection. CVD, cardiovascular disease; FGF23, fibroblast growth factor 23.

* Corresponding author at: Department of Nutrition and Food Hygiene, Shenzhen Center for Disease Control and Prevention, 8 Longyuan Road, Nanshan District, 518055 Shenzhen, China. Tel.: +86 755 25617321; fax: +86 755 25500660.

*E-mail address:* xiaoyunjun2002@yahoo.com.cn (Y. Xiao).

[1] The authors contributed equally to this work.

**Table 1**
Characteristics of 14 prospective cohort studies of FGF23 and all-cause mortality and cardiovascular events.

| Source | Location | Population | Sex/age, yrs | Recruitment time | Duration | FGF23 measurement | Outcomes |
|---|---|---|---|---|---|---|---|
| Jean (2009) [10] | France | 219 long haemodialysis patients | Male/female, 66.6 ± 14 | September 2006 | 695 days | C-terminal, 2740 (1192–8667) RU/ml | All-cause death |
| Parker (2010) [19] | United States | 833 CAD patients | Male/female, 67 ± 11 | 2000–2002 | 6.0 yrs | C-terminal, 43.1 (28.9–72.3) RU/ml | All-cause death, CVD events |
| Olauson (2010) [12] | Sweden | 229 incident dialysis patients | Male/female, 55 (33, 68) | December 1994–April 2008 | 23 months | Intact, 2526 (431–19495) ng/L | All-cause death |
| Wolf (2011) [13] | United States | 984 stable kidney transplant recipients | Male/female, 51 ± 13 | February–August 2007 | 37 months | C-terminal, 28 (20–43) RU/ml | All-cause death, allograft loss |
| Kendrick (2011) [14] | United States | 1099 advanced CKD patients | Male/female, 69 ± 11 | September 2001–October 2003 | 2.9 yrs | C-terminal, 392 (216–945) RU/ml | All-cause death, CVD events, initiation of chronic dialysis |
| Isakova (2011) [11] | United States | 3879 CKD stages 2–4 patients | Male/female, 58.2 ± 11.0 | June 2003–September 2008 | 3.5 yrs | C-terminal, 145.5 (96–239) RU/ml | All-cause mortality and ESRD |
| Arnlov (2012) [21] | Sweden | 727 community-based men | Male, 77.6 ± 0.76 | 1998–2001 | 9.7 yrs | Intact, 44 (9–162) pg/ml | All-cause and cardiovascular death |
| Ix (2012) [20] | United States | 3107 community-based adults | Male/female, 78 ± 5 | 1996–1997 | 10.5 yrs | C-terminal, 70 (53–99) RU/ml | All-cause death, heart failure, CVD events |
| Nakano (2012) [15] | Japan | 738 predialysis outpatients | Male/female, 64 (54, 72) | May 2005–July 2007 | 4.4 yrs | Intact, 49.5 (31.7–80.5) pg/ml | All-cause death, CVD events |
| Baia (2013) [16] | Netherlands | 593 stable kidney transplant recipients | Male/female, 52 ± 12 | August 2001–July 2003 | 7.0 yrs | C-terminal, 140 (95–219) RU/ml | All-cause and cardiovascular death, graft failure |
| Lee (2013) [18] | United States | 380 Type 2 diabetes patients | Male/female, 54 ± 10 | 1991–1995 | 8–12 yrs | C-terminal, Alive 50 (36–75), ESRD 117 (65–238), Death 84 (53–133) RU/ml | All-cause and cardiovascular death, ESRD |
| Westerberg (2013) [22] | Sweden | 3014 population-based men | Male, 75.5 ± 3.2 | 2001–2004 | 4.5 yrs | Intact, 43.5 (32.4–57.5) pg/ml | All-cause and cardiovascular death |
| Scialla (2013) [17] | United States | 3860 CKD stages 2–4 patients | Male/female, 21–74 | 2003–2008 | 3.7 yrs | C-terminal, 145.4 (96.0–238.8) RU/ml | Atherosclerotic events, congestive heart failure |
| Arnlov (2013) [23] | Sweden | 973 community-based men | Male, 70 | January 2001–June 2004 | 5.1 yrs | Intact, 47 ± 24 pg/ml | CVD events |

CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; FGF23, fibroblast growth factor 23.

Fourteen prospective cohort studies were finally included in our present meta-analysis. Fig. 1 shows details of the study selection. The main characteristics of studies in the meta-analysis were presented in Table 1. Among the 14 studies included here, 12 studies reported all-cause mortality and 6 studies reported CVD events. Outcome assess-ments, duration of follow up, assessment of FGF23, and methodological quality varied across studies. Overall, high FGF23 levels were associated with a significantly increased risk of all-cause mortality (RR: 1.34 [95% CI: 1.20 to 1.48]; $p < 0.001$). Substantial heterogeneity was observed ($I^2 = 71.1\%$, $p < 0.001$) (Fig. 2). The overall combined RR in relation to
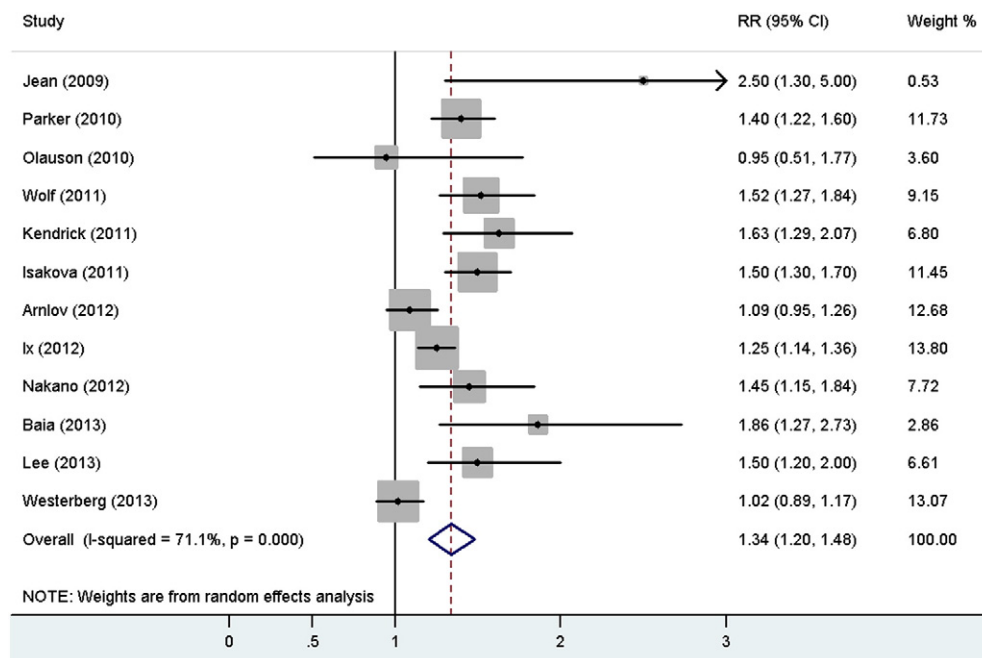


**Fig. 2.** Association between FGF23 and risk of all-cause mortality. FGF23, fibroblast growth factor 23.