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ORIGINAL RESEARCH

Fatty Acid Binding Protein-4 and Risk of Cardiovascular Disease: The Cardiovascular Health Study

Obiora Egbuche, MD, MPH; Mary L. Biggs, PHD; Joachim H. Ix, MD; Jorge R. Kizer, MD, MSc; Mary F. Lyles, MD; David S. Siscovick, MD, MPH; Luc Djoussé, MD, MPH, ScD; Kenneth J. Mukamal, MD, MPH

BACKGROUND: FABP-4 (fatty acid binding protein-4) is a lipid chaperone in adipocytes and has been associated with prognosis in selected clinical populations. We investigated the associations between circulating FABP-4, risk of incident cardiovascular disease (CVD), and risk of CVD mortality among older adults with and without established CVD.

METHODS AND RESULTS: In the Cardiovascular Health Study, we measured FABP4 levels in stored specimens from the 1992–993 visit and followed participants for incident CVD if they were free of prevalent CVD at baseline and for CVD mortality through June 2015. We used Cox regression to estimate hazard ratios for incident CVD and CVD mortality per doubling in serum FABP-4 adjusted for age, sex, race, field center, waist circumference, blood pressure, lipids, fasting glucose, and C-reactive protein. Among 4026 participants free of CVD and 681 with prevalent CVD, we documented 1878 cases of incident CVD and 331 CVD deaths, respectively. In adjusted analyses, FABP-4 was modestly associated with risk of incident CVD (mean, 34.24; SD, 18.90; HR, 1.10 per doubling in FABP-4, 95% CI, 1.00–1.21). In contrast, FABP-4 was more clearly associated with risk of CVD mortality among participants without (HR hazard ratio 1.24, 95% CI, 1.10–1.40) or with prevalent CVD (HR hazard ratio 1.57, 95% CI, 1.24–1.98). These associations were not significantly modified by sex, age, and waist circumference.

CONCLUSIONS: Serum FABP-4 is modestly associated with risk of incident CVD even after adjustment for standard risk factors, but more strongly associated with CVD mortality among older adults with and without established CVD.

Key Words: cardiovascular disease ■ CVD mortality ■ FABP-4 ■ risk

Although obesity is clearly associated with a higher risk of cardiovascular disease (CVD),[1] and several promising physiological pathways have been implicated in this relationship,[1] adipocyte-derived products have not consistently been associated with risk of CVD and CVD mortality in populations.[2] For example, initial reports related higher plasma adiponectin to a lower incidence of coronary heart disease in predominantly healthy middle-aged men,[3,4] but other studies have demonstrated contrasting findings in various cohorts, including the CHS (Cardiovascular Health Study) and Dallas Heart Study.[5–8] The adipokine, resistin, has been associated with risk in diabetic patients of European ancestry[9] and in elderly, nondiabetic chronic kidney disease patients,[10] but a recent meta-analysis demonstrated significant heterogeneity in results from prospective cohort studies, only 10% of which accounted for participant age.[11]

FABP-4 (fatty acid binding protein-4), also known as aP2 (adipocyte P2),[12] is the adipose-specific isoform of the family of fatty-acid–binding proteins and makes up around 6% of the total protein of adipocytes. It is also present in dendritic cells, macrophages, and in the bloodstream (after release from adipocytes).[12–16] As a lipid chaperone, FABP-4 orchestrates intracellular pathways that lead to inflammatory activation, development of atherosclerosis,[13,14] insulin resistance,

Correspondence to: Obiora Egbuche, MD, MPH, Division of Cardiovascular Disease, Morehouse School of Medicine, 720 Westview Dr, Atlanta, GA 30310. E-mail: oegbuche@msm.edu

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CLINICAL PERSPECTIVE

What Is New?

- Obesity has been clearly associated with a higher risk of cardiovascular disease but adipocyte-derived products have not consistently been associated with risk of cardiovascular disease and cardiovascular disease mortality in populations.
- FABP-4 (fatty acid binding protein-4), an adipocyte derived product, is strongly associated with cardiovascular disease mortality and may serve as a useful measure of metabolically adverse obesity.

What Are the Clinical Implications?

- Pharmacologic inhibition of FABP-4 may present a viable therapeutic target for reducing obesity-related cardiovascular mortality among older adults.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
aP2	adipocyte P2
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHS	Cardiovascular Health Study
CRP	C-reactive protein
CV	coefficients of variation
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
FABP-4	fatty acid binding protein-4
GRACE	Global Registry of Acute Coronary Events
HDL	high-density lipoprotein
HR	hazard ratio
LDL	low-density Lipoprotein
LLC	limited liability corporation
VEGF	vascular-endothelial growth factor

and adipokine secretion in adipocytes,[17–19]including reduced adiponectin production.[20]

FABP-4 promotes development and progression of atherosclerosis in some animal models.[18,21–24] In one, a small-molecule inhibitor of FABP-4 reduced development of diabetes mellitus and atherosclerosis.[24] A variant in the gene encoding FABP-4 has been associated with a lower risk for coronary heart disease in 2 parallel cohorts.[23] A cross-sectional study of Chinese adults found that FABP-4 levels were associated with carotid plaque, but only in women,[25] but a study of diabetic patients in Spain found no such association.[26]

In people with known coronary artery disease, FABP-4 has been associated with complex coronary lesions,[27] left ventricular hypertrophy, systolic dysfunction,[12] myocardial perfusion abnormality, clinical heart failure,[15] and adverse events in patients with stable coronary artery disease,[28,29] as well as after acute coronary syndrome.[30]

To determine whether an association exists between FABP-4 and risk of CVD and CVD mortality, we assessed levels of circulating FABP-4 in the CHS, a prospective, population-based study of nearly 6000 older adults recruited from 4 field centers across the United States, who have been followed for approximately 30 years.

METHODS

Requests to access the data set by qualified researchers trained in human subject confidentiality protocols may be sent to "The Cardiovascular Health Study" by contacting the CHS research coordinator, Erika Enright (phone: +1-206-897-1922), and/or e-mail to: CHSDATA@uw.edu

Study Designs and Populations

The CHS is a prospective study of 5888 men and women aged ≥65 years who were recruited from randomly generated Medicare-eligibility lists in Pittsburgh, Pennsylvania; Forsyth County, North Carolina; Sacramento, California; and Washington County, Maryland. Participants were not institutionalized or wheelchair dependent, did not require a proxy for consent, were not under treatment for cancer at the time of enrollment, and were expected to remain in their respective regions for at least 3 years. In 1989–1990, 5201 participants were recruited and examined (the original cohort); in 1992–1993, an additional 687 predominantly black participants were recruited and examined. The institutional review board at each participating center approved the study, and each participant gave informed consent.

The CHS study design and objectives have been published previously.[31] The baseline examination included standardized medical history questionnaires, physical examination, resting ECG, and laboratory examination. Follow-up contact has occurred every 6 months, alternating between telephone calls and clinic visits for the first decade of follow-up and by telephone calls since. For this analysis, the 1992–1993 CHS clinic visit served as the baseline examination for follow-up of CVD; most of the procedures performed at the original 1989–1990 baseline were repeated in 1992–1993. Participants were excluded from these analyses

if they did not participate in (n=288) or had died before the 1992–1993 visit (n=335) or did not have sufficient stored plasma for FABP-4 measurement (n=558).

Measurement of FABP-4 and Other Biomarkers

FABP-4 was measured from plasma collected at the 1992–1993 visit and subsequently stored at −80°F or below at the CHS Central Laboratory at the University of Vermont (Colchester, VT). As previously described,[32] technicians at the Central Laboratory measured plasma FABP-4 using standard ELISA kits (BioVendor, LLC, Asheville, NC). Interassay coefficients of variation were 2.61% to 5.32%, with a detectable range of 5 to 250 ng/mL.

The Central Laboratory also measured standard cardiovascular risk factors from samples collected in 1992–1993, including fasting glucose, lipids, and high-sensitivity C-reactive protein.[33]

Determination of Incident CVD and CVD Mortality

Details of the CHS protocols for confirmation of prevalent and incident cardiovascular events, including the algorithms used for classification, have been published.[34,35] Participants reported incident CVD at annual clinic visits and interim telephone interviews when questioned regarding hospitalizations and other acute events. Discharge summaries and diagnoses were obtained for all hospitalizations. For all potential incident events, additional information, including history of chest pain, cardiac enzyme levels, and serial ECGs, was collected. The CHS Cardiovascular Events Committee reviewed and classified all potential CVD events. In addition, the CHS Events Committee reviewed all deaths and classified these as cardiovascular or noncardiovascular. For these analyses, we used a primary composite outcome of incident CVD that included incident myocardial infarction (nonfatal and fatal), stroke, and CVD mortality, among participants free of prevalent CVD at baseline; we also examined these components separately. Our primary outcome among participants with prevalent CVD at baseline was CVD mortality.

Statistical Analysis

Our study included 4707 eligible CHS participants who had available FABP-4 measures. For analysis of incident CVD, 4026 participants who were free from any CVD at baseline were included. The analysis of CVD mortality included 681 participants who had a known diagnosis of CVD at baseline. Missing covariate data were replaced by previously measured values, if available, or values estimated through imputation.[36] We conducted a descriptive analysis of both of the study populations stratified according to baseline FABP-4 quartiles, calculating mean and SD for continuous variables and frequencies for categorical variables. Time to event was calculated as the interval between the baseline examination in 1992–1993 to the earliest date of event of interest (myocardial infarction, stroke), date of CVD death, or date of last follow-up (up until June 2015). Cox proportional hazard regression models were used to estimate hazard ratios for incident CVD and CVD mortality. We created initial models that included age, sex, race, field center, and waist circumference and a more extensively adjusted model that further included systolic blood pressure, use of antihypertensive medications, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, fasting glucose, use of medications for control of blood glucose, and C-reactive protein. We modeled FABP-4 concentrations in 2 ways—as quartiles within each population and per doubling of FABP-4 concentration (using a logarithmic transformation to base 2). We used generalized additive model plots to evaluate the associations of transformed FABP-4 with outcome with no meaningful departures from linearity. To assess subgroups in which FABP-4 concentrations might be differentially associated with outcome, we created multiplicative interaction terms of FABP-4 with age, sex, and waist circumference; of note, FABP-4 was most strongly associated with risk of diabetes mellitus among lean men in previous analyses from the CHS.[32] Statistical analyses were performed using Stata aoftware (version 14.2; StataCorp LP, College Station, TX). All *P* values were 2-tailed.

RESULTS

Baseline characteristics of participants free of CVD are summarized in Table 1 and those of participants with prevalent CVD in Table S1. Women tended to have higher FABP4 levels than men. As expected, mean levels of cardiometabolic predictors (including body mass index, waist circumference, systolic blood pressure, low-density lipoprotein-cholesterol, triglycerides, and C-reactive protein) were higher in ascending FABP-4 quartiles.

Among 4026 participants free of CVD followed for 46 016 person-years, we documented 1878 cases of incident CVD. In adjusted analyses (Table 2), FABP-4 was not associated with individual outcomes of incident myocardial infarction or stroke, but was significantly associated with higher CVD mortality. FABP-4 had a borderline association with the composite outcome of incident CVD (*P*=0.058).

Among 681 participants with prevalent CVD followed for 5963 person-years (Table 3), in whom we documented 331 CVD deaths, FABP-4 was strongly

Table 1. Characteristics of CHS Participants Free of CVD at 1992–1993 Examination, by FABP-4

	FABP-4, ng/mL (N=4026)			
	≤22.36	>22.36 to 29.92	>29.92 to 40.64	>40.64
n	1008	1009	1009	1000
FABP-4, ng/mL	18.0	26.2	34.7	58.1
Age, y	74.6±4.9	74.6±5.2	74.7±5.4	74.8±5.3
Male	72.2%	44.4%	25.0%	13.0%
Black	13.4%	15.6%	16.7%	21.5%
Field center				
North Carolina	26.2%	28.1%	28.8%	22.3%
California	26.4%	28.9%	23.9%	29.1%
Maryland	19.0%	18.9%	21.7%	23.8%
Pennsylvania	28.4%	24.0%	25.6%	24.8%
Body mass index, kg/m^2	24.5±3.5	26.0±3.9	27.2±4.1	29.9±5.7
Waist circumference, cm	92.0±10.7	95.5±12.1	97.9±12.3	104.1±15.5
Systolic BP, mm Hg	134.9±20.9	135.3±20.7	136.6±21.2	138.4±21.7
Diastolic BP, mm Hg	72.0±11.3	71.6±11.0	71.8±10.8	70.8±12.0
Heart rate	63.4±10.8	65.2±10.4	65.9±10.3	68.1±11.6
Grip strength, kg	32.8±10.7	28.2±9.7	25.3±8.9	23.7±7.6
LDL-cholesterol, mg/dL	114.8±31.4	119.0±32.4	122.7±33.7	123.4±37.0
Triglycerides, mg/dL	116.5±66.8	134.1±73.5	148.4±82.8	167.2±93.9
HDL-cholesterol, mg/dL	53.8±14.7	54.5±15.0	54.8±14.3	53.2±13.9
C-reactive protein, mg/L	3.9±9.8	4.5±7.1	5.0±8.9	7.8±12.2
Fibrinogen, mg/dL	311.5±62.2	323.0±62.2	325.9±62.8	349.4±75.5
$eGFR_{cys}$	81.5±16.9	76.8±16.8	73.2±17.3	63.6±17.9
Alcoholic beverages/wk	3.1±6.4	2.3±5.3	1.8±5.4	1.3±7.9
Total physical activity, kcal	1864.6±2047.7	1496.0±1783.0	1401.8±1710.5	1033.7±1332.9
Antihypertensive medication	34.6%	42.8%	48.4%	60.8%
Prevalent diabetes mellitus	10.4%	12.0%	13.4%	19.3%
Smoking status				
Never	37.7%	42.7%	53.3%	53.5%
Former	51.2%	45.6%	37.2%	38.3%
Current	11.1%	11.7%	9.5%	8.2%
Self-reported health				
Excellent	9.4%	7.9%	7.6%	4.0%
Very good	38.0%	35.1%	31.5%	26.0%
Good	38.3%	40.5%	43.4%	44.6%
Fair	13.2%	15.0%	16.7%	22.2%
Poor	1.1%	1.5%	0.8%	3.1%

BP indicates blood pressure; CHS, Cardiovascular Health Study; CVD, cardiovascular disease; FABP-4, fatty acid binding protein-4; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

associated with risk of CVD mortality, with a nearly 60% higher rate for each doubling in circulating FABP-4 concentration, even in the most extensively adjusted model. Similarly, across quartiles, FABP-4 was associated with just over a doubling in risk of CVD mortality among participants with prevalent CVD.

We observed no statistically significant interaction between age or waist circumference and FABP-4 for either of our primary outcomes (P>0.10 for all).

Given marked differences in FABP-4 levels by sex (Table 1) and previous evidence from the CHS that FABP-4 might be more strongly associated with incident diabetes mellitus, we performed a sex-stratified analysis and explored any possible interaction by sex (Tables S1 through S4). Among participants free of CVD, interaction with sex was significant after further adjustments only in model 2, with a modestly higher hazard ratio among men than women; the difference in the association by sex was not significant in model 3.

Table 2. Hazard Ratios (95% CIs) of Cardiovascular Outcomes Associated With Circulating Levels of FABP-4

	Q1	Q2	Q3	Q4	Per Doubling
Myocardial infarction*					
Model 1†	(Ref.)	1.12 (0.92–1.38)	1.08 (0.86–1.35)	1.21 (0.94–1.56)	1.09 (0.94–1.25)
Model 2‡	(Ref.)	1.09 (0.89–1.34)	1.02 (0.81–1.28)	1.07 (0.82–1.38)	0.99 (0.85–1.65)
Stroke§					
Model 1†	(Ref.)	1.19 (0.96–1.48)	1.05 (0.83–1.33)	1.28 (0.99–1.66)	1.13 (0.98–1.31)
Model 2‡	(Ref.)	1.20 (0.97–1.50)	1.04 (0.82–1.32)	1.22 (0.94–1.58)	1.07 (0.92–1.24)
Cardiovascular mortality‖					
Model 1†	(Ref.)	1.19 (1.00–1.40)	1.14 (0.95–1.37)	1.53 (1.25–1.87)	1.33 (1.18–1.49)
Model 2‡	(Ref.)	1.17 (0.99–1.39)	1.10 (0.91–1.33)	1.39 (1.13–1.71)	1.23 (1.10–1.39)
Total incident cardiovascular disease¶					
Model 1†	(Ref.)	1.16 (1.01–1.33)	1.11 (0.96–1.29)	1.34 (1.14–1.58)	1.19 (1.08–1.30)
Model 2‡	(Ref.)	1.15 (1.01–1.32)	1.07 (0.92–1.24)	1.22 (1.03–1.44)	1.10 (1.00–1.20)

BP indicates blood pressure; CRP, C-reactive protein; FABP-4, fatty acid binding protein-4; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Ref., reference.

*Median follow-up time=11.4 years.

†Adjusted for age, sex, race, field center, and waist circumference.

‡Adjusted for age, sex, race, field center, waist circumference, systolic BP, antihypertensive medications, HDL, LDL, triglycerides, CRP, fasting glucose, and hypoglycemic medications.

§Median follow-up time=11.7 years.

‖Median follow-up time=12.7 years.

¶Median follow-up time=10.8 years.

Among participants with baseline CVD, we observed no evidence for interaction whatsoever, with essentially identical estimates in both sexes.

DISCUSSION

Our prospective, population-based, cohort study provides evidence for the association of circulating FABP-4 with CVD mortality among older adults. Circulating FABP-4 concentrations were not associated with incident nonfatal CVD among older adults without previous CVD, but were more clearly associated with CVD mortality among individuals without or with known CVD, even beyond traditional CVD risk factors.

Our results mirror those of selected previous studies, particularly in the strong association of FABP-4 with CVD mortality in the clinical population of patients with previous CVD. In one 10-year prospective study among German adults, circulating FABP-4 levels were associated with prognosis among patients with coronary heart disease.[29] Chow et al demonstrated that circulating FABP-4 levels predicted development of CVD after adjustment for traditional risk factors in a community-based Chinese cohort. FABP-4 has also been associated with left ventricular hypertrophy, systolic and diastolic cardiac dysfunction,[12] clinical heart failure,[37] coronary atherosclerotic burden, number and complexity of stenotic coronary arteries,[27] increased carotid intima-media thickness, and ischemic stroke.[14,15,25,38–41] In patients with established coronary artery disease, FABP-4 has been reported to be associated with subsequent adverse cardiovascular events[13,27,28,30] with a similar prognostic performance as the GRACE (Global Registry of Acute Coronary Events) in-hospital risk score.[30] Interestingly, FABP-4 was not associated with subsequent adverse cardiovascular events in the subset of asymptomatic participants with CAD.[30] Liu et al[42] also demonstrated an association between

Table 3. Hazard Ratios (95% CIs) of CVD Mortality* Associated With Circulating Levels of FABP-4 Among Participants With Prevalent CVD

	Q1	Q2	Q3	Q4	Per Doubling
Model 1†	(Ref.)	1.48 (1.05–2.07)	1.95 (1.38–2.75)	2.63 (1.80–3.84)	1.80 (1.47–2.20)
Model 2‡	(Ref.)	1.44 (1.02–2.03)	1.75 (1.22–2.51)	2.23 (1.47–3.37)	1.63 (1.31–2.04)

BP indicates blood pressure; CRP, C-reactive protein; FABP-4, fatty acid binding protein-4; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Ref., reference.

*Median follow-up time=7.8 years.

†Adjusted for age, sex, race, field center, and waist circumference.

‡Adjusted for age, sex, race, field center, waist circumference, systolic BP, antihypertensive medications, HDL, LDL, triglycerides, CRP, fasting glucose, and hypoglycemic medications.

circulating FABP-4 levels and CVD mortality in men with type 2 diabetes mellitus.

The relationship of FABP-4 with outcomes was attenuated after adjustment for lipids, blood pressure, glucose, and C-reactive protein. This may suggest that part of the pathogenic effect of circulating FABP-4 (and adipose mass, from which FABP-4 derives) is, in part, mediated through these other traditional risk factors, although formal analyses will require cohorts in which all of these factors are measured repeatedly over time. Blood pressure, hyperglycemia, and inflammation, in particular, have been strongly associated with risk of CVD in CHS.[43–47]

FABP-4 is expressed in macrophages and dendritic cells and therefore may contribute to inflammation-related alteration, resulting in progression of atherosclerosis and cardiac dysfunction. Beyond the metabolic risks, other pathogenic effects of FABP-4 have been proposed. As a lipid chaperone involved in lipid oxidation, signaling, and trafficking, FABP-4 has been correlated with adiposity[48,49] and, in particular, with epicardial fat deposition.[50] FABP-4 produced by epicardial fat may contribute to development of coronary atherosclerosis.[51] FABP-4 levels in atherosclerotic plaques are also associated with an unstable plaque phenotype.[52] In samples from human endarterectomies, increased FABP-4 expression in macrophages has been linked to unstable carotid plaques.[53] However, we cannot exclude the possibility of any confounding factors in these associations.

To our knowledge, there are no available literature to explain the differential associations of FABP-4 levels with incident CVD and CVD mortality. We hypothesize that FABP-4 levels may more closely reflect the downstream pathological processes that occur after development of CVD compared with its influence on development and progression of atherosclerosis. One intriguing speculation is that circulating FABP-4 levels may partly reflect levels in vascular endothelium, where FABP-4 is under direct control of VEGF (vascular endothelial growth factor) by VEGF receptor-2.[54] If so, then FABP-4 levels may reflect conditions in which this pathway is active, such as ischemia. This speculation requires further investigation.

STRENGTHS AND LIMITATIONS

For our analysis, we utilized a single snapshot measurement of serum FABP-4 concentration. Regardless, our preliminary results suggest its association with incident CVD and CVD death. This finding suggests that future studies utilizing longitudinal measures of serum FABP-4 concentration might show even stronger associations. Our study population included exclusively older adults. Older-aged individuals have a higher risk of adverse CVD outcomes. We do not know how serum FABP-4 concentrations would perform in middle-aged adults at lower risk for CVD. As an observational study, we cannot exclude the possibility of residual or unmeasured confounding as an alternative explanation of observed associations. However, we included multiple covariates to minimize confounding. Other strengths of our study include a reproducible method for measuring FABP-4, long-term follow-up, and standardized adjudication of CVD and mortality.

CONCLUSIONS

FABP-4, a lipid chaperone and major protein constituent of adipocytes, is modestly associated with development of CVD in older adults, but is considerably more strongly associated with CVD mortality and may serve as a useful measure of metabolically adverse obesity. Although some studies support the association of FABP-4 with cardiac dysfunction, obesity-related CVD, and adverse cardiovascular events, the role of pharmacological inhibition of FABP-4 has not been fully explored. Strategies that are centered on reducing or suppressing the effect of circulating FABP-4 may be viable therapeutic targets for reducing obesity-related cardiovascular mortality among older adults.

ARTICLE INFORMATION

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Affiliations

From the Division of Cardiovascular Disease, Morehouse School of Medicine, Atlanta, GA (O.E.); Cardiovascular Health Research Unit, University of Washington, Seattle, WA (M.L.B.); Division of Nephrology, Department of Medicine (J.H.I.), and Division of Cardiology, Veterans Affairs Medical Center (J.R.K.), University of California, San Diego, CA; Department of Gerontology, School of Medicine, Wake Forest University, Winston-Salem, NC (M.F.L.); The New York Academy of Medicine, New York, NY (D.S.S.); Division of Aging, Department of Medicine, Brigham and Women's Hospital, Boston, MA (L.D.); Division of General Medicine, Beth Israel Deaconess Medical Center, Boston, MA (K.J.M.).

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Disclosures

None.

Supplementary Materials

Tables S1–S4

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Supplemental Material

Table S1. CVD Mortality among participants free of CVD According to Sex-Specific Quartiles.

FABP-4 Range	Person-Time	Deaths	Rate	95% CI
Men				
≤18.64	5329.6	117	21.9	18.3-26.3
18.65-23.63	4894.6	129	26.4	22.2-31.3
23.64-30.58	4554.7	131	28.8	24.2-34.1
>30.58	3421.2	115	33.6	28.0-40.3
Women				
≤27.56	8531.6	162	19.0	16.3-22.1
27.57-35.25	8917.3	173	19.4	16.7-22.5
35.26-45.91	8665.7	197	22.7	19.8-26.1
>45.91	7531.4	189	25.1	21.8-28.9

FABP-4: Fatty acid binding protein

Table S2. Hazard ratios (95% confidence intervals) of cardiovascular mortality associated with circulating levels of FABP-4 among participants free of CVD in sex-specific quartiles.

	Q1	Q2	Q3	Q4	per doubling
Cardiovascular Mortality[+]					
WOMEN					
	≤27.56	>27.56-35.25	>35.25-45.91	>45.91	
Model 1[#]	(Ref.)	0.99 (0.79-1.23	1.16 (0.93-1.44)	1.25 (0.99-1.58)	1.23 (1.07-1.42)
Model 2[*]	(Ref.)	0.94 (0.75-1.17)	1.16 (0.93-1.44)	1.09 (0.86-1.38)	1.14 (0.99-1.32)
Model 3[+]	(Ref.)	0.95 (0.76-1.18)	1.16 (0.93-1.44)	1.10 (0.87-1.39)	1.14 (0.99-1.32)
MEN					
	≤18.65	>18.64-23.63	>23.63-30.58	>30.58	
Model 1[#]	(Ref.)	1.20 (0.92-1.55)	1.33 (1.02-1.73)	1.64 (1.23-2.21)	1.54 (1.27-1.87)
Model 2[*]	(Ref.)	1.13 (0.87-1.46)	1.22 (0.93-1.60)	1.49 (1.10-2.00)	1.41 (1.16-1.71)
Model 3[+]	(Ref.)	1.08 (0.83-1.40)	1.17 (0.89-1.53)	1.35 (1.00-1.83)	1.33 (1.09-1.63)

[#] Adjusted for age, sex, race, field center, waist circumference

[*]Adjusted for age, sex, race, field center, waist circumference, systolic BP, anti-hypertensive medications, HDL, LDL, triglycerides, CRP, fasting glucose, hypoglycemic medications

[+]Adjusted for age, sex, race, field center, waist circumference, systolic BP, anti-hypertensive medications, HDL, LDL, triglycerides, CRP, fasting glucose, hypoglycemic medications, diastolic BP, grip strength, physical activity, heart rate

P-values for interaction per doubling:

Model 1: p=0.18

Model 2: p=0.03

Model 3: p=0.07

Table S3. CVD Mortality among participants with prevalent CVD according to Sex-Specific Quartiles.

FABP-4 Range	Person-Time	Deaths	Rate	95% CI
Men				
≤18.64	838.0	33	39.4	28.0-55.4
18.65-23.63	775.7	49	63.2	47.7-83.6
23.64-30.58	761.6	48	63.0	47.5-83.6
>30.58	884.6	72	81.4	64.6-102.5
Women				
≤27.56	570.7	17	29.8	18.5-47.9
27.57-35.25	760.2	30	39.4	27.6-56.4
35.26-45.91	618.2	28	45.3	31.3-65.6
>45.91	767.0	54	70.4	53.9-91.9

FABP-4: Fatty acid binding protein

Table S4. Hazard ratios (95% confidence intervals) of cardiovascular mortality associated with circulating levels of FABP-4 among participants with prevalent CVD according to sex-specific quartiles.

	Q1	Q2	Q3	Q4	per doubling
Cardiovascular Mortality[+]					
WOMEN					
	≤27.56	>27.56-35.25	>35.25-45.91	>45.91	
Model 1[#]	(Ref.)	1.44 (0.79-2.65)	1.75 (0.93-3.31)	2.65 (1.47-4.79)	1.74 (1.26-2.40)
Model 2[*]	(Ref.)	1.52 (0.80-2.87)	1.68 (0.84-3.36)	2.44 (1.27-4.67)	1.62 (1.12-2.33)
Model 3[+]	(Ref.)	1.64 (0.86-3.13)	1.78 (0.89-3.58)	2.60 (1.35-4.99)	1.65 (1.14-2.38)
MEN					
	≤18.65	>18.64-23.63	>23.63-30.58	>30.58	
Model 1[#]	(Ref.)	1.90 (1.19-3.04)	2.02 (1.23-3.32)	2.82 (1.74-4.55)	1.86 (1.43-2.43)
Model 2[*]	(Ref.)	1.91 (1.18-3.08)	1.91 (1.15-3.16)	2.52 (1.51-4.19)	1.69 (1.27-2.24)
Model 3[+]	(Ref.)	1.84 (1.12-3.00)	1.84 (1.10-3.09)	2.37 (1.40-4.00)	1.61 (1.19-2.16)

[#] Adjusted for age, sex, race, field center, waist circumference

[*] Adjusted for age, sex, race, field center, waist circumference, systolic BP, anti-hypertensive medications, HDL, LDL, triglycerides, CRP, fasting glucose, hypoglycemic medications

[+]Adjusted for age, sex, race, field center, waist circumference, systolic BP, anti-hypertensive medications, HDL, LDL, triglycerides, CRP, fasting glucose, hypoglycemic medications, diastolic BP, grip strength, physical activity, heart rate

P-values for interaction per doubling:
Model 1: p=0.96
Model 2: p=1.0
Model 3: p=0.83