Electronic Supplementary Material (ESM)

Tables

ESM Table 1. Baseline characteristics of participants in the VITAL-DKD trial, by follow-up status

ESM Table 2. Concentrations of serum IL-6, hsCRP, and NT-proBNP at baseline and follow-up, among entire analytic population

ESM Table 3. Effects of vitamin D_3 on serum concentrations of IL-6, hsCRP, and NT-proBNP among highly adherent participants

ESM Table 4. Effects of *n*-3 fatty acids on serum concentrations of IL-6, hsCRP, and NT-proBNP among highly adherent participants

ESM Table 5. Effects of vitamin D_3 on serum concentrations of IL-6 across pre-specified subgroups

ESM Table 6. Effects of vitamin D_3 on serum concentrations of hsCRP across pre-specified subgroups

ESM Table 7. Effects of vitamin D_3 on serum concentrations of NT-proBNP across pre-specified subgroups

ESM Table 8. Effects of *n*-3 fatty acids on serum concentrations of IL-6 across pre-specified subgroups

ESM Table 9. Effects of *n*-3 fatty acids on serum concentrations of hsCRP across pre-specified subgroups

ESM Table 10. Effects of *n*-3 fatty acids on serum concentrations of NT-proBNP across pre-specified subgroups

Figures

ESM Fig. 1. Correlation between IL-6, hsCRP, and NT-proBNP measurements after immediate processing versus upon processing after being frozen for 24 hours

ESM Fig. 2. CONSORT Flow Diagram for the Vitamin D and Omega-3 Trial to Prevent and Treat Diabetic Kidney Disease (VITAL-DKD)

ESM Fig. 3. Forest plot depicting effects of vitamin D_3 on serum concentrations of IL-6 across pre-specified subgroups (corresponding to ESM Table 5)

ESM Fig. 4. Forest plot depicting effects of vitamin D_3 on serum concentrations of hsCRP across pre-specified subgroups (corresponding to ESM Table 6)

ESM Fig. 5. Forest plot depicting effects of vitamin D_3 on serum concentrations of NT-proBNP across pre-specified subgroups (corresponding to ESM Table 7)

ESM Fig. 6. Forest plot depicting effects of *n*-3 fatty acids on serum concentrations of IL-6 across pre-specified subgroups (corresponding to ESM Table 8)

ESM Fig. 7. Forest plot depicting effects of *n*-3 fatty acids on serum concentrations of hsCRP across pre-specified subgroups (corresponding to ESM Table 9)

ESM Fig. 8. Forest plot depicting effects of *n*-3 fatty acids on serum concentrations of NT-proBNP across pre-specified subgroups (corresponding to ESM Table 10)

ESM Table 1. Baseline characteristics of participants in the VITAL-DKD trial, by follow-up status

Characteristic	No follow-up measurements	At least 1 follow-up measurement
N	222	1090
Demographics		
Female sex	116 (52)	493 (45)
Age, years	66.9 (8.2)	67.7 (6.6)
Race & ethnicity (N = 1284)		
Non-Hispanic white	129 (59)	728 (68)
Black	55 (25)	223 (21)
Hispanic	13 (6)	62 (6)
Asian/Pacific Islander	8 (4)	27 (3)
American Indian/Alaskan Native	1 (0)	12 (1)
Greater than high school education	172 (77)	927 (85)
Medical history and lifestyle		
Duration of diabetes, years		
< 1	4 (2)	38 (3)
1-2	36 (16)	141 (13)
3-5	46 (21)	244 (22)
6-10	59 (27)	301 (28)
11-20	49 (22)	266 (24)
> 20	27 (12)	97 (9)
Current smoking	20 (9)	59 (5)
Current alcohol use[a]	100 (47)	594 (55)
Medication and supplement use at randomization		
Glucose-lowering medications		
Biguanides	141 (64)	748 (69)
Sulfonylureas	75 (34)	318 (29)
Insulin	50 (23)	208 (19)
Thiazolidinediones	17 (8)	107 (10)
DPP-4 inhibitors	21 (9)	94 (9)
GLP1 receptor agonists	10 (5)	38 (3)
Antihypertensive medications	176 (79)	869 (81)
Number of classes	1.5 (1.2)	1.4 (1.2)
ACE inhibitor or ARB	121 (55)	682 (63)
ACE inhibitors	80 (36)	485 (44)
Diuretics	70 (32)	294 (27)
β-blockers	65 (29)	230 (21)
Calcium channel blockers	54 (24)	221 (20)
ARBs	44 (20)	216 (20)
Mineralocorticoid receptor antagonists	0 (0)	9 (1)
Cholesterol-lowering medication	135 (62)	775 (73)
Supplemental vitamin D (≤ 800 IU/day) at randomization	63 (28)	473 (43)

Supplemental calcium (≤ 1200 mg/day) at randomization	44 (20)	268 (25)
Physical characteristics		
Body mass index, kg/m^2	32.6 (7.4)	31.2 (6.6)
Laboratory values at baseline		
Serum creatinine (μmol/l)	73.7 (24.0)	76.2 (23.7)
Cystatin-C (mg/l)	0.9 (0.3)	0.9 (0.3)
Baseline eGFR (ml/min/1.73m^2)	87.6 (23.7)	85.5 (21.8)
Urine ACR (mg/mmol Cr), median (IQR)	0.41 (0.14-0.96)	0.32 (0.06-0.81)
25(OH)D, nmol/l	66.6 (25.8)	75.7 (25.0)
< 50 nmol/l	61 (28)	165 (16)
50 to < 75 nmol/l	79 (37)	377 (36)
≥ 75 nmol/l	76 (35)	499 (48)
IL-6 (pg/ml), median (IQR)	1.2 (0.8-1.8)	0.9 (0.7-1.5)
hsCRP (mg/l), median (IQR)	2.6 (1.2-5.4)	1.8 (0.8-4.1)
NT-proBNP (ng/l), median (IQR)	287 (104-717)	260 (111-613)

Entries are mean (SD) for continuous variables and N (%) for categorical variables, except as noted. Percentages are calculated as percent of non-missing responses.

[a] Daily, weekly, or monthly use of alcohol.

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; eGFR = estimated glomerular filtration rate; ACR = albumin creatinine ratio; 25(OH)D = 25-hydroxyvitamin D; IL-6 = interleukin-6; hsCRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

ESM Table 2. Concentrations of serum IL-6, hsCRP, and NT-proBNP at baseline and follow-up, among entire analytic population (N = 1312)

Biomarker	N available measurements	Geometric mean (SD)[a]	Change from baseline to year 5 (ratio), geometric mean (SD)
IL-6 (pg/ml)			
Baseline	1302	1.21 (3.02)	--
Year 2	988	1.35 (4.02)	1.11 (4.41)
Year 5	933	1.28 (3.67)	1.06 (4.46)
hsCRP (mg/l)			
Baseline	1306	1.94 (3.13)	--
Year 2	988	1.95 (3.17)	1.01 (2.70)
Year 5	916	1.89 (3.37)	0.97 (2.86)
NT-proBNP (ng/l)			
Baseline	1306	262 (3.7)	--
Year 2	989	315.2 (3.8)	1.2 (2.75)
Year 5	934	406.6 (4.1)	1.55 (3.15)

[a] Values incorporate multiple imputation.

IL-6 = interleukin-6; hsCRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

ESM Table 3. Effects of vitamin D_3 on serum concentrations of IL-6, hsCRP, and NT-proBNP among highly adherent participants (N = 1032)[a]

	Vitamin D_3			Placebo			Difference in change from baseline[b]	
Biomarker	N	Geometric mean (SD)	Change from baseline (ratio), geometric mean (SD)	N	Geometric mean (SD)	Change from baseline (ratio), geometric mean (SD)	Ratio of change from baseline, active to placebo (95% CI)	p-value
IL-6 (pg/ml)								
Baseline	539	1.11 (2.87)	1.00 (Ref.)	484	1.13 (2.59)	1.00 (Ref.)	1.00 (Ref.)	
Year 2	481	1.27 (3.75)	1.16 (3.98)	414	1.20 (3.58)	1.1 (4.04)	1.05 (0.87, 1.27)	
Year 5	460	1.17 (3.50)	1.05 (4.19)	404	1.26 (3.42)	1.15 (4.04)	0.92 (0.76, 1.11)	0.36
hsCRP (mg/l)								
Baseline	543	1.79 (3.18)	1.00 (Ref.)	485	1.85 (2.98)	1.00 (Ref.)	1.00 (Ref.)	
Year 2	482	1.76 (3.17)	1.01 (2.56)	413	1.87 (2.91)	1.03 (2.76)	0.98 (0.86, 1.11)	
Year 5	456	1.60 (3.22)	0.92 (2.61)	392	1.92 (3.36)	1.05 (3.02)	0.88 (0.77, 1.01)	0.15
NT-proBNP (ng/l)								
Baseline	543	245.9 (3.6)	1.00 (Ref.)	484	267.0 (3.4)	1.00 (Ref.)	1.00 (Ref.)	
Year 2	481	318.4 (3.9)	1.27 (2.7)	415	289.3 (3.5)	1.12 (2.7)	1.14 (0.99, 1.30)	
Year 5	461	409.3 (3.9)	1.69 (3.07)	404	359.2 (3.8)	1.36 (2.94)	1.24 (1.09, 1.43)	0.0067

[a] High adherence was defined as adherence to at least two-thirds of study medications.

[b] From a linear mixed model that includes adjustment for age, sex, baseline eGFR, and baseline urine creatinine to albumin ratio, and accounts for missing data using multiple imputation

p-value comes from a global test of the ratio of change from baseline at Years 2 and 5.

IL-6 = interleukin-6; hsCRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; Ref. = reference group

ESM Table 4. Effects of *n*-3 fatty acids on serum concentrations of IL-6, hsCRP, and NT-proBNP among highly adherent participants (N = 1032)[a]

	n-3 fatty acids			Placebo			Difference in change from baseline[b]	
Biomarker	N	Geometric mean (SD)	Change from baseline (ratio), geometric mean (SD)	N	Geometric mean (SD)	Change from baseline (ratio), geometric mean (SD)	Ratio of change from baseline, active to placebo (95% CI)	p-value
IL-6 (pg/ml)								
Baseline	515	1.13 (2.67)	1.00 (Ref.)	509	1.13 (2.87)	1.00 (Ref.)	1.00 (Ref.)	
Year 2	455	1.17 (3.09)	1.07 (3.33)	441	1.31 (4.24)	1.18 (4.74)	0.91 (0.75, 1.11)	
Year 5	438	1.26 (3.72)	1.13 (4.16)	425	1.17 (3.21)	1.05 (4.12)	1.06 (0.87, 1.30)	0.37
hsCRP (mg/l)								
Baseline	517	1.91 (3.06)	1.00 (Ref.)	512	1.75 (3.12)	1.00 (Ref.)	1.00 (Ref.)	
Year 2	456	1.86 (3.11)	1 (2.6)	440	1.81 (3.06)	1.04 (2.71)	0.95 (0.84, 1.09)	
Year 5	428	1.72 (3.31)	0.92 (2.81)	419	1.79 (3.27)	1.05 (2.8)	0.87 (0.76, 0.99)[c]	0.11
NT-proBNP (ng/l)								
Baseline	516	280.0 (3.4)	1.00 (Ref.)	512	231.4 (3.6)	1.00 (Ref.)	1.00 (Ref.)	
Year 2	456	363.1 (3.7)	1.25 (2.73)	441	251.9 (3.7)	1.15 (2.74)	1.08 (0.95, 1.23)	
Year 5	438	428.1 (3.9)	1.51 (2.91)	426	346.5 (3.8)	1.56 (3.18)	0.98 (0.85, 1.12)	0.29

[a] High adherence was defined as adherence to at least two-thirds of study medications.
[b] From a linear mixed model that includes adjustment for age, sex, baseline eGFR, and baseline urine creatinine to albumin ratio, and accounts for missing data using multiple imputation
[c] p-value = 0.04 for ratio of change from baseline at Year 5

p-value comes from a global test of the ratio of change from baseline at Years 2 and 5.

IL-6 = interleukin-6; hsCRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; Ref. = reference group

ESM Table 5. Effects of vitamin D_3 on serum concentrations of IL-6 across pre-specified subgroups

Category	Vitamin D_3		Placebo		Ratio of change (95% CI)	p-value for interaction[b]
	N at baseline	Geometric mean (SD) change[a]	N at baseline	Geometric mean (SD) change[a]		
Overall		1.03 (4.45)		1.09 (4.43)	0.96 (0.79, 1.16)	
Race						
White	451	1.1 (4.11)	406	1.08 (4.21)	1.01 (0.80, 1.27)	0.74
Black	148	0.9 (5.54)	130	1.07 (4.57)	0.86 (0.57, 1.31)	
Baseline UACR (mg/mmol Cr)						
< 3	627	1.04 (4.54)	557	1.09 (4.49)	0.96 (0.79, 1.18)	0.88
≥ 3	75	0.96 (3.79)	52	1.07 (3.89)	0.91 (0.48, 1.76)	
Baseline 25(OH)D (nmol/l)						
< 50	128	0.93 (4.26)	98	0.98 (3.66)	0.95 (0.60, 1.51)	0.80
50 to < 75	244	1.02 (4.36)	212	1.15 (4.60)	0.89 (0.66, 1.21)	
≥ 75	300	1.10 (4.62)	275	1.08 (4.60)	1.02 (0.77, 1.35)	
Baseline eGFR (ml/min/1.73m^2)						
≥ 60	612	1.02 (4.35)	531	1.11 (4.17)	0.93 (0.76, 1.14)	0.40
< 60	89	1.14 (5.44)	76	0.95 (6.41)	1.18 (0.70, 1.98)	
Body mass index (kg/m^2)						
< 25	87	1.07 (3.32)	87	0.87 (4.65)	1.23 (0.76, 1.99)	0.44
25 to < 30	228	0.97 (4.31)	205	1.15 (4.56)	0.85 (0.61, 1.17)	
≥ 30	364	1.07 (4.83)	294	1.11 (4.27)	0.97 (0.74, 1.27)	
Baseline IL-6 (pg/ml)						
< 0.8	248	1.55 (2.50)	217	1.72 (3.48)	0.91 (0.68, 1.22)	0.70
0.8 to < 1.3	217	1.14 (2.93)	179	1.30 (3.50)	0.88 (0.63, 1.24)	
≥ 1.3	231	0.61 (7.94)	210	0.58 (5.36)	1.07 (0.75, 1.51)	
n-3 fatty acid randomization						
Placebo	333	0.97 (4.47)	320	1.07 (4.69)	0.89 (0.68, 1.17)	0.49
n-3 FA	370	1.10 (4.44)	289	1.10 (4.16)	1.02 (0.79, 1.32)	

[a] Changes presented are from baseline to year 5.

[b] p-values are a test of the ratio of changes at year

UACR = urine albumin to creatinine ratio; 25(OH)D = 25-hydroxyvitamin D; eGFR = estimated glomerular filtration rate; IL-6 = interleukin-6.

ESM Table 6. Effects of vitamin D_3 on serum concentrations of hsCRP across pre-specified subgroups

Category	Vitamin D_3		Placebo		Ratio of change (95% CI)	p-value for interaction[b]
	N at baseline	Geometric mean (SD) change[a]	N at baseline	Geometric mean (SD) change[a]		
Overall		0.93 (2.69)		1.02 (3.04)	0.91 (0.80, 1.03)	
Race						
White	451	0.94 (2.67)	406	1.05 (3.23)	0.90 (0.77, 1.05)	0.88
Black	148	0.89 (2.52)	130	0.93 (2.55)	0.97 (0.74, 1.27)	
Baseline UACR (mg/mmol Cr)						
< 3	627	0.92 (2.64)	557	0.99 (3.02)	0.93 (0.81, 1.07)	0.18
≥ 3	75	0.98 (3.05)	52	1.43 (3.08)	0.69 (0.46, 1.05)	
Baseline 25(OH)D (nmol/l)						
< 50	128	0.84 (2.63)	98	0.91 (2.74)	0.91 (0.67, 1.26)	0.84
50 to < 75	244	0.91 (2.60)	212	1.05 (3.06)	0.87 (0.71, 1.06)	
≥ 75	300	0.98 (2.78)	275	1.04 (3.13)	0.94 (0.78, 1.14)	
Baseline eGFR (ml/min/1.73m^2)						
≥ 60	612	0.94 (2.59)	531	1.01 (3.00)	0.94 (0.82, 1.07)	0.23
< 60	89	0.84 (3.36)	76	1.15 (3.27)	0.74 (0.51, 1.08)	
Body mass index (kg/m^2)						
< 25	87	0.93 (2.91)	87	1.17 (3.21)	0.80 (0.57, 1.12)	0.70
25 to < 30	228	0.95 (2.68)	205	1.03 (3.14)	0.92 (0.74, 1.15)	
≥ 30	364	0.91 (2.64)	294	0.98 (2.91)	0.93 (0.79, 1.11)	
Baseline hsCRP (mg/l)						
< 1.2	234	1.38 (2.36)	192	1.65 (2.52)	0.84 (0.68, 1.04)	0.74
1.2 to < 3.4	230	0.97 (2.49)	214	1.03 (2.98)	0.93 (0.76, 1.15)	
≥ 3.4	235	0.59 (2.71)	201	0.64 (3.01)	0.93 (0.73, 1.19)	
n-3 fatty acid randomization						
Placebo	333	1.04 (2.70)	320	1.04 (3.11)	1.00 (0.82, 1.22)	0.21
n-3 FA	370	0.83 (2.64)	289	1.00 (2.96)	0.84 (0.70, 1.01)	

[a] Changes presented are from baseline to year 5.

[b] p-values are a test of the ratio of changes at year 5.

UACR = urine albumin to creatinine ratio; 25(OH)D = 25-hydroxyvitamin D; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein.

ESM Table 7. Effects of vitamin D_3 on serum concentrations of NT-proBNP across pre-specified subgroups

Category	Vitamin D_3		Placebo		Ratio of change (95% CI)	p-value for interaction[b]
	N at baseline	Geometric mean (SD) change[a]	N at baseline	Geometric mean (SD) change[a]		
Overall		1.72 (3.27)		1.39 (3.00)	1.24 (1.09, 1.41)	
Race						
White	451	1.64 (3.06)	406	1.40 (2.91)	1.17 (1.00, 1.38)	0.47
Black	148	1.87 (3.57)	130	1.30 (3.32)	1.43 (1.07, 1.90)	
Baseline UACR (mg/mmol Cr)						
< 3	627	1.66 (3.22)	557	1.38 (2.97)	1.19 (1.04, 1.37)	0.16
≥ 3	75	2.39 (3.52)	52	1.42 (3.38)	1.67 (1.08, 2.57)	
Baseline 25(OH)D (nmol/l)						
< 50	128	2.37 (3.60)	98	1.37 (3.28)	1.74 (1.26, 2.41)	0.06
50 to < 75	244	1.71 (3.06)	212	1.44 (3.04)	1.19 (0.95, 1.49)	
≥ 75	300	1.52 (3.23)	275	1.36 (2.88)	1.12 (0.93, 1.34)	
Baseline eGFR (ml/min/1.73m^2)						
≥ 60	612	1.65 (3.23)	531	1.35 (2.94)	1.22 (1.07, 1.40)	0.55
< 60	89	2.30 (3.39)	76	1.65 (3.40)	1.38 (0.95, 2.00)	
Body mass index (kg/m^2)						
< 25	87	1.63 (3.22)	87	1.31 (2.42)	1.25 (0.89, 1.74)	0.67
25 to < 30	228	1.58 (3.06)	205	1.38 (3.18)	1.15 (0.93, 1.42)	
≥ 30	364	1.84 (3.41)	294	1.42 (3.06)	1.30 (1.08, 1.56)	
Baseline NT-proBNP (ng/l)						
< 150	254	2.66 (3.36)	182	2.24 (3.04)	1.18 (0.95, 1.47)	0.95
150 to < 450	210	1.60 (3.12)	221	1.35 (2.80)	1.19 (0.97, 1.48)	
≥ 450	236	1.15 (2.81)	203	0.93 (2.70)	1.24 (1.00, 1.54)	
n-3 fatty acid randomization						
Placebo	333	1.67 (3.32)	320	1.42 (3.06)	1.18 (0.99, 1.41)	0.43
n-3 FA	370	1.77 (3.22)	289	1.35 (2.94)	1.30 (1.09, 1.57)	

[a] Changes presented are from baseline to year 5.

[b] p-values are a test of the ratio of changes at year 5.

UACR = urine albumin to creatinine ratio; 25(OH)D = 25-hydroxyvitamin D; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

ESM Table 8. Effects of *n*-3 fatty acids on serum concentrations of IL-6 across pre-specified subgroups

Category	*n*-3 fatty acids		Placebo		Ratio of change (95% CI)	p-value for interaction[b]
	N at baseline	Geometric mean (SD) change[a]	N placebo	Geometric mean (SD) change[a]		
Overall		1.10 (4.31)		1.02 (4.58)	1.08 (0.89, 1.31)	
Baseline EPA+DHA index (%)						
≤ 2.2	332	1.04 (3.86)	347	0.92 (5.03)	1.13 (0.87, 1.47)	0.68
> 2.2	308	1.18 (4.80)	292	1.12 (4.13)	1.04 (0.80, 1.37)	
Baseline UACR (mg/mmol Cr)						
< 3	590	1.11 (4.35)	594	1.02 (4.68)	1.07 (0.88, 1.31)	0.83
≥ 3	68	1.06 (4.00)	59	0.94 (3.63)	1.15 (0.60, 2.21)	
Baseline fish intake						
< 1.5 servings/wk	354	1.11 (4.41)	329	0.99 (4.13)	1.13 (0.87, 1.45)	0.66
≥ 1.5 servings/wk	295	1.09 (4.22)	310	1.04 (5.00)	1.03 (0.77, 1.38)	
Body mass index (kg/m^2)						
< 25	94	0.87 (3.72)	80	1.08 (4.28)	0.79 (0.48, 1.30)	0.38
25 to < 30	213	1.12 (3.70)	220	1.00 (5.20)	1.12 (0.81, 1.54)	
≥ 30	328	1.16 (4.89)	330	1.01 (4.27)	1.16 (0.89, 1.51)	
Baseline IL-6 (pg/ml)						
< 0.8	226	1.64 (2.97)	239	1.62 (2.94)	1.00 (0.74, 1.36)	0.45
0.8 to < 1.3	203	1.22 (3.04)	193	1.20 (3.36)	1.00 (0.73, 1.38)	
≥ 1.3	226	0.68 (6.49)	215	0.52 (6.77)	1.31 (0.93, 1.84)	
Vitamin D randomization						
Placebo	289	1.10 (4.16)	320	1.07 (4.69)	1.01 (0.77, 1.32)	0.49
Vitamin D	370	1.10 (4.44)	333	0.96 (4.47)	1.15 (0.89, 1.50)	

[a] Changes presented are from baseline to year 5.

[b] p-values are a test of the ratio of changes at year 5.

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; UACR = urine albumin to creatinine ratio; IL-6 = interleukin-6.

ESM Table 9. Effects of *n*-3 fatty acids on serum concentrations of hsCRP across pre-specified subgroups

Category	*n*-3 fatty acids		Placebo		Ratio of change (95% CI)	p-value for interaction[b]
	N at baseline	Geometric mean (SD) change[a]	N at baseline	Geometric mean (SD) change[a]		
Overall		0.90 (2.79)		1.04 (2.90)	0.87 (0.76, 0.98)	
Baseline EPA+DHA index (%)						
≤ 2.2	332	0.88 (2.64)	347	1.05 (2.97)	0.84 (0.71, 0.99)	0.62
> 2.2	308	0.92 (2.96)	292	1.03 (2.84)	0.89 (0.75, 1.06)	
Baseline UACR (mg/mmol Cr)						
< 3	590	0.89 (2.75)	594	1.02 (2.88)	0.87 (0.77, 0.99)	0.75
≥ 3	68	1.04 (3.13)	59	1.28 (3.04)	0.81 (0.54, 1.22)	
Baseline fish intake						
< 1.5 servings/wk	354	0.94 (2.87)	329	1.01 (2.82)	0.91 (0.77, 1.08)	0.40
≥ 1.5 servings/wk	295	0.87 (2.71)	310	1.07 (2.97)	0.82 (0.68, 0.98)	
Body mass index (kg/m^2)						
< 25	94	0.92 (2.92)	80	1.20 (3.22)	0.76 (0.55, 1.07)	0.73
25 to < 30	213	0.92 (2.86)	220	1.05 (2.92)	0.86 (0.70, 1.07)	
≥ 30	328	0.89 (2.72)	330	1.00 (2.80)	0.89 (0.75, 1.07)	
Baseline hsCRP (mg/l)						
< 1.2	207	1.41 (2.43)	219	1.59 (2.44)	0.89 (0.73, 1.08)	0.97
1.2 to < 3.4	226	0.93 (2.75)	218	1.08 (2.69)	0.86 (0.70, 1.05)	
≥ 3.4	223	0.58 (2.66)	213	0.65 (3.04)	0.89 (0.70, 1.12)	
Vitamin D randomization						
Placebo	289	1.00 (2.96)	320	1.04 (3.11)	0.96 (0.79, 1.16)	0.21
Vitamin D	370	0.83 (2.64)	333	1.04 (2.70)	0.80 (0.67, 0.95)	

[a] Changes presented are from baseline to year 5.
[b] p-values are a test of the ratio of changes at year 5.

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; UACR = urine albumin to creatinine ratio; hsCRP = high-sensitivity C-reactive protein.

ESM Table 10. Effects of *n*-3 fatty acids on serum concentrations of NT-proBNP across pre-specified subgroups

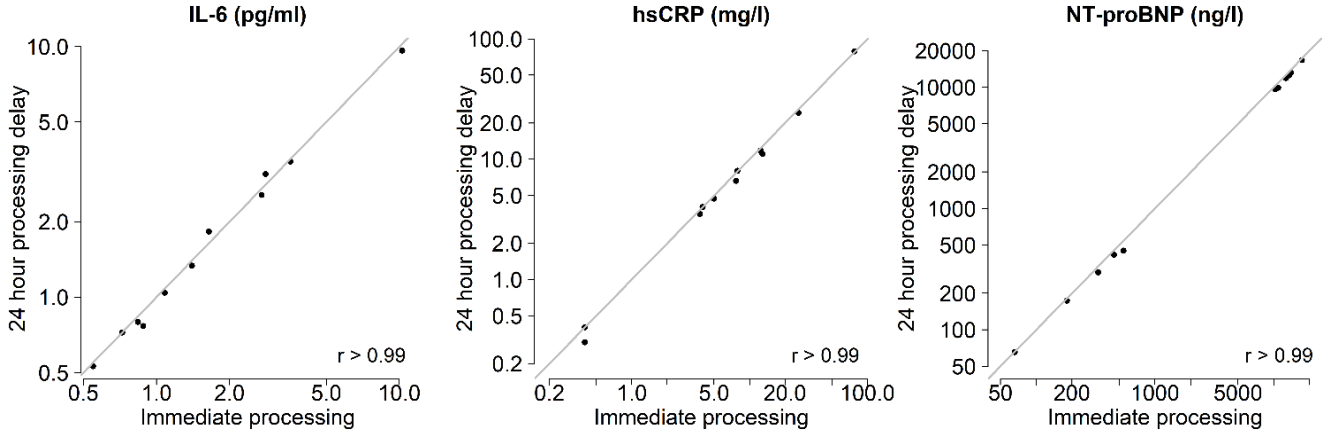
Category	*n*-3 fatty acids		Placebo		Ratio of change (95% CI)	p-value for interaction[b]
	N at baseline	Geometric mean (SD) change[a]	N at baseline	Geometric mean (SD) change[a]		
Overall		1.57 (3.12)		1.54 (3.20)	1.02 (0.89, 1.17)	
Baseline EPA+DHA index (%)						
≤ 2.2	332	1.63 (3.16)	347	1.48 (3.18)	1.10 (0.91, 1.33)	0.23
> 2.2	308	1.52 (3.08)	292	1.61 (3.22)	0.94 (0.79, 1.13)	
Baseline UACR (mg/mmol Cr)						
< 3	590	1.51 (3.05)	594	1.54 (3.18)	0.98 (0.85, 1.13)	0.10
≥ 3	68	2.29 (3.54)	59	1.59 (3.47)	1.43 (0.93, 2.20)	
Baseline fish intake						
< 1.5 servings/wk	354	1.60 (3.05)	329	1.55 (3.13)	1.01 (0.85, 1.20)	0.86
≥ 1.5 servings/wk	295	1.55 (3.19)	310	1.54 (3.27)	1.03 (0.86, 1.24)	
Body mass index (kg/m^2)						
< 25	94	1.49 (2.61)	80	1.42 (3.09)	1.05 (0.75, 1.48)	0.60
25 to < 30	213	1.42 (3.02)	220	1.54 (3.22)	0.93 (0.74, 1.16)	
≥ 30	328	1.70 (3.33)	330	1.58 (3.22)	1.08 (0.89, 1.31)	
Baseline NT-proBNP (ng/l)						
< 150	204	2.36 (3.26)	232	2.59 (3.21)	0.91 (0.73, 1.13)	0.28
150 to < 450	225	1.57 (2.84)	206	1.37 (3.09)	1.14 (0.92, 1.41)	
≥ 450	227	1.10 (2.91)	212	0.99 (2.62)	1.11 (0.89, 1.38)	
Vitamin D randomization						
Placebo	289	1.35 (2.94)	320	1.42 (3.06)	0.96 (0.79, 1.16)	0.43
Vitamin D	370	1.77 (3.22)	333	1.67 (3.32)	1.06 (0.89, 1.26)	

[a] Changes presented are from baseline to year 5.

[b] p-values are a test of the ratio of changes at year 5.

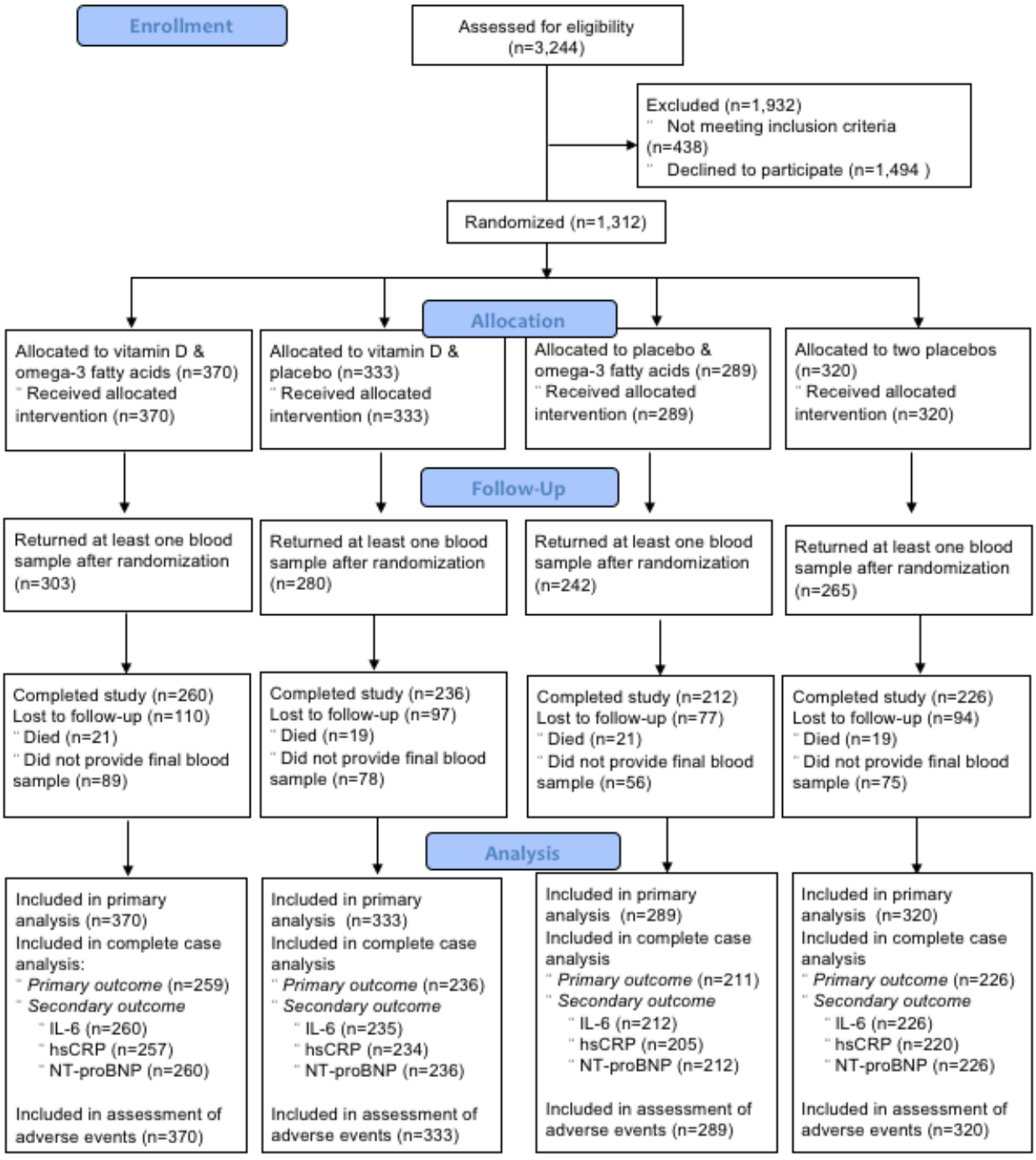
EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; UACR = urine albumin to creatinine ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

ESM Fig. 1. Correlation between IL-6, hsCRP, and NT-proBNP measurements after immediate processing versus upon processing after being frozen for 24 hours

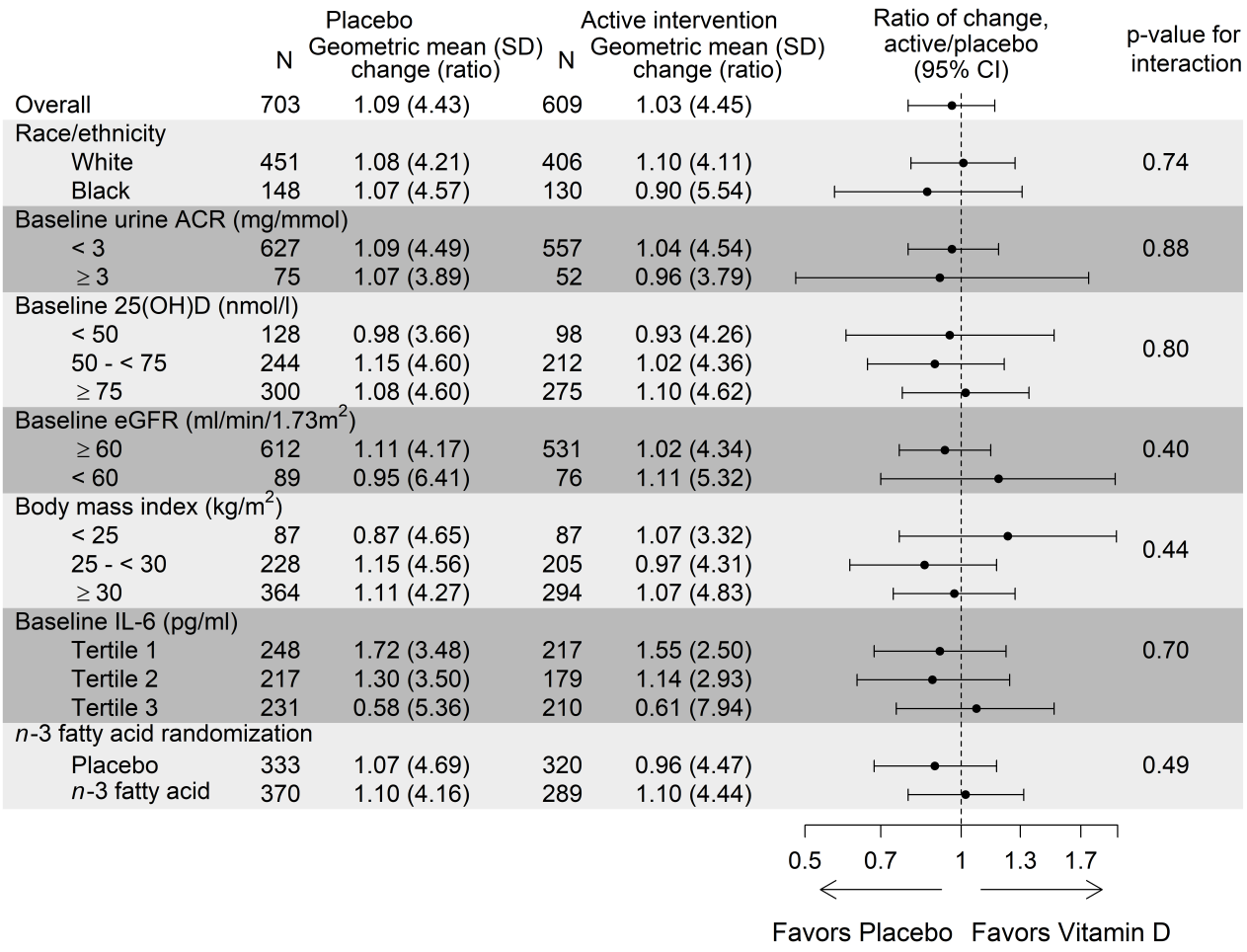


IL-6 = interleukin-6; hsCRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

ESM Fig. 2. CONSORT Flow Diagram for the Vitamin D and Omega-3 Trial to Prevent and Treat Diabetic Kidney Disease (VITAL-DKD)

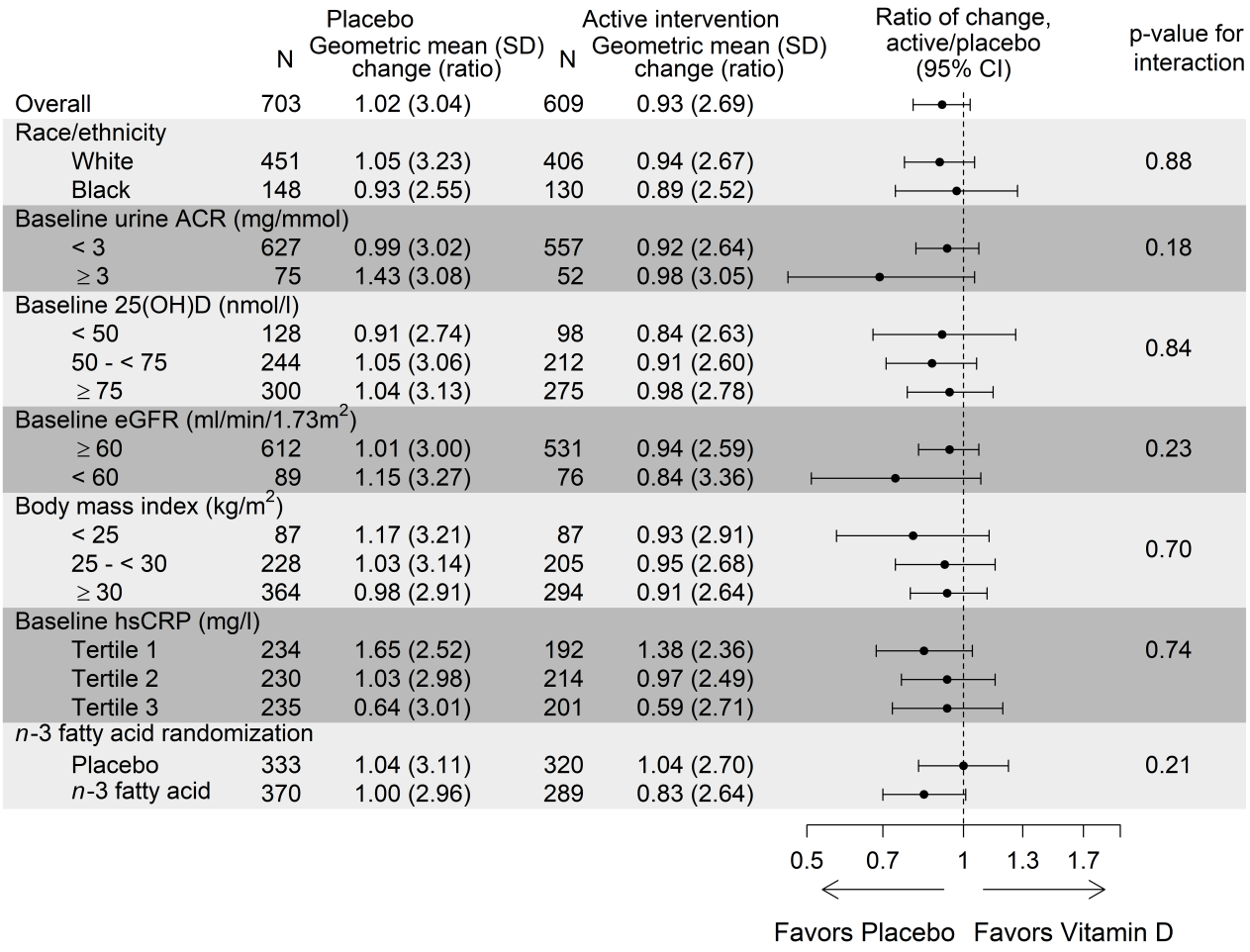


ESM Fig. 3. Forest plot depicting effects of vitamin D_3 on serum concentrations of IL-6 across pre-specified subgroups (corresponding to ESM Table 5)



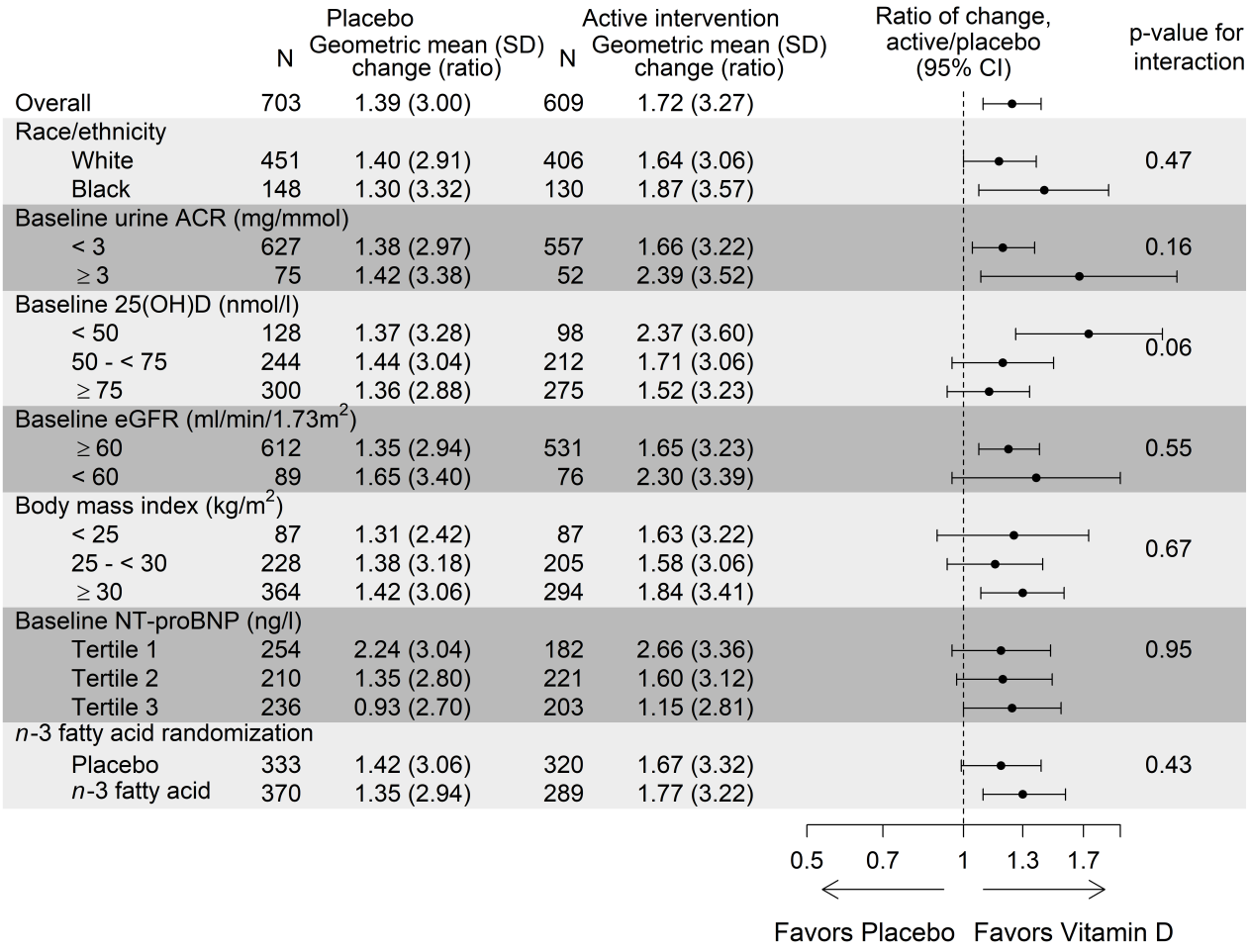
ACR = albumin to creatinine ratio; 25(OH)D = 25-hydroxyvitamin D; eGFR = estimated glomerular filtration rate; IL-6 = interleukin-6.

ESM Fig. 4. Forest plot depicting effects of vitamin D_3 on serum concentrations of hsCRP across pre-specified subgroups (corresponding to ESM Table 6)



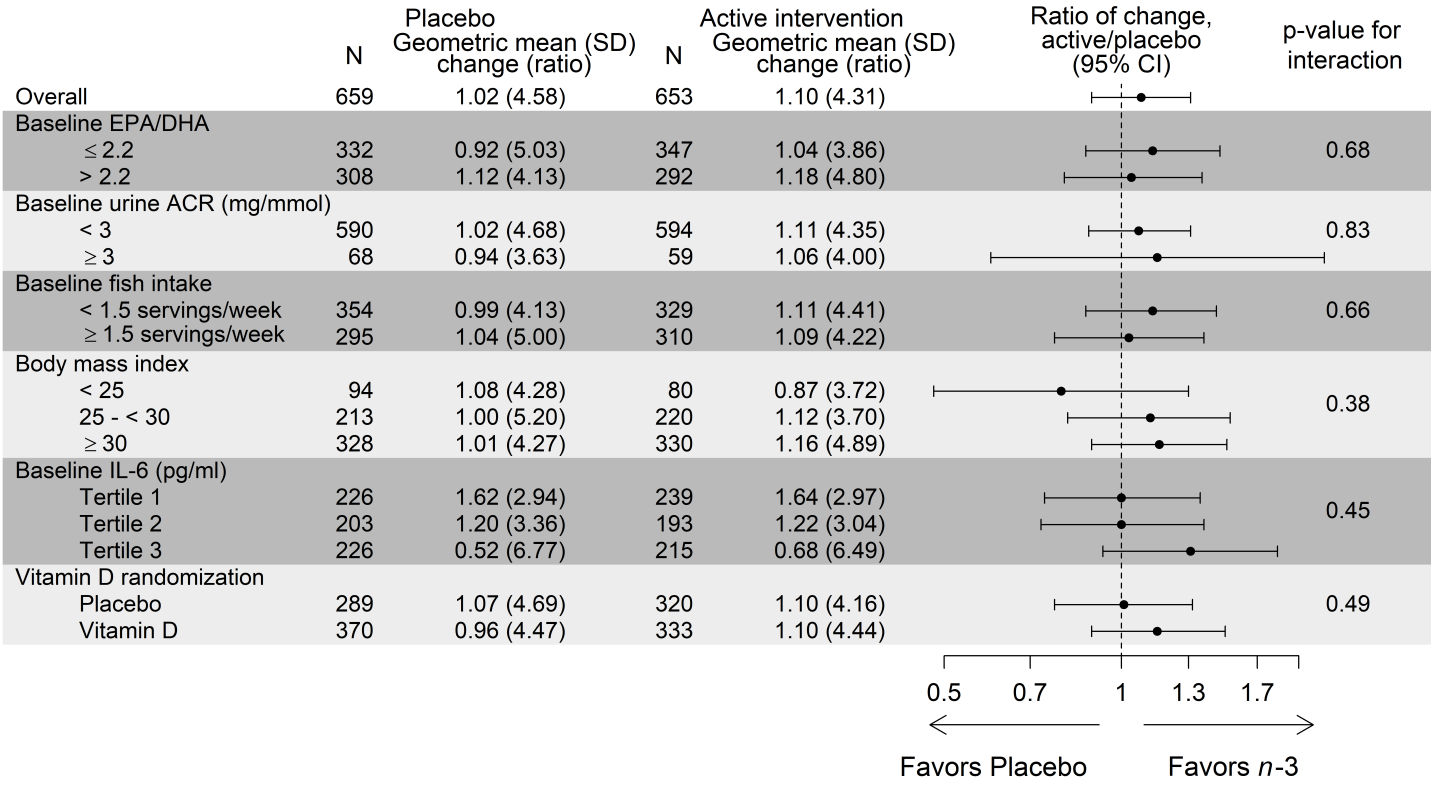
ACR = albumin to creatinine ratio; 25(OH)D = 25-hydroxyvitamin D; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein.

ESM Fig. 5. Forest plot depicting effects of vitamin D_3 on serum concentrations of NT-proBNP across pre-specified subgroups (corresponding to ESM Table 7)



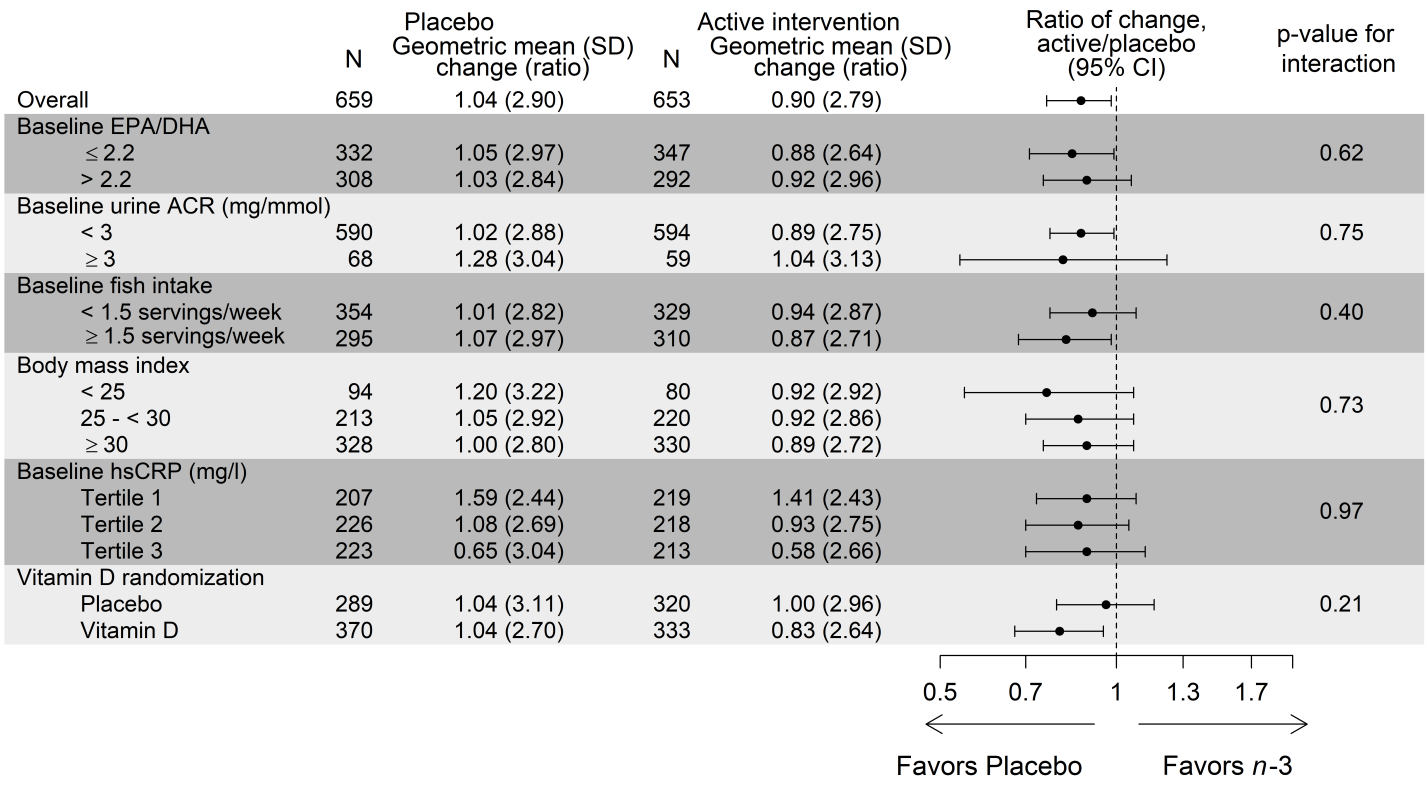
ACR = urine albumin to creatinine ratio; 25(OH)D = 25-hydroxyvitamin D; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

ESM Fig. 6. Forest plot depicting effects of *n*-3 fatty acids on serum concentrations of IL-6 across pre-specified subgroups (corresponding to ESM Table 8)



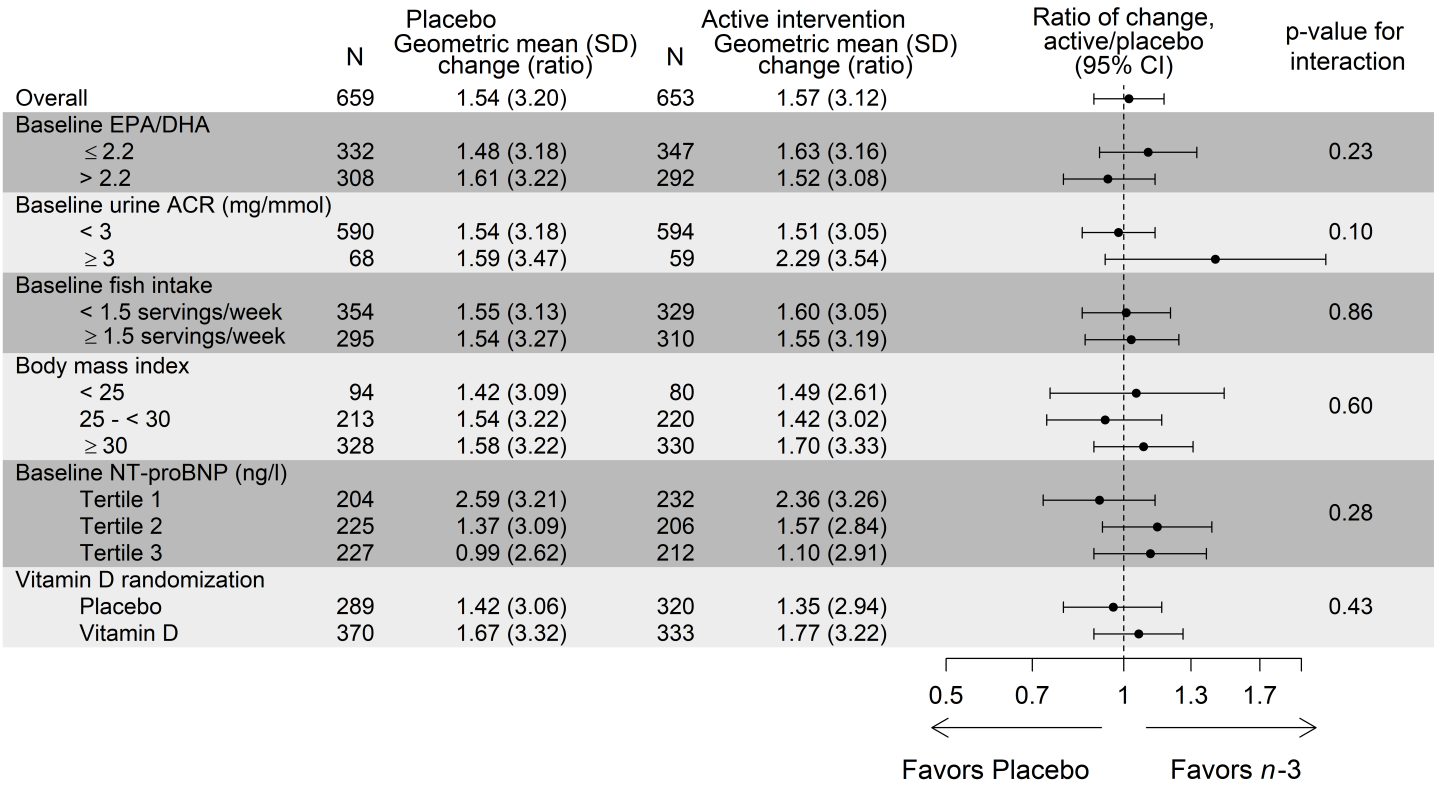
EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; ACR = albumin to creatinine ratio; IL-6 = interleukin-6.

ESM Fig. 7. Forest plot depicting effects of *n*-3 fatty acids on serum concentrations of hsCRP across pre-specified subgroups (corresponding to ESM Table 9)



EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; ACR = albumin to creatinine ratio; hsCRP = high-sensitivity C-reactive protein.

ESM Fig. 8. Forest plot depicting effects of *n*-3 fatty acids on serum concentrations of NT-proBNP across pre-specified subgroups (corresponding to ESM Table 10)



EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; ACR = urine to albumin creatinine ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.