

## Supplementary Online Content

Song M, Lee I-M, Manson JE, et al. Effect of supplementation with  $\omega$ -3 fatty acid on risk of colorectal adenomas and serrated polyps in the US general population: a prespecified ancillary study of a randomized clinical trial. *JAMA Oncol*. Published online November 21, 2019. doi:10.1001/jamaoncol.2019.4587

**eFigure.** Flowchart of Colorectal Polyp Identification in VITAL

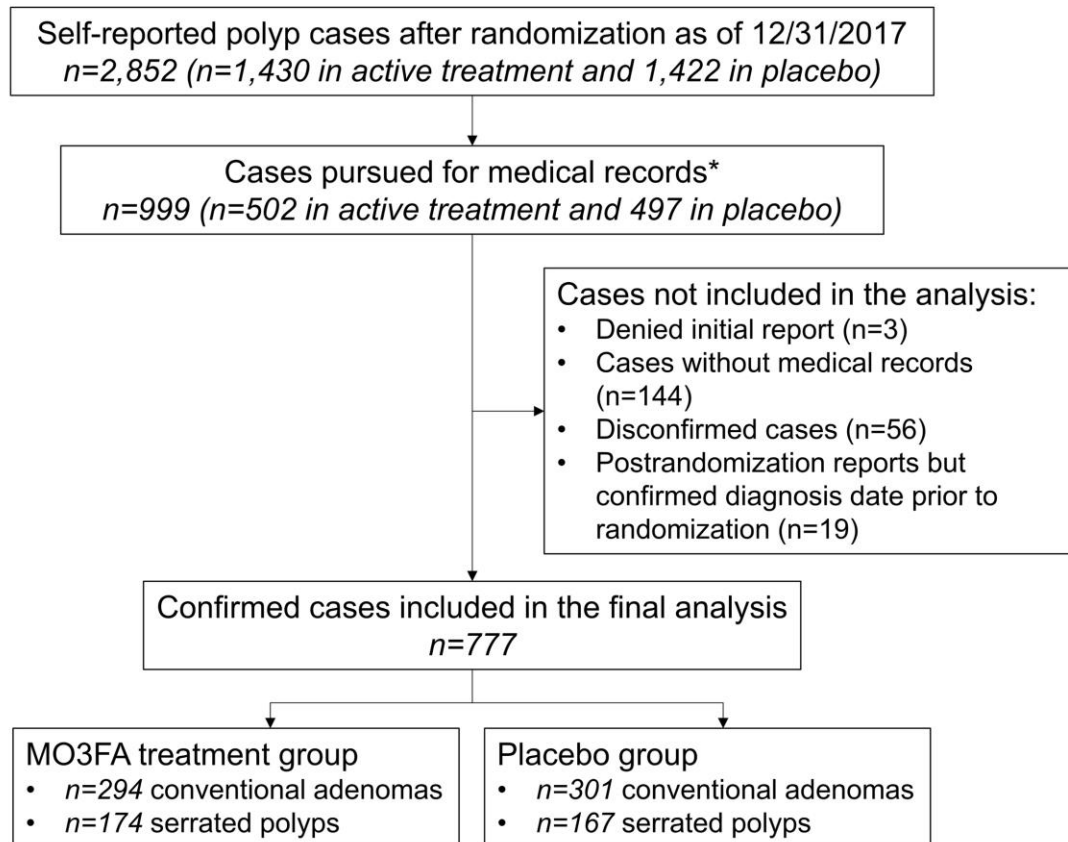
**eTable 1.** Association of Marine Omega-3 Fatty Acid Supplementation With Risk of Conventional Adenomas and Serrated Polyps According to Histopathological Features

**eTable 2.** Stratified Association of Marine Omega-3 Fatty Acid Supplementation With Risk of Conventional Adenoma and Serrated Polyp

**eTable 3.** Baseline Characteristics of Participants According to Race/Ethnicity

This supplementary material has been provided by the authors to give readers additional information about their work.

**eFigure.** Flowchart of Colorectal Polyp Identification in VITAL



\*We only pursued medical record collection for cases who were asked by their doctors to have a repeat colonoscopy/sigmoidoscopy in 5 years or less.

**eTable 1.** Association of Marine Omega-3 Fatty Acid Supplementation With Risk of Conventional Adenomas and Serrated Polyps According to Histopathological Features

	Conventional adenomas			Serrated polyps		
	No. of cases in placebo group	No. of cases in omega-3 group	OR (95% CI) <sup>a</sup>	No. of cases in placebo group	No. of cases in omega-3 group	OR (95% CI) <sup>a</sup>
Size						
<10mm	222	218	0.98 (0.82-1.19)	122	124	1.02 (0.79-1.31)
≥10mm	58	56	0.98 (0.67-1.41)	31	32	1.04 (0.63-1.70)
<i>P</i> for heterogeneity <sup>b</sup>			0.84			0.93
Location						
Proximal colon	149	150	1.01 (0.80-1.27)	57	65	1.14 (0.80-1.63)
Distal colon	74	52	0.71 (0.49-1.01)	37	43	1.17 (0.75-1.81)
Rectum	17	15	0.89 (0.44-1.77)	32	36	1.13 (0.70-1.82)
Multiple location	61	77	1.27 (0.91-1.79)	41	30	0.73 (0.46-1.18)
<i>P</i> for heterogeneity <sup>b</sup>			0.15			0.40
Multiplicity						
Single	159	147	0.93 (0.74-1.16)	80	99	1.24 (0.92-1.66)
Multiple	135	141	1.05 (0.83-1.33)	80	66	0.83 (0.60-1.15)
<i>P</i> for heterogeneity <sup>b</sup>			0.44			0.11
Histology						

Tubular adenoma	262	242	0.93 (0.78-1.11)	-	-
Tubulovillous adenoma	20	23	1.16 (0.64-2.11)	-	-
Villous or high-grade dysplasia	5	13	2.65 (0.95-7.44)	-	-
<i>P</i> for heterogeneity <sup>b</sup>			0.16	-	-

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Logistic regression was adjusted for age, sex, vitamin D treatment assignment, and use of colonoscopy or sigmoidoscopy in the past 10 years prior to randomization.

<sup>b</sup>*P* for heterogeneity was calculated by a case-only analysis.

**eTable 2.** Stratified Association of Marine Omega-3 Fatty Acid Supplementation With Risk of Conventional Adenoma and Serrated Polyp<sup>a</sup>

	Conventional adenomas			Serrated polyps		
	No. of cases in placebo group	No. of cases in omega-3 group	OR (95% CI)	No. of cases in placebo group	No. of cases in omega-3 group	OR (95% CI)
Age, year						
<60	43	36	0.83 (0.53-1.30)	25	26	1.04 (0.60-1.81)
60-69	197	182	0.93 (0.76-1.14)	109	114	1.05 (0.81-1.37)
≥70	61	76	1.26 (0.90-1.77)	33	34	1.01 (0.62-1.64)
<i>P</i> for interaction <sup>b</sup>			0.24			0.99
Sex						
Women	118	133	1.13 (0.88-1.45)	65	84	1.29 (0.93-1.79)
Men	183	161	0.88 (0.71-1.09)	102	90	0.89 (0.67-1.18)
<i>P</i> for interaction <sup>b</sup>			0.14			0.08
Race/ethnicity						
Non-Hispanic white	231	245	1.06 (0.89-1.28)	131	145	1.11 (0.87-1.41)
African American	37	22	0.59 (0.35-1.00)	20	12	0.60 (0.29-1.23)
Others	27	22	0.86 (0.48-1.52)	13	14	1.10 (0.51-2.36)
<i>P</i> for interaction <sup>b</sup>			0.11			0.28
Plasma omega-3 index, %						
<2.5%	106	83	0.76 (0.57-1.02)	59	67	1.12 (0.79-1.60)
≥2.5%	99	114	1.19 (0.90-1.56)	59	61	1.06 (0.74-1.52)

<i>P</i> for interaction <sup>b</sup>			0.03			0.83
Total fish intake, serving/week						
<1.5	156	145	0.92 (0.73-1.16)	77	96	1.24 (0.91-1.67)
≥1.5	140	148	1.08 (0.85-1.36)	87	78	0.91 (0.67-1.24)
<i>P</i> for interaction <sup>b</sup>			0.35			0.17
Body mass index, kg/m <sup>2</sup>						
<25	79	97	1.25 (0.92-1.68)	49	48	0.99 (0.66-1.48)
25-29.9	133	106	0.81 (0.62-1.04)	70	65	0.94 (0.67-1.33)
≥30	80	86	1.06 (0.78-1.44)	45	57	1.24 (0.84-1.84)
<i>P</i> for interaction <sup>b</sup>			0.09			0.57
Physical activity, MET-hours/week						
<15	137	124	0.91 (0.71-1.16)	62	70	1.14 (0.81-1.60)
≥15	162	168	1.04 (0.84-1.30)	103	102	0.99 (0.75-1.31)
<i>P</i> for interaction <sup>b</sup>			0.41			0.56
Smoking						
Never	151	155	1.04 (0.83-1.30)	76	77	1.02 (0.74-1.41)
Past	127	119	0.93 (0.72-1.20)	70	82	1.16 (0.84-1.60)
Current	20	19	0.98 (0.52-1.84)	17	13	0.78 (0.38-1.61)
<i>P</i> for interaction <sup>b</sup>			0.82			0.53
Alcohol use						
<1/week	90	86	0.96 (0.71-1.30)	43	55	1.28 (0.86-1.91)
≥1/week	207	207	1.00 (0.82-1.22)	123	119	0.97 (0.75-1.25)

<i>P</i> for interaction <sup>b</sup>			0.82				0.25
Aspirin use							
No	156	141	0.90 (0.72-1.14)		90	90	1.00 (0.75-1.34)
Yes	141	152	1.09 (0.86-1.37)		72	81	1.14 (0.83-1.57)
<i>P</i> for interaction <sup>b</sup>			0.27				0.57
History of colorectal polyps							
No	285	282	0.98 (0.83-1.16)		159	171	1.07 (0.86-1.33)
Yes	16	12	0.77 (0.36-1.64)		8	3	0.39 (0.10-1.46)
<i>P</i> for interaction <sup>b</sup>			0.54				0.14
History of colonoscopy/sigmoidoscopy in the past 10 years							
No	70	66	0.96 (0.68-1.35)		46	43	0.95 (0.62-1.44)
Yes	231	228	0.98 (0.82-1.18)		121	131	1.08 (0.84-1.39)
<i>P</i> for interaction <sup>b</sup>			0.93				0.61
Randomization in vitamin D portion of trial							
Placebo group	136	151	1.12 (0.88-1.41)		82	87	1.06 (0.79-1.44)
Vitamin D group	165	143	0.87 (0.69-1.09)		85	87	1.03 (0.76-1.39)
<i>P</i> for interaction <sup>b</sup>			0.13				0.86

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MET, metabolic equivalent; OR, odds ratio.

<sup>a</sup>All stratified variables were assessed at baseline enrollment. For dietary fish intake and plasma measurements, median level was used the cutoff. Logistic regression was used to calculate the odds ratio with adjustment for age, sex, vitamin D treatment assignment, and use of colonoscopy or sigmoidoscopy in the past 10 years prior to randomization.

<sup>b</sup>*P* for interaction was calculated by Wald test for the product term between intervention assignment and the stratified variable.

**eTable 3.** Baseline Characteristics of Participants According to Race/Ethnicity<sup>a</sup>

Variable	African American	Non-Hispanic white	Others	P value
Age, year	63.4 (6.9)	68.1 (6.8)	67.6 (6.9)	<0.001
Women, %	3,159 (62)	8,685 (48)	904 (42)	<0.001
Family history of colorectal cancer, %	568 (13)	2320 (14)	226 (12)	0.03
Colonoscopy in the past 10 years, %	3,436 (67)	13,569 (75)	1,506 (70)	<0.001
Sigmoidoscopy in the past 10 years, %	439 (9)	2,425 (14)	282 (14)	<0.001
Smoking status, %				<0.001
Never	2,530 (51)	9,233 (52)	1,136 (54)	
Past	1,744 (35)	7,662 (43)	829 (39)	
Current	711 (14)	935 (5)	149 (7)	
Body mass index, kg/m <sup>2</sup>	30.6 (6.8)	27.4 (5.2)	28.0 (5.7)	<0.001
Physical activity, MET-hours/week	19.5 (28.9)	23.5 (24.3)	23.6 (29.6)	<0.001
Use of aspirin, %	1,950 (39)	8,446 (45)	899 (42)	<0.001
Use of vitamin D supplements, % <sup>b</sup>	1,460 (29)	8,632 (48)	702 (33)	<0.001
Use of calcium supplements, %	635 (12)	4,054 (22)	363 (17)	<0.001
Use of multivitamin supplements, %	1,995 (40)	8,332 (47)	832 (40)	<0.001
Alcohol use, %				<0.001
Never	2,271 (46)	4,777 (27)	741 (36)	
Rarely to less than once per week	461 (9)	1217 (7)	184 (9)	
1-6/week	1,604 (32)	6,383 (36)	731 (35)	
Daily	605 (12)	5480 (30)	424 (20)	
Plasma fatty acid composition, %				
EPA	0.55 (0.34)	0.61 (0.36)	0.57 (0.37)	<0.001
DHA	2.28 (0.71)	1.98 (0.64)	2.01 (0.72)	<0.001
Omega-3 index <sup>c</sup>	2.83 (0.93)	2.58 (0.90)	2.58 (0.98)	<0.001
Dark meat fish intake, serving/week	1.4 (3.1)	0.9 (1.1)	1.1 (2.7)	<0.001
Other fish and seafood, serving/week	1.6 (4.4)	1.0 (1.2)	1.2 (2.5)	<0.001
Processed meat, serving/week	2.0 (3.5)	1.3 (2.0)	1.4 (2.5)	<0.001

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MET, metabolic equivalent.

<sup>a</sup>Mean (standard deviation) and percentage are presented for continuous and categorical variables, respectively.

<sup>b</sup>To be eligible for the trial, participants are required to limit consumption of supplemental vitamin D to no more than 800 IU/day from all supplemental sources combined.

<sup>c</sup>Omega-3 index was calculated as the sum of plasma EPA and DHA composition.