

## Supplementary Materials:

**Table S1.** Search strategy and number of articles retrieved in PubMed.

**Table S2.** Search strategy and number of articles retrieved in Embase.

**Table S3.** Characteristics of the trials with low-dose OM3.

**Table S4.** Primary outcome of atherosclerosis and the result of each trial with low-dose OM3.

**Table S5.** Risk of bias for trails with low-dose OM3.

**Figure S1.** Effect of low-dose marine omega-3 fatty acids on atherosclerosis.

**Table S1.** Search strategy and number of articles retrieved in PubMed.

|    |                                                                                                                                                                                                                                                                                                               |           |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1  | fish oils[MH] OR fatty acids, omega-3[MH] OR dietary supplements[MH] OR eicosapentaenoic acid[MH] OR docosahexaenoic acids[MH] OR fatty acids[MH]                                                                                                                                                             |           |
| 2  | fish oil[TIAB] OR fatty fish[TIAB] OR omega-3 fatty acids[TIAB] OR omega-3 fatty acid[TIAB] OR n-3 fatty acids[TIAB] OR n-3 polyunsaturated fatty acids[TIAB] OR eicosapentaenoic acid[TIAB] OR docosahexaenoic acid[TIAB] OR dietary supplementation[TIAB] OR lovaza[TIAB] OR epanova[TIAB] OR vascepa[TIAB] |           |
| 3  | #1 OR #2                                                                                                                                                                                                                                                                                                      | 506,467   |
| 4  | atherosclerosis[MH] OR atherosclerosis, coronary[MH] OR arteriosclerosis[MH] OR plaque, atherosclerotic[MH] OR coronary stenosis[MH] OR carotid stenosis[MH]                                                                                                                                                  |           |
| 5  | atherosclerosis[TIAB] OR arteriosclerosis[TIAB] OR atherosclerotic plaque[TIAB] OR coronary stenosis[TIAB] OR carotid stenosis[TIAB]                                                                                                                                                                          |           |
| 6  | #4 OR #5                                                                                                                                                                                                                                                                                                      | 256,170   |
| 7  | randomized controlled trial[PT] OR controlled clinical trial[PT] OR clinical trial[PT] OR clinical study[PT]                                                                                                                                                                                                  |           |
| 8  | controlled clinical trials as topic[MH] OR randomized controlled trial[MH] OR placebos[MH] OR double-blind method[MH]                                                                                                                                                                                         |           |
| 9  | randomized[TIAB] OR placebo[TIAB] OR randomly[TIAB] OR trial[TIAB] OR blind[TIAB] OR groups[TIAB]                                                                                                                                                                                                             |           |
| 10 | #7 OR #8 OR #9                                                                                                                                                                                                                                                                                                | 3,097,327 |
| 11 | diagnostic imaging[MH] OR image processing, computer-assisted[MH] OR angiography[MH] OR magnetic resonance imaging[MH] OR ultrasound[MH] OR tomography[MH] OR angioscopy[MH] OR magnetic resonance spectroscopy[MH]                                                                                           |           |
| 12 | imaging[TIAB] OR diagnostic imaging[TIAB] OR magnetic resonance*[TIAB] OR intravascular*[TIAB] OR angioscopy*[TIAB] OR tomography*[TIAB] OR angioscopy*[TIAB] OR optical*[TIAB]                                                                                                                               |           |
| 13 | #11 OR #12                                                                                                                                                                                                                                                                                                    | 3,312,160 |
| 14 | #3 AND #6 AND #10 #13                                                                                                                                                                                                                                                                                         | 493       |

**Table S2.** Search strategy and number of articles retrieved in Embase.

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |           |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1  | 'omega 3 fatty acid'/exp OR 'fish oil'/exp OR 'icosapentaenoic acid'/exp OR 'docosapentaenoic acid'/exp OR 'docosahexaenoic acid'/exp OR 'dietary supplement'/exp OR 'diet supplementation'/exp OR 'omega 3 acid ethyl ester'/exp OR 'omega 3 fatty acid ester'/exp                                                                                                                                                                                                                                                                                                                                                                                  |           |
| 2  | 'omega 3 fatty acid':ab,ti OR 'fish oil':ab,ti OR 'icosapentaenoic acid':ab,ti OR 'icosapentaenoic acid ethyl ester':ab,ti OR 'omega 3 acid ethyl ester':ab,ti OR 'omega 3 fatty acid ester':ab,ti OR 'docosapentaenoic acid':ab,ti OR 'docosahexaenoic acid':ab,ti OR 'fish':ab,ti OR 'dietary supplement':ab,ti OR 'diet supplementation':ab,ti                                                                                                                                                                                                                                                                                                    |           |
| 3  | #1 OR #2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 306,256   |
| 4  | 'atherosclerosis'/exp OR 'coronary artery atherosclerosis'/exp OR 'aortic atherosclerosis'/exp OR 'brain atherosclerosis'/exp OR 'peripheral occlusive artery disease'/exp OR 'carotid atherosclerosis'/exp OR 'nephrosclerosis'/exp OR 'peripheral occlusive artery disease'/exp OR 'atherosclerotic plaque'/exp                                                                                                                                                                                                                                                                                                                                    |           |
| 5  | 'atherosclerosis':ab,ti OR 'coronary artery atherosclerosis':ab,ti OR 'aortic atherosclerosis':ab,ti OR 'atherosclerotic plaque':ab,ti                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |           |
| 6  | #4 OR #5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 391,824   |
| 7  | 'diagnostic imaging equipment'/exp OR 'diagnostic imaging'/exp OR 'imaging and display'/exp OR 'nuclear magnetic resonance imaging'/exp OR 'cardiac imaging'/exp OR 'digital imaging'/exp OR 'fluorescence imaging'/exp OR 'image analysis'/exp OR 'computer assisted diagnosis'/exp OR 'echography'/exp OR 'quantitative diagnosis'/exp OR 'radiodiagnosis'/exp                                                                                                                                                                                                                                                                                     |           |
| 8  | 'diagnostic imaging equipment':ab,ti OR 'diagnostic imaging':ab,ti OR 'angiography':ab,ti OR 'arteriography':ab,ti OR 'magnetic resonance angiography':ab,ti OR 'digital subtraction angiography':ab,ti OR 'coronary angiography':ab,ti OR 'fluorescence angiography':ab,ti OR 'echography':ab,ti OR 'echocardiography':ab,ti OR 'ultrasound':ab,ti OR 'doppler glowmetry':ab,ti OR 'angioscopy':ab,ti OR 'emission tomography':ab,ti OR 'computer assisted emission tomography':ab,ti OR 'positron emission tomography':ab,ti OR 'photone emission tomography':ab,ti OR 'optical coherence tomography':ab,ti OR 'computed tomography scanner':ab,ti |           |
| 9  | #7 OR #8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 3,602,675 |
| 10 | 'clinical trial (topic)'/exp OR 'controlled clinical trial (topic)'/exp OR 'randomized controlled trial (topic)'/exp OR 'multicenter study (topic)'/exp OR 'phase 1 clinical trial (topic)'/exp OR 'phase 2 clinical trial (topic)'/exp OR 'phase 3 clinical trial (topic)'/exp OR 'phase 4 clinical trial (topic)'/exp                                                                                                                                                                                                                                                                                                                              |           |
| 11 | 'randomized controlled trial':ab,ti OR 'controlled clinical trial':ab,ti OR 'controlled study':ab,ti OR 'clinical trial':ab,ti OR 'placebo':ab,ti                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |           |
| 12 | #10 OR #11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 769,632   |
| 13 | #3 AND #6 AND #9 AND #12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 85        |

**Table S3.** Characteristics of the trials with low-dose marine omega-3 fatty acids.

| Author, year, location, reference | Number of participants<br>Treatment/control | Age (years)<br>Treatment / Control | Characteristics of the participants    | Use of statin | Use of placebo | Dose and type of OM3 (g/day)         | Purity of OM3 (%) | Duration of intervention (months) |
|-----------------------------------|---------------------------------------------|------------------------------------|----------------------------------------|---------------|----------------|--------------------------------------|-------------------|-----------------------------------|
| Ahn, 2016, South Korea [45]       | 38/36                                       | 60 ± 9 vs. 61 ± 1                  | CHD                                    | Yes           | Yes            | 1.395 EPA + 1.125 DHA                | 84%               | 12                                |
| Angerer, 2002, Germany [46]       | 112/111                                     | 57 ± 9 vs. 59 ± 8                  | CHD                                    | No            | Yes            | 1.65 (EPA + DHA)                     | 55%               | 21                                |
| Baldassarre, 2006, Italy [47]     | 32/32                                       | 54 ± 7 vs. 54 ± 7                  | Hyperlipidemia without CVD             | No            | Yes            | 1.08 EPA + 0.72 DHA <sup>(5)</sup>   | 32%               | 24                                |
| Lonn, 2013, 7 countries [48]      | 585/599                                     | 63 vs. 63                          | Dysglycemia + (CVD or CV risk factors) | Yes           | Yes            | 0.465 EPA + 0.375 DHA                | 84%               | 59                                |
| von Schacky, 1999, Germany [49]   | 112/111                                     | 58 ± 10 vs. 59 ± 8                 | CHD                                    | No            | Yes            | 1.062 EPA + 0.645 DHA <sup>(6)</sup> | 57%               | 21                                |

OM3: marine omega-3 fatty acids, CHD: coronary heart disease, CVD: cardiovascular disease, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid.

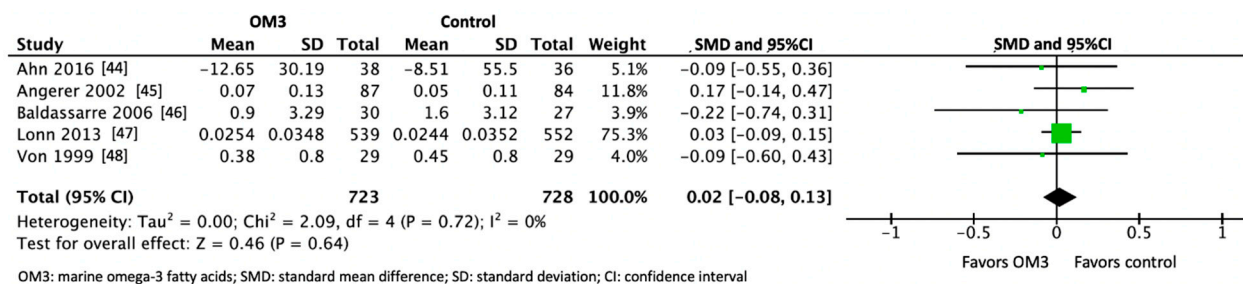
**Table S4.** Primary outcome of atherosclerosis and the result of each trial with low-dose marine omega-3 fatty acids.

| First Author,<br>Year, Country,<br>reference | Imaging<br>techniques | Primary Outcome                                   | Baseline<br>Measurement<br>Treatment vs.<br>control<br>groups | Difference in primary<br>outcome between the<br>end of intervention<br>and baseline in each<br>of treatment and<br>control groups<br>Treatment vs. control<br>groups | Net<br>differenc<br>e<br>between<br>treatmen<br>t and<br>control<br>groups | p-value<br>for Net<br>differenc<br>e |
|----------------------------------------------|-----------------------|---------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------|
| Ahn, 2016,<br>South Korea [45]               | IVUS                  | Percent change in<br>atheroma volume<br>index (%) | 5.51 ± 5.50 vs.<br>7.09 ± 4.83                                | -12.65 ± 30.19 vs.<br>-8.51 ± 55.5                                                                                                                                   | -4.14                                                                      | 0.77                                 |
| Angerer, 2002,<br>Germany [46]               | B-mode<br>ultrasound  | Change in mean<br>carotid IMT (mm)                | 1.26 ± 0.41 vs.<br>1.31 ± 0.41                                | 0.07 ± 0.13 vs.<br>0.05 ± 0.11                                                                                                                                       | 0.02                                                                       | 0.24                                 |
| Baldassarre,<br>2006, Italy [47]             | B-mode<br>ultrasound  | Change in mean<br>carotid IMT (mm)                | 0.79 ± 0.15 vs.<br>0.83 ± 0.16                                | 0.9 ± 3.29 vs.<br>1.6 ± 3.12                                                                                                                                         | -0.7                                                                       | >0.05                                |
| Lonn, 2013,<br>7 countries [48]              | B-mode<br>ultrasound  | Change in mean<br>carotid IMT (mm)                | 1.08 ± 0.33 vs.<br>1.10 ± 0.35                                | 0.0254 ± 0.0348 vs.<br>0.0244 ± 0.0352                                                                                                                               | 0.0009                                                                     | >0.65                                |
| von Schacky,<br>1999, Germany<br>[49]        | QCA                   | Loss in coronary<br>minimal luminal<br>diameter   | N/A                                                           | 0.38 ± 0.8 vs.<br>0.45 ± 0.8                                                                                                                                         | -0.07                                                                      | >0.05                                |

IVUS: intravascular ultrasound; QCA: Quantitative coronary angiography; IMT: intima-media thickness; SD: standard deviation; NS: non-significant; N/A: not available.

**Table S5.** Risk of bias for trails with low-dose marine omega-3 fatty acids.

| Study                                       | Selection bias                   |                           | Performance<br>bias                             | Detection<br>bias                    | Attrition<br>bias             | Reporting<br>bias                 | Other<br>bias              | Total                           |
|---------------------------------------------|----------------------------------|---------------------------|-------------------------------------------------|--------------------------------------|-------------------------------|-----------------------------------|----------------------------|---------------------------------|
|                                             | Random<br>sequence<br>generation | Allocation<br>concealment | Blinding of<br>participants<br>and<br>personnel | Blinding of<br>outcome<br>assessment | Incomplete<br>outcome<br>data | Selective<br>outcome<br>reporting | Other<br>source<br>of bias | Low<br>on<br>risk<br>of<br>bias |
| Ahn, 2016,<br>South Korea<br>[45]           | low                              | low                       | low                                             | low                                  | low                           | low                               | low                        | 7/7                             |
| Angerer,<br>2002,<br>Germany<br>[46]        | low                              | low                       | low                                             | low                                  | low                           | low                               | low                        | 7/7                             |
| Baldassarre,<br>2006, Italy<br>[47]         | low                              | low                       | low                                             | unclear                              | low                           | low                               | low                        | 6/7                             |
| Lonn, 2013,<br>7 countries<br>[48]          | low                              | low                       | low                                             | low                                  | low                           | low                               | low                        | 7/7                             |
| von<br>Schacky,<br>1999,<br>Germany<br>[49] | low                              | low                       | low                                             | low                                  | high                          | low                               | low                        | 7/7                             |



**Figure S1.** Effect of low-dose marine omega-3 fatty acids on atherosclerosis.