Special Article

Lipid-modifying effects of krill oil in humans: systematic review and meta-analysis of randomized controlled trials

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Context: *Some experimental and clinical trials have shown that krill oil, extracted from small red crustaceans, might be an effective lipid-modifying agent, but the evidence is not conclusive.* ***Objective:*** *The effect of krill oil supplements on plasma lipid concentrations was assessed through a systematic review of the literature and a meta-analysis of available randomized controlled trials.* ***Data sources:*** *PubMed and Scopus were searched up to March 25, 2016, to identify RCTs investigating the effect of krill oil supplements on plasma lipids.* ***Study selection:*** *Randomized controlled trials that investigated the impact of at least 2 weeks of supplementation with krill oil on plasma/serum concentrations of at least one of the main lipid parameters (ie, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides) and that reported sufficient information on plasma/serum lipid levels at baseline and at the end of study in both krill oil and control groups were eligible for inclusion.* ***Data extraction:*** *Two reviewers independently extracted the following data: first author's name, year of publication, study location, study design, number of participants in the krill oil and control groups, dosage of krill oil, type of control allocation, treatment duration, demographic characteristics of study participants, and baseline and follow-up plasma concentrations of lipids. Effect size was expressed as the weighted mean difference (WMD) and 95% confidence interval (95%CI).* ***Results:*** *Meta-analysis of data from 7 eligible trials (14 treatment arms) with 662 participants showed a significant reduction in plasma concentrations of low-density lipoprotein cholesterol (WMD, −15.52 mg/dL; 95%CI, −28.43 to −2.61; $P = 0.018$) and triglycerides (WMD, −14.03 mg/dL; 95%CI, −21.38 to −6.67; $P < 0.001$) following supplementation with krill oil. A significant elevation in plasma concentrations of high-density lipoprotein cholesterol was also observed (WMD, 6.65 mg/dL; 95%CI, 2.30 to 10.99; $P = 0.003$), while a reduction in plasma concentrations of total cholesterol did not*

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reach statistical significance (WMD, −7.50 mg/dL; 95%CI, −17.94 to 2.93; P = 0.159). ***Conclusion:*** *Krill oil supplementation can reduce low-density lipoprotein cholesterol and triglycerides. Additional clinical studies with more participants are needed to assess the impact of krill oil supplementation on other indices of cardiometabolic risk and on the risk of cardiovascular outcomes.*

INTRODUCTION

Krill are red shrimp-like crustaceans that live in the cold waters of the southern (Antarctic) and northern (Arctic) polar seas.[1] Although krill is the main food source for whales, it remains an abundant biomass on earth because of its high proliferation properties.[2] Krill have a short lifespan (1–2 years) and, because they live in clean waters, are free of heavy metals, pesticides, and dioxins.[2] The major krill species, *Euphausia superba*, known as Antarctic krill, is the source of extracted krill oil.[3] Many experimental and clinical trials have reported a protective role of krill oil in chronic inflammation,[2] dyslipidemia,[4] premenstrual syndrome,[5] osteosarcoma,[6] and rheumatoid arthritis.[7] Krill oil is rich in phospholipids that contain n-3 polyunsaturated fatty acids, mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[8] It also contains various potent antioxidants, such as the carotenoid astaxanthin, and vitamins A and E.[9] The association between phospholipids and long-chain n-3 fatty acids greatly facilitates the passage of fatty acid molecules through the intestinal wall, thereby increasing their bioavailability and improving the ratio of n-3 to n-6 fatty acids.[3,10]

Most of krill oil's benefits have been attributed to its high EPA and DHA content.[11] The well-recognized metabolic effects of EPA and DHA include lowering of triglyceride (TG) and very low-density lipoprotein cholesterol levels.[12] Choline, an ingredient in krill oil, reduces homocysteine, transports different lipids, and is involved in the synthesis of neurotransmitters (acetylcholine) and phospholipids (sphingomyelin, lyso-phosphatidylcholine, phosphatidylcholine, and choline plasmalogen).[13]

The lipid-modifying effects of krill oil have been demonstrated in some trials, but the data are still inconclusive. Therefore, all published trials on krill oil supplementation were reviewed systematically and assessed to determine the overall efficacy of krill oil on plasma lipids using meta-analysis.

METHODS

Search strategy

This systematic review and meta-analysis was performed in compliance with the PRISMA guidelines.[14] The Scopus and MEDLINE databases were searched using the following search terms in titles and abstracts (also in combination with MeSH terms): ("randomized controlled trial" OR "randomized" OR "placebo" OR "cholesterol" OR "triglyceride" OR "LDL" OR "LDL-C" OR "LDL-cholesterol" OR "HDL" OR "HDL-C" OR "HDL-cholesterol" OR "hyperlipidemia" OR "hyperlipidemic" OR "hypolipidemic" OR "dyslipidemia" OR "dyslipidemic") and ("krill oil" OR "euphausiaceae" OR "euphausia superba"). The wild-card term "*" was used to increase the sensitivity of the search strategy. The literature search was limited to papers published in English and to studies conducted in humans. The literature was searched from inception to March 25, 2016.

Two investigators (S.U. and M-C.S.) independently assessed each article, carried out data extraction, and performed quality assessment. Disagreements were resolved by consensus and discussion with a third party (M.B.).

The PICOS (Participants, Intervention/exposure, Comparison, Outcomes, Study design) criteria used to define the research question are shown in Table 1.

Study selection

The following criteria were used for the inclusion of original articles in the meta-analysis: a randomized controlled design; investigation of the effects of krill oil on plasma/serum concentrations of at least one of the main lipid parameters (ie, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or TGs; measurement of either plasma/serum concentrations of lipids at baseline and at the end of study in both krill oil and control groups or the net change in lipid levels during the study; and administration of krill oil for a period of at least 2 weeks. The following exclusion criteria were applied: experimental studies; uncontrolled trials; administration of krill oil preparations for <2 weeks; and lack of reporting of baseline or follow-up lipid concentrations or the net change in lipid levels during the study.

Data extraction

Studies meeting the inclusion criteria were reviewed, and data regarding authors, study location, publication

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Parameter	Description
Participants	Healthy individuals and dyslipidemic individuals
Intervention/exposure	Krill oil supplementation administered for at least 2 wk
Comparison	Individuals supplemented with krill oil vs control individuals
Outcomes	Plasma/serum concentrations of at least one of the main lipid parameters (ie, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides)
Study design	Randomized controlled trials with a parallel or crossover design

date, size of study population, trial design, dose and duration of intervention, control group allocation, baseline characteristics of study population (including age, gender, and body mass index), and changes in plasma concentrations of lipids were extracted.

Quality assessment

Risk of bias in the studies considered in this meta-analysis was evaluated according to the Cochrane instructions.[15] Selection bias, performance bias, attrition bias, detection bias, reporting bias, and other sources of bias were judged to be high, low, or unclear in each of the studies included.

Quantitative data synthesis

Comprehensive Meta-Analysis V2 software (Biostat, NJ, USA)[16] was used for statistical procedures. Plasma concentrations of lipids and lipoproteins were collated in milligram per deciliter. Inverse variance-weighted mean differences (WMDs) and 95% confidence limits were used as the summary statistics and calculated as previously described,[17,18] considering a correlation coefficient of 0.5. When standard deviation values were not reported in a study, they were imputed by the pooled standard deviations from other studies.

Meta-analysis was performed under fixed- and random-effects models when I^2 (heterogeneity) values were $<50\%$ and $\geq 50\%$, respectively. For trials with more than one treatment arm and a single control group, the number of subjects in the control group was divided into a corresponding number of smaller groups. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove (leave-one-out) approach. Leave-one-out sensitivity analysis is a simple method to check if the overall estimate of effect is significantly driven by a single study or treatment arm. In this method, all included treatment arms are iteratively removed from the analysis, the effect size is calculated, and the significance of the pooled estimate is evaluated.[19]

Meta-regression

As potential confounders of treatment response, dosage and duration of supplementation with krill oil were entered into a meta-regression model to explore their association with the estimated effect size in each lipid species.

Publication bias

Funnel plot evaluation, Begg's rank correlation, and Egger's weighted regression tests were employed to assess the presence of publication bias in the meta-analysis. When there was evidence of funnel plot asymmetry, potentially missing studies were imputed using the trim-and-fill method. In the case of a significant result, the number of potentially missing studies required to make the *P* value nonsignificant was estimated using the fail-safe N method as another marker of publication bias.[20–23]

RESULTS

Search results and trial flow

The initial screening for potential relevance removed the articles whose titles and/or abstracts were obviously irrelevant. Of the 15 full-text articles assessed for eligibility, 8 were excluded for the following reasons: did not measure plasma lipid levels (n = 4), investigated bioavailability of fatty acids only (n = 1), and did not have an appropriate randomized controlled trial [RCT] design) (n = 3) (Figure 1).

After assessment, 7 RCTs (equivalent to 14 treatment arms) met the inclusion criteria and were used for the final meta-analysis. In total, 427 participants were allocated to a krill oil supplementation group and 235 to a control group in the selected studies.[4,24–29] The number of participants in these trials ranged from 20 to 267. Included studies were published between 2004 and 2015 and were conducted in Canada (n = 3), Norway (n = 2), and the United States (n = 2). All studies used 500-mg capsules or softgels of krill oil, and the dosages ranged from 500 mg/d to 4 g/d. Duration of supplementation with krill oil ranged between 4 weeks and

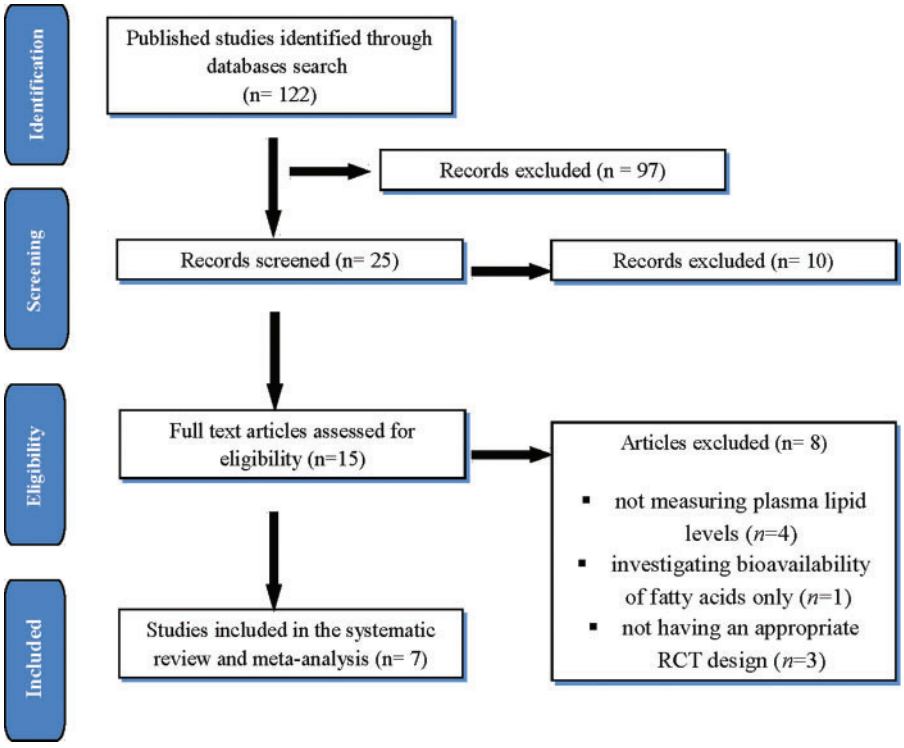


Figure 1 **Flow diagram of the literature search process.**

3 months. Four trials were designed as parallel-group studies and 3 had a crossover design. Three studies were multicenter. Demographic and baseline parameters of the included studies are shown in Table 2.[4,24–29] The common side effects usually observed after administration of fish oil supplements, such as reflux, fishy aftertaste, or belching of fish flavors, were not reported after krill oil intake. Except for a few cases of mild to moderate gastrointestinal symptoms, krill oil was safe and well tolerated in all of the RCTs included in this review. No adverse events related to the supplementation were reported.

Risk-of-bias assessment

The risk of bias with respect to sequence generation and allocation concealment was unclear, but studies were of low risk in terms of other sources of bias. The systematic assessment of bias in the included studies is shown in Table 3.[4,24–29]

Quantitative data synthesis

Total cholesterol. The meta-analysis of RCTs showed a reduction in plasma total cholesterol levels following supplementation with krill oil, but this reduction did not reach statistical significance (WMD, −7.5 mg/dL; 95%CI, −17.94 to 2.93; $P = 0.159$) (Figure 2). This effect size was robust in the sensitivity analysis (Figure 3). The effect of krill oil on plasma total cholesterol concentrations was not different in subgroups of RCTs with dosages of either <2 g/d or ≥2 g/d. With respect to treatment duration, there was a significant reduction in total cholesterol concentrations in the subset of RCTs lasting ≥12 weeks but not in the subset lasting <12 weeks (Table 4).

Visual inspection of the funnel plot as well as the results of Begg's rank correlation and Egger's linear regression tests suggested potential publication bias in the meta-analysis of krill oil's effects on plasma total cholesterol concentrations (Table 5 and Figure 4).

Low-density lipoprotein cholesterol. A significant reduction in plasma concentrations of LDL-C was observed following supplementation with krill oil (WMD, −15.52 mg/dL; 95%CI, −28.43 to −2.61; $P = 0.018$) (Figure 2). This effect size was sensitive to one of the included studies[4] (Figure 3). The effect of krill oil on LDL-C concentrations did not reach statistical significance in subgroups of RCTs with dosages of either <2 g/d or ≥2 g/d. Regarding treatment duration, there was a significant reduction in plasma LDL-C in the subset of RCTs with supplementation durations ≥12 weeks

Table 2 **Demographic characteristics and baseline parameters of the included studies**

Study		Berge et al. (2014)[24]	Bunea et al. (2004)[4]	Maki et al. (2009)[25]	Ramprasath et al. (2013)[26]	Ulven et al. (2011)[27]	Lobraico et al. (2015)[28]	Ramprasath et al. (2015)[29]
Location		Norway	Canada	USA	Canada	Norway	USA	Canada
Design		Multicenter randomized double-blind placebo-controlled parallel trial	Multicenter randomized double-blind placebo-controlled parallel trial	Multicenter randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled cross-over trial	Randomized parallel group trial	Randomized double-blind placebo-controlled cross-over trial	Randomized double-blind placebo-controlled cross-over trial
Duration of trial		12 wk	3 mo	4 wk	4 wk	7 wk	4 wk	4 wk
Inclusion criteria		Subjects aged 21–79 y with a low habitual fatty fish and seafood intake (defined as intake of fatty fish and seafood ≤2 times per month) and borderline high or high fasting serum TG levels (defined as a fasting TG level of 150–499 mg/dL at screening visit, inclusive)	Patients aged 18–85 y with at least a 6-mo diagnosis of mildly high to very high blood cholesterol (193.9–347.9 mg/dL) and TG levels (203.8–354.4 mg/dL)	Healthy men and women aged 35–64 y with a waist circumference of ≥102 cm (men) or ≥88 cm (women)	Healthy volunteers	Healthy volunteers of both genders with normal or slightly elevated total blood cholesterol (<7.5 mmol/L) and normal or slightly elevated blood triglyceride level (<4.0 mmol/L)	Adults diagnosed with type 2 diabetes who were on oral glucose-lowering agents and/or insulin that could be confirmed by a healthcare provider	Healthy males and non-pregnant women aged 18–49 y
Krill oil form		500-mg capsule	500-mg softgel	500-mg capsule	500-mg capsule	500-mg capsule	500-mg capsule	500-mg capsule
Krill oil intervention		500 mg/d 1 g/d 2 g/d 4 g/d	1 g/d 1.5 g/d 2 g/d 3 g/d	2 g/d	3 g/d	3 g/d	1 g/d	1.5 g/d 3 g/d
No. of participants	Cases	53 53 51 58	23 7 19 11	25	24	36	47	20
	Controls	52	30	25		37		

(continued)

Table 2 **Continued**

Study		Berge et al. (2014)[24]	Bunea et al. (2004)[4]	Maki et al. (2009)[25]	Ramprasath et al. (2013)[26]	Ulven et al. (2011)[27]	Lobraico et al. (2015)[28]	Ramprasath et al. (2015)[29]
Location		Norway	Canada	USA	Canada	Norway	USA	Canada
Age (y)[a]	Cases	46.4 ± 12.7 40.5 ± 13.1 44.3 ± 12.1 45.5 ± 11.9	51 ± 9.46	49.4 ± 1.7[b]	28.23 ± 5.35[b]	40.3 ± 14.8	64.8 ± 8.8	NS
	Controls	43.5 ± 11		47.4 ± 1.6[b]		40.5 ± 12.1		
Male (%)	Cases	66 64 73 67	NS	12.0	50.0	29.5	66.0	55.0
	Controls	65		20.0		33.3		
BMI (kg/m^2)[a]	Cases	29.9 ± 3.3 29.0 ± 3.3 29.7 ± 2.6 29.3 ± 2.9	25.4 ± 3.9 (male) 28.2 ± 5.1 (female)	32.6 ± 1.5[b]	23.76 ± 2.96[b]	23.6 ±3 .3	30.5 ± 6.9	23.79 ± 0.71[b] 23.62 ± 0.68[b]
	Controls	30.2 ± 3.0		33.3 ± 1.7[b]		23.9 ± 3.0		23.61 ± 0.63[b]
Total cholesterol (mg/dL)[a]	Cases	221.1 ± 37.1 209.4 ± 40.3 221.4 ± 36.1 216.2 ± 31.2	235.83[c] 231.19[c] 247.42[c] 250.52[c]	201.6 ± 6.1[b]	168.85 ± 5.45[b]	192.61 ± 31.46	153.7 ± 32.6	173.62 ± 7.06[b] 168.02 ± 6.26[b]
	Controls	207.9 ± 32.4	221.91[c]	201.2 ± 7.3[b]	172.55 ± 5.69[b]	191.07 ± 35.70		169.56 ± 5.53[b]
LDL-C (mg/dL)[a]	Cases	132.7 ± 4.6 120.8 ± 4.6 133.1 ± 4.7 125.8 ± 4.4	167.78[c] 164.74[c] 182.86[c] 172.81[c]	129.7 ± 5.5[b]	93.05 ± 4.66[b]	118.50 ± 27.95	78.7 ± 28.4	96.93 ± 7.25[b] 94.28 ± 5.47[b]
	Controls	122.8 ± 4.7	136.47[c]	125.5 ± 6.6[b]	95.03 ± 4.82[b]	115.03 ± 31.81		93.89 ± 5.07[b]
HDL-C (mg/dL)[a]	Cases	44.5 ± 10.8 42.1 ± 10.6 42.1 ± 9.2 46.2 ± 10	57.22[c] 58.76[c] 51.03[c] 64.18[c]	46.5 ± 2.8[b]	55.74 ± 2.91[b]	57.90 ± 14.20	44.6 ± 13.7	55.48 ± 3.33[b] 54.52 ± 3.14[b]
	Controls	39.5 ± 9.3	56.83[c]	45.4 ± 2.1[b]	56.22 ± 3.38[b]	61.37 ± 13.66		54.71 ± 3.02[b]
TGs (mg/dL)[a]	Cases	230.1 ± 71.4 238.9 ± 69.8 237.4 ± 73.1 220.2 ± 63	120.50[c] 126.70[c] 160.37[c] 152.77[c]	126.9 ± 9.3[b]	101.10 ± 10.53[b]	97.35 ± 56.46	155.6 ± 95.3	106.2 ± 9.62[b] 98.02 ± 11.76[b]
	Controls	236.5 ± 80.9	143.53[c]	152.8 ± 18.1[b]	103.41 ± 9.84[b]	81.42 ± 36.64		99.91 ± 10.02[b]

Abbreviations: SD: standard deviation; SEM: standard error of the mean; BMI: body mass index; NS: not stated; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG, triglyceride.
[a]Values are expressed as mean ± SD unless otherwise indicated.
[b]Values are expressed as mean ± SEM.
[c]Mean value.

Table 3 **Risk of bias in the included studies as assessed using Cochrane criteria**

Reference	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Berge et al. (2014)[24]	Unclear	Unclear	Low	Low	Low	Low	Low
Bunea et al. (2004)[4]	Unclear	Unclear	Low	Low	Low	Low	Low
Maki et al. (2009)[25]	Unclear	Unclear	Low	Low	Low	Low	Low
Ramprasath et al. (2013)[26]	Unclear	Unclear	Low	Low	Low	Low	Low
Ulven et al. (2011)[27]	Unclear	Unclear	Low	Low	Low	Low	Low
Lobraico et al. (2015)[28]	Low	Low	Low	Low	Low	Low	Low
Ramprasath et al (2015)[29]	Unclear	Unclear	Low	Low	Low	Low	Low

but not in the subset with supplementation lasting <12 weeks (Table 4).

Visual inspection of the funnel plot as well as the results of Begg's rank correlation and Egger's linear regression tests suggested potential publication bias in the meta-analysis of krill oil's effects on plasma LDL-C concentrations (Table 4 and Figure 4).

High-density lipoprotein cholesterol. The meta-analysis of RCT data suggested a significant elevation in plasma HDL-C concentrations following krill oil supplementation (WMD, 6.65 mg/dL; 95%CI, 2.30–10.99; $P = 0.003$) (Figure 2). This effect size was robust in the sensitivity analysis, and iterative removal of each single study from the meta-analysis did not affect the statistical significance of the effect size (Figure 3). In the subgroup analysis, there was a significant increase in plasma HDL-C concentrations in the subset of trials with krill oil dosages of ≥2 g/d but not in the subset with dosages of <2 g/d. With respect to the duration of supplementation, HDL-C elevations remained significant in both study subsets with supplementation durations of <12 weeks and ≥12 weeks, though a greater reduction was observed in the latter subgroup (Table 4).

Visual inspection of the funnel plot as well as the results of Begg's rank correlation and Egger's linear regression tests suggested potential publication bias in the meta-analysis of krill oil's effects on plasma HDL-C concentrations (Table 5 and Figure 4).

Triglycerides. A significant reduction in plasma TG concentrations following krill oil supplementation was found in the meta-analysis of RCTs (WMD, −14.03 mg/dL; 95%CI, −21.38 to −6.67; $P < 0.001$) (Figure 2). This effect size was robust in the sensitivity analysis, and iterative removal of each single study from the meta-analysis did not affect the statistical significance of the effect size (Figure 3). In the subgroup analysis, there was a significant reduction in plasma TG concentrations in both subsets of trials with krill oil doses of <2 g/d and ≥2 g/d. However, with respect to supplementation duration, significant reduction of plasma TG concentrations was observed only in the subset of RCTs lasting ≥12 weeks and not in the subset lasting <12 weeks (Table 4). Although the results of Begg's rank correlation and Egger's linear regression tests did not indicate any publication bias (Table 5), the funnel plot was slightly asymmetric, suggesting potential publication bias in the meta-analysis of krill oil's effects on plasma TG concentrations. Using Duval and Tweedie trim-and-fill correction, 3 potentially missing studies were imputed on the left side of funnel plot, yielding a corrected effect size of −15.12 mg/dL (95%CI, −22.00 to −8.23) (Figure 4).

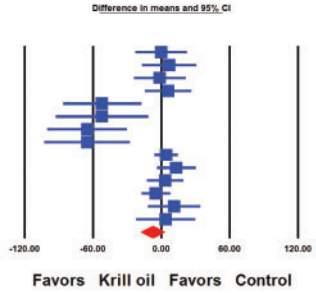
DISCUSSION

To the best of knowledge, the current systematic review and meta-analysis is the first to analyze evidence from RCTs on the effect of krill oil supplementation on plasma lipids. The results showed a significant reduction in plasma concentrations of LDL-C and TGs and a significant elevation in plasma HDL-C concentrations following supplementation with krill oil, while a reduction in plasma total cholesterol levels did not reach statistical significance. When the studies were stratified according to their duration, there was a significant reduction in total cholesterol, LDL-C, and TGs in the subset of RCTs lasting ≥12 weeks but not in the subset lasting <12 weeks, while HDL-C elevations remained significant in both study subsets.

The favorable effects of krill oil on the lipid profile found in the current meta-analysis suggest the use of this marine product as an interesting add-on therapy in dyslipidemic patients. However, the exact mechanisms responsible for the lipid-lowering effects of krill oil are not completely understood. It has been shown that krill oil acts more as an antihyperlipidemic product than a hypolipidemic one, since TGs and cholesterol levels are lowered in patients with elevated blood lipids, but not in healthy volunteers.[26] It has been proved that krill oil reduces the expression of genes required for lipid and isoprenoid/cholesterol synthesis.[30] In contrast, fish oil modulates expression of several genes, such as peroxisome proliferator-activated receptor (PPAR)-α, sterol regulatory element-binding proteins (SREBP)-1, and

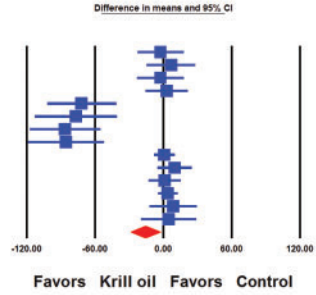
TC

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Berge et al., 2014a (ref. 24)	-0.010	11.339	128.562	-22.233	22.213	-0.001	0.999
Berge et al., 2014b (ref. 24)	7.220	12.045	145.071	-16.387	30.827	0.599	0.549
Berge et al., 2014c (ref. 24)	-1.120	11.558	133.580	-23.773	21.533	-0.097	0.923
Berge et al., 2014d (ref. 24)	6.110	10.226	104.580	-13.933	26.153	0.597	0.550
Bunea et al., 2014a (ref. 4)	-51.810	17.425	303.647	-85.963	-17.657	-2.973	0.003
Bunea et al., 2014b (ref. 4)	-51.800	20.638	425.937	-92.250	-11.350	-2.510	0.012
Bunea et al., 2014c (ref. 4)	-64.940	17.750	315.068	-99.730	-30.150	-3.659	0.000
Bunea et al., 2014d (ref. 4)	-64.950	19.038	362.430	-102.263	-27.637	-3.412	0.001
Maki et al., 2009 (ref. 25)	4.630	5.135	26.365	-5.434	14.694	0.902	0.367
Ramprasath et al., 2013 (ref. 26)	13.360	8.526	72.691	-3.350	30.070	1.567	0.117
Ulven et al., 2011 (ref. 27)	3.480	7.978	63.642	-12.156	19.116	0.436	0.663
Lobraico et al., 2015 (ref. 28)	-4.700	6.343	40.238	-17.133	7.733	-0.741	0.459
Ramprasath et al., 2015a (ref. 29)	11.590	11.576	134.007	-11.099	34.279	1.001	0.317
Ramprasath et al., 2015b (ref. 29)	4.060	13.177	173.640	-21.767	29.887	0.308	0.758
	-7.505	5.324	28.341	-17.939	2.929	-1.410	0.159



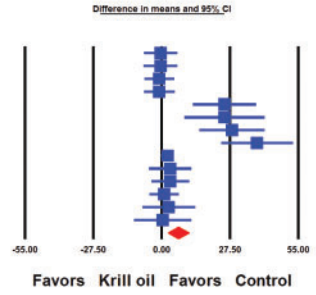
LDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Berge et al., 2014a (ref. 24)	-2.310	10.273	105.530	-22.444	17.824	-0.225	0.822
Berge et al., 2014b (ref. 24)	6.920	10.868	118.115	-14.381	28.221	0.637	0.524
Berge et al., 2014c (ref. 24)	-2.310	10.482	109.870	-22.854	18.234	-0.220	0.826
Berge et al., 2014d (ref. 24)	3.080	9.414	88.627	-15.371	21.531	0.327	0.744
Bunea et al., 2014a (ref. 4)	-71.510	15.435	238.240	-101.762	-41.258	-4.633	0.000
Bunea et al., 2014b (ref. 4)	-76.590	18.429	339.636	-112.711	-40.469	-4.156	0.000
Bunea et al., 2014c (ref. 4)	-86.210	15.737	247.662	-117.055	-55.365	-5.478	0.000
Bunea et al., 2014d (ref. 4)	-85.430	16.937	286.854	-118.625	-52.235	-5.044	0.000
Maki et al., 2009 (ref. 25)	1.210	4.694	22.033	-7.990	10.410	0.258	0.797
Ramprasath et al., 2013 (ref. 26)	10.040	7.550	57.004	-4.758	24.838	1.330	0.184
Ulven et al., 2011 (ref. 27)	1.550	7.127	50.791	-12.418	15.518	0.217	0.828
Lobraico et al., 2015 (ref. 28)	4.090	4.348	18.902	-4.431	12.611	0.941	0.347
Ramprasath et al., 2015a (ref. 29)	8.830	10.532	110.933	-11.813	29.473	0.838	0.402
Ramprasath et al., 2015b (ref. 29)	4.980	12.345	152.391	-19.215	29.175	0.403	0.687
	-15.519	6.588	43.401	-28.432	-2.607	-2.356	0.018



HDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Berge et al., 2014a (ref. 24)	-0.490	3.365	11.325	-7.086	6.106	-0.146	0.884
Berge et al., 2014b (ref. 24)	-0.490	3.432	11.780	-7.217	6.237	-0.143	0.886
Berge et al., 2014c (ref. 24)	-0.980	3.013	9.076	-6.885	4.926	-0.325	0.745
Berge et al., 2014d (ref. 24)	-0.980	3.160	9.985	-7.173	5.213	-0.310	0.756
Bunea et al., 2014a (ref. 4)	25.260	6.462	41.635	12.613	37.907	3.915	0.000
Bunea et al., 2014b (ref. 4)	25.260	8.217	67.521	9.155	41.365	3.074	0.002
Bunea et al., 2014c (ref. 4)	28.350	6.631	43.973	15.353	41.347	4.275	0.000
Bunea et al., 2014d (ref. 4)	38.400	7.340	53.868	24.015	52.785	5.232	0.000
Maki et al., 2009 (ref. 25)	2.350	1.268	1.609	-0.136	4.836	1.853	0.064
Ramprasath et al., 2013 (ref. 26)	3.380	4.353	18.947	-5.151	11.911	0.777	0.437
Ulven et al., 2011 (ref. 27)	3.470	3.796	14.413	-3.971	10.911	0.914	0.361
Lobraico et al., 2015 (ref. 28)	0.990	3.005	9.032	-4.900	6.880	0.329	0.742
Ramprasath et al., 2015a (ref. 29)	2.900	5.408	29.251	-7.700	13.500	0.536	0.592
Ramprasath et al., 2015b (ref. 29)	0.390	5.860	34.334	-11.094	11.874	0.067	0.947
	6.647	2.217	4.916	2.301	10.993	2.998	0.003



TG

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Berge et al., 2014a (ref. 24)	-29.400	3.933	15.468	-37.109	-21.691	-7.475	0.000
Berge et al., 2014b (ref. 24)	-15.500	3.956	15.649	-23.253	-7.747	-3.918	0.000
Berge et al., 2014c (ref. 24)	-22.500	3.946	15.569	-30.234	-14.766	-5.702	0.000
Berge et al., 2014d (ref. 24)	-4.300	3.746	14.030	-11.641	3.041	-1.148	0.251
Bunea et al., 2014a (ref. 4)	0.880	34.936	1220.471	-67.592	69.352	0.025	0.980
Bunea et al., 2014b (ref. 4)	-0.890	43.579	1899.132	-86.303	84.523	-0.020	0.984
Bunea et al., 2014c (ref. 4)	-30.130	35.808	1282.229	-100.313	40.053	-0.841	0.400
Bunea et al., 2014d (ref. 4)	-26.330	39.273	1542.390	-103.304	50.644	-0.670	0.503
Maki et al., 2009 (ref. 25)	-6.540	14.882	221.468	-35.708	22.628	-0.439	0.660
Ramprasath et al., 2013 (ref. 26)	-1.280	14.025	196.692	-28.768	26.208	-0.091	0.927
Ulven et al., 2011 (ref. 27)	-8.850	11.719	137.345	-31.820	14.120	-0.755	0.450
Lobraico et al., 2015 (ref. 28)	6.240	19.187	368.124	-31.365	43.845	0.325	0.745
Ramprasath et al., 2015a (ref. 29)	-4.720	18.457	340.667	-40.895	31.455	-0.256	0.798
Ramprasath et al., 2015b (ref. 29)	-6.590	17.650	311.506	-41.182	28.002	-0.373	0.709
	-14.026	3.751	14.070	-21.378	-6.674	-3.739	0.000

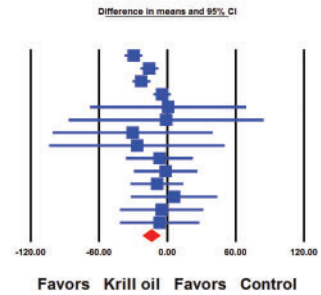
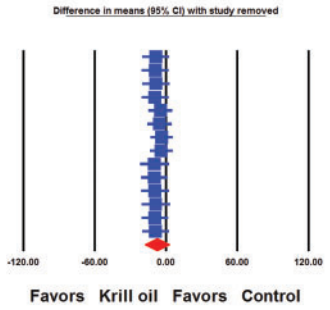


Figure 2 **Forest plots detailing weighted mean differences and 95% confidence intervals for the effect of krill oil supplementation on plasma lipid concentrations.** *Abbreviations:* HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

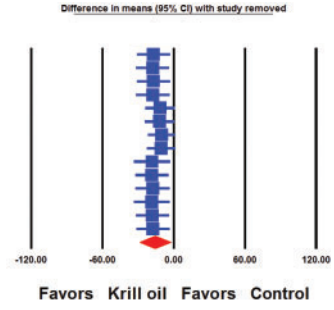
TC

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Berge et al., 2014a (ref. 24)	-8.413	5.721	32.726	-19.626	2.799	-1.471	0.141
Berge et al., 2014b (ref. 24)	-8.872	5.667	32.120	-19.980	2.236	-1.565	0.117
Berge et al., 2014c (ref. 24)	-8.310	5.714	32.645	-19.509	2.888	-1.455	0.146
Berge et al., 2014d (ref. 24)	-8.978	5.734	32.877	-20.217	2.260	-1.566	0.117
Bunea et al., 2014a (ref. 4)	-4.536	5.047	25.472	-14.428	5.356	-0.899	0.369
Bunea et al., 2014b (ref. 4)	-5.211	5.169	26.719	-15.343	4.920	-1.008	0.313
Bunea et al., 2014c (ref. 4)	-3.489	4.734	22.409	-12.767	5.789	-0.737	0.461
Bunea et al., 2014d (ref. 4)	-3.918	4.840	23.425	-13.404	5.568	-0.810	0.418
Maki et al., 2009 (ref. 25)	-9.624	6.128	37.555	-21.635	2.387	-1.570	0.116
Ramprasath et al., 2013 (ref. 26)	-9.635	5.662	32.062	-20.733	1.463	-1.702	0.089
Ulven et al., 2011 (ref. 27)	-9.050	5.875	34.516	-20.565	2.465	-1.540	0.123
Lobraico et al., 2015 (ref. 28)	-8.505	6.038	36.462	-20.340	3.330	-1.409	0.159
Ramprasath et al., 2015a (ref. 29)	-9.192	5.637	31.778	-20.241	1.857	-1.631	0.103
Ramprasath et al., 2015b (ref. 29)	-8.569	5.555	31.975	-19.652	2.514	-1.515	0.130
	-7.505	5.324	28.341	-17.939	2.929	-1.410	0.159



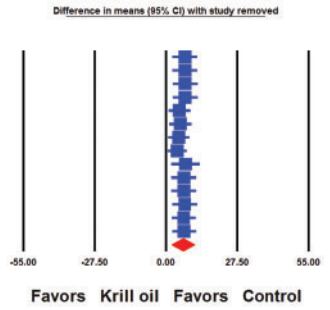
LDL-C

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Berge et al., 2014a (ref. 24)	-16.830	7.054	49.764	-30.657	-3.004	-2.386	0.017
Berge et al., 2014b (ref. 24)	-17.471	7.003	49.038	-31.196	-3.746	-2.495	0.013
Berge et al., 2014c (ref. 24)	-16.814	7.045	49.638	-30.623	-3.005	-2.387	0.017
Berge et al., 2014d (ref. 24)	-17.329	7.083	50.167	-31.211	-3.447	-2.447	0.014
Bunea et al., 2014a (ref. 4)	-11.208	6.185	38.250	-23.329	0.914	-1.812	0.070
Bunea et al., 2014b (ref. 4)	-11.609	6.286	39.515	-23.929	0.712	-1.847	0.065
Bunea et al., 2014c (ref. 4)	-9.938	5.851	34.236	-21.406	1.530	-1.698	0.089
Bunea et al., 2014d (ref. 4)	-10.484	6.008	36.091	-22.258	1.291	-1.745	0.081
Maki et al., 2009 (ref. 25)	-17.950	7.692	59.173	-33.026	-2.873	-2.333	0.020
Ramprasath et al., 2013 (ref. 26)	-18.050	7.121	50.711	-32.007	-4.093	-2.535	0.011
Ulven et al., 2011 (ref. 27)	-17.481	7.259	52.691	-31.708	-3.254	-2.408	0.016
Lobraico et al., 2015 (ref. 28)	-18.224	7.699	59.267	-33.313	-3.135	-2.367	0.018
Ramprasath et al., 2015a (ref. 29)	-17.638	7.001	49.019	-31.361	-3.916	-2.519	0.012
Ramprasath et al., 2015b (ref. 29)	-17.204	6.967	48.540	-30.859	-3.549	-2.469	0.014
	-15.519	6.588	43.401	-28.432	-2.607	-2.356	0.018



HDL-C

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Berge et al., 2014a (ref. 24)	7.442	2.403	5.773	2.733	12.152	3.097	0.002
Berge et al., 2014b (ref. 24)	7.433	2.399	5.756	2.730	12.135	3.098	0.002
Berge et al., 2014c (ref. 24)	7.530	2.416	5.839	2.794	12.265	3.116	0.002
Berge et al., 2014d (ref. 24)	7.507	2.408	5.796	2.788	12.225	3.118	0.002
Bunea et al., 2014a (ref. 4)	5.285	2.105	4.432	1.159	9.411	2.510	0.012
Bunea et al., 2014b (ref. 4)	5.676	2.169	4.705	1.424	9.927	2.617	0.009
Bunea et al., 2014c (ref. 4)	5.060	2.050	4.201	1.043	9.077	2.469	0.014
Bunea et al., 2014d (ref. 4)	4.436	1.861	3.463	0.789	8.083	2.384	0.017
Maki et al., 2009 (ref. 25)	7.738	2.763	7.636	2.322	13.154	2.800	0.005
Ramprasath et al., 2013 (ref. 26)	7.030	2.374	5.636	2.377	11.683	2.961	0.003
Ulven et al., 2011 (ref. 27)	7.071	2.398	5.749	2.371	11.770	2.949	0.003
Lobraico et al., 2015 (ref. 28)	7.387	2.442	5.964	2.600	12.173	3.025	0.002
Ramprasath et al., 2015a (ref. 29)	6.993	2.343	5.489	2.401	11.585	2.985	0.003
Ramprasath et al., 2015b (ref. 29)	7.123	2.329	5.426	2.557	11.688	3.058	0.002
	6.647	2.217	4.916	2.301	10.993	2.998	0.003



TG

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Berge et al., 2014a (ref. 24)	-12.168	2.804	7.862	-17.663	-6.672	-4.339	0.000
Berge et al., 2014b (ref. 24)	-13.043	4.608	21.233	-22.074	-4.011	-2.830	0.005
Berge et al., 2014c (ref. 24)	-12.018	4.339	18.829	-20.523	-3.514	-2.770	0.006
Berge et al., 2014d (ref. 24)	-18.756	2.876	8.274	-24.394	-13.118	-6.521	0.000
Bunea et al., 2014a (ref. 4)	-14.115	3.834	14.701	-21.630	-6.600	-3.681	0.000
Bunea et al., 2014b (ref. 4)	-14.034	3.834	14.697	-21.548	-6.520	-3.661	0.000
Bunea et al., 2014c (ref. 4)	-13.760	3.840	14.748	-21.287	-6.233	-3.583	0.000
Bunea et al., 2014d (ref. 4)	-13.816	3.842	14.763	-21.347	-6.286	-3.596	0.000
Maki et al., 2009 (ref. 25)	-14.324	3.920	15.365	-22.007	-6.642	-3.654	0.000
Ramprasath et al., 2013 (ref. 26)	-14.726	3.874	15.004	-22.318	-7.134	-3.802	0.000
Ulven et al., 2011 (ref. 27)	-14.295	3.962	15.860	-22.100	-6.489	-3.589	0.000
Lobraico et al., 2015 (ref. 28)	-14.720	3.798	14.425	-22.163	-7.276	-3.876	0.000
Ramprasath et al., 2015a (ref. 29)	-14.283	3.883	15.079	-21.894	-6.672	-3.678	0.000
Ramprasath et al., 2015b (ref. 29)	-14.225	3.898	15.192	-21.864	-6.585	-3.650	0.000
	-14.026	3.751	14.070	-21.378	-6.674	-3.739	0.000

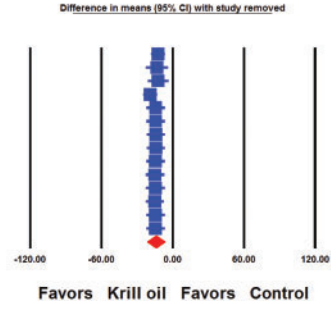


Figure 3 **Leave-one-out sensitivity analysis for the effects of krill oil supplementation on plasma lipid concentrations.** *Abbreviations:* HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 4 **Meta-analysis of the effects of krill oil on plasma lipid concentrations in the subgroups of studies with different dosages and durations of supplementation**

	Total cholesterol (mg/dL)		LDL-C (mg/dL)		HDL-C (mg/dL)		Triglycerides (mg/dL)	
	WMD (95%CI)	*P* value	WMD (95%CI)	*P* value	WMD (95%CI)	*P* value	WMD (95%CI)	*P* value
Dosage <2 g/d	−11.12 (−27.53 to 5.29)	0.184	−18.85 (−42.32 to 4.61)	0.115	6.44 (−1.06 to 13.95)	0.092	−21.31 (−26.63 to −16.00)	<0.001
Dosage ≥2 g/d	−5.55 (−19.80 to 8.69)	0.445	−14.33 (−31.98 to 3.32)	0.112	7.25 (1.27 to 13.24)	0.018	−12.16 (−17.11 to −7.21)	<0.001
Duration <12 wk	3.86 (−2.17 to 9.89)	0.210	3.91 (−1.14 to 8.95)	0.129	2.29 (0.24 to 4.33)	0.028	−4.60 (−16.82 to 7.61)	0.460
Duration ≥12 wk	−24.12 (−45.37 to −2.86)	0.026	−37.14 (−64.96 to −9.31)	0.009	12.53 (3.44 to 21.63)	0.007	−17.67 (−27.15 to −8.19)	<0.001

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; WMD, weighted mean difference.

Figure 4 **Funnel plots detailing publication bias in the studies selected for analysis. Trim-and-fill method was used to impute for potentially missing studies.** Open circles represent observed published studies; closed circles represent imputed unpublished studies. *Abbreviations:* HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 5 **Publication bias in the meta-analysis of studies reporting the effects of krill oil supplementation on plasma lipids**

Plasma lipid	Begg's rank correlation test			Egger's linear regression test				
	Kendall's tau[a]	*z* value	*P* value[b]	Intercept (95%CI)	*t*	*df*	*P* value[b]	No. of studies[c]
Total cholesterol	−0.46	2.30	0.021	−3.00 (−5.20 to −0.80)	3.82	9	0.004	N/A
LDL-C	−0.55	2.74	0.006	−4.15 (−6.95 to −1.34)	3.22	12	0.007	44
HDL-C	0.59	2.96	0.003	2.35 (0.21 to 4.49)	2.40	12	0.034	91
Triglycerides	−0.07	0.33	0.743	0.59 (−0.72 to 1.89)	0.98	12	0.346	105

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]With continuity correction.
[b]Two-tailed.
[c]Number of studies (calculated using the fail-safe N method) required to make the *P* value nonsignificant.

(SREBP)-2, all involved in triacylglycerol and fatty acid catabolism in skeletal muscle and liver.[31]

A higher bioavailability of long-chain n-3 polyunsaturated fatty acids and a higher therapeutic effect[1] has been observed in studies comparing the efficacy of krill oil with that of fish oil.[5,26,27,32] The association between long-chain n-3 fatty acids and phospholipids is responsible for lipogenic effects of krill oil, while the association between n-3 fatty acids and TGs is culpable for the lipogenic effects of fish oil.[3] Phospholipids are amphipathic molecules that do not require emulsification via bile salts like the hydrophobic TGs, hence they are able to move easily across the intestinal wall and cell membranes.[5] Therefore, the association between long-chain n-3 fatty acids and phospholipids might have an important role in improving the bioavailability and absorption of fatty acids through the intestinal wall and enhancing the n-3:n-6 ratio.[27] The different effects of krill oil as compared with fish oil on lipid parameters in experimental studies might be also explained by the different effects of these oils on the secretion of very low-density lipoprotein and the distinct modulation of gene expression in the intestine and the liver.[33] Moreover, experimental studies showed that krill oil is capable of upregulating the activity of the mitochondrial respiratory chain and downregulating the activity of pathways involved in lipid and cholesterol synthesis and hepatic glucose production, while fish oil did not modulate the same metabolic pathways regulated by krill oil.[30]

While fish oil upregulates the cholesterol synthesis pathway, the effect of krill oil is the opposite.[30] An experimental study in rats fed a krill-oil-enriched diet has shown that krill oil might have the capacity to inhibit de novo lipogenesis by decreasing the activity of both cytosolic acetyl coenzyme A carboxylase and the mitochondrial citrate carrier and to increase the oxidation of fatty acids by decreasing the fatty acid synthetase activity.[34,35] Another unique feature of krill oil is related to its powerful antioxidant astaxanthin, which has a slight, but not significant, glucose-lowering effect on plasma lipid concentrations.[36] Another important antioxidant found in krill oil is vitamin E, known for its capacity to protect biological membranes against lipid peroxidation.[37] Nevertheless, krill oil is a rich source of high-quality protein in the range of 60% to 65% dry weight, including all 9 essential amino acids required by adults.[38]

One study showed that daily consumption of 3 g of krill oil formulated with 543 mg of EPA and DHA raises the plasma EPA and DHA concentrations exactly the same as intake of fish oil containing 864 mg of EPA and DHA.[27] Another new study in healthy subjects showed that the proportion of EPA and DHA in plasma phospholipid fatty acids measured during a 72-hour follow-up as an incremental area under the curve was significantly larger after krill oil ingestion than after fish oil ingestion.[9] The adverse effects observed after krill oil consumption are observed only in individuals with known allergies to different crustaceans or shellfish, such as shrimp or crabs.[1,39] Moreover, patients who take krill oil and anticoagulant/antiplatelet drugs simultaneously might have an increased risk of bleeding.

The present meta-analysis has some limitations. Most of the included studies had a small number of participants and were heterogeneous with regard to the characteristics of patients. Moreover, the lipid profile and content of krill oil could fluctuate appreciably according to conditions such as the krill species used, the age of the krill, the season harvested, and the delay time between collection and freezing. The effects of krill on small, dense LDL subfractions and HDL function do not seem to have been investigated. The function of HDL may be even more relevant than its measured levels.[13] However, the effect of krill oil on TG and HDL-C levels suggests there will be an improvement in small, dense LDL subfractions.[40] The baseline dietary data and the prescribed diet were not clearly described in all the studies included. In this meta-analysis, the most significant effects on plasma lipids were reported in the treatment arms in the study by Bunea et al.[4] Although the impact of each treatment arm on the overall estimated effect size was explored in the sensitivity analysis, another attempt was made to assess the impact of this study on the effect size by removing all treatment arms in this study from the meta-analysis. The results revealed that, although the TG-lowering effect of krill oil remains significant, the effects on LDL-C and

HDL-C were no longer evident when the study of Bunea et al.[4] was excluded. This highlights the need for future studies to better evaluate whether krill oil supplementation exerts a LDL-lowering effect. Finally, the value of adding krill oil to conventional and novel lipid-lowering medications[41–44] remains unknown.

CONCLUSION

The present meta-analysis of RCTs suggests the efficacy of krill oil supplementation in lowering plasma concentrations of LDL-C and TGs as well as increasing those of HDL-C. Further, well-designed clinical studies with higher numbers of participants are necessary to assess the impact of krill oil supplementation on other indices of cardiometabolic risk and on the risk of cardiovascular outcomes. The value of adding krill oil to statins and other routinely administered lipid-lowering therapies is also open to question.

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Declaration of interest. The authors have no relevant interests to declare.

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