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A combination of omega-3 fatty acids, folic acid and B-group vitamins is superior at lowering homocysteine than omega-3 alone: A meta-analysis

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ABSTRACT

The aim of the study was to assess whether omega-3 polyunsaturated fatty acid supplementation alone or in combination with folic acid and B-group vitamins is effective in lowering homocysteine. The Medline Ovid, Embase and Cochrane databases were searched for randomized-controlled trial studies that intervened with omega-3 supplementation (with or without folic acid) and measured changes in homocysteine concentration. Studies were pooled using a random effects model for meta-analysis. Three different models were analyzed: all trials combined, omega-3 polyunsaturated fatty acid trials, and omega-3 polyunsaturated fatty acids with folic acid and B-group vitamin trials. Nineteen studies were included, consisting of 3267 participants completing 21 trials. Studies were heterogeneous; varying by dose, duration and participant health conditions. Across all trials, omega-3 supplementation was effective in lowering homocysteine by an average of 1.18 μmol/L (95%CI: (−1.89, −0.48), $P = .001$). The average homocysteine-lowering effect was greater when omega-3 supplementation was combined with folic acid and B-group vitamins (−1.37 μmol/L, 95%CI: (−2.38, −0.36), $P < .01$) compared to omega-3 supplementation alone (−1.09 μmol/L 95%CI: (−2.04, −0.13), $P = .03$). Omega-3 polyunsaturated fatty acid supplementation was associated with a modest reduction in homocysteine. For the purposes of reducing homocysteine, a combination of omega-3 s (0.2–6 g/day), folic acid (150 – 2500 μg/day) and vitamins B6 and B12 may be more effective than omega-3 supplementation alone.

1. Introduction

Homocysteine is an amino acid that is synthesized endogenously during methionine metabolism [1]. Normal healthy levels of total plasma homocysteine range between 5-15 μmol/L [2]. Elevated homocysteine concentration is associated with lower bone mineral density in women [3] and an increased risk of vascular and neurological disease [2,4,5]. Over the past two

Abbreviations: DHA, Docosahexaenoic Acid; EPA, Eicosapentaenoic Acid; MTHFR, Methylenetetrahydrofolate Reductase; PUFA, Polyunsaturated Fatty Acid.

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decades, omega-3 polyunsaturated fatty acids (PUFAs) have been postulated to lower homocysteine. Animal and in-vitro studies reveal that omega-3 PUFAs enhance lipid metabolism and decrease homocysteine concentration by up-regulating metabolic enzymes and improving substrate availability for homocysteine degradation [6,7]. While these studies have been hypothesis generating, it is unclear how applicable they are to human metabolism.

In humans, the effect of omega-3 PUFA supplementation for homocysteine-lowering is inconclusive. Trial results are inconsistent and study characteristics are heterogeneous [8–15]. Many omega-3 trials have included supplemental folic acid and B-group vitamins [16–19]. This is a confounder because B-group vitamins are well established supplements for lowering homocysteine because of their direct involvement in homocysteine degradation [1]. Indeed, folic acid lowers homocysteine concentration by between 1.5–4.5 μmol/L [20]. It is uncertain whether omega-3 PUFAs can effectively lower homocysteine, or whether the observed homocysteine reductions have simply been due to the additional supplementation of folic acid and B-group vitamins.

Recent studies suggest that lowering homocysteine with folic acid offers little or no reduction to cardiovascular disease risk [20,21]. Given the general health benefits of omega-3 PUFAs [22], it is possible that there may be differences in disease risk if omega-3 PUFAs were used to lower homocysteine. It is therefore worthwhile to evaluate the efficacy of omega-3 alone for lowering homocysteine.

It is hypothesized that omega-3 PUFAs will be efficacious at lowering homocysteine. It is also hypothesized that the homocysteine-lowering effect will be superior when omega-3 PUFAs are combined with folic acid and B-group vitamins compared to omega-3 PUFA supplementation alone. This study uses meta-analysis to quantify and compare the homocysteine-lowering effect of omega-3 PUFAs separately and in combination with folic acid and B-group vitamins, and it extends a previous meta-analysis that supported omega-3 PUFAs for lowering homocysteine [15].

2. Methods and materials

2.1. Search strategy

To gather studies for the meta-analysis, the Medline Ovid, Embase and Cochrane databases were searched without date limitations. Articles with a randomized-controlled trial study design were searched for homocysteine and analogous terms for omega-3 PUFAs.

2.2. Inclusion criteria

Randomized-controlled trial studies were eligible for inclusion if they included supplementation with a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 PUFAs and measured quantitative changes in homocysteine concentration. Studies needed to be written in English and published in a peer-reviewed journal. No constraints were placed on settings, patient population, intervention duration or omega-3 PUFAs dosage. To gather a large dataset, trials meeting the inclusion criteria were included even when homocysteine-lowering was not the primary objective of the study. Titles and abstracts were screened for the inclusion criteria. Full articles were read and assessed for inclusion (Fig. 1).

2.3. Data extraction

Two datasets were created: one for omega-3 PUFA supplementation trials, and another for omega-3 PUFAs plus folic acid and B-group vitamins trials. Homocysteine measurement data were abstracted for baseline and follow-up, and where necessary means were approximated from medians and standard deviations were derived [23]. For missing data, authors were contacted and data was requested. Individual study bias was evaluated using RevMan [24].

2.4. Statistical analyses

To determine the validity of pooling studies, publication bias was evaluated using a contour-enhanced funnel plot [25]. The mean difference in homocysteine (μmol/L) was plotted against the inverse standard error as an indicator of study precision. Funnel plot asymmetry was statistically assessed using Egger's regression asymmetry test and the adjusted rank correlation test.

Heterogeneity was assessed statistically and by considering study characteristics. Cochran's Q was used to test the null hypothesis that the effect was consistent across studies [26]. I^2 was also evaluated and if it was greater than 25% then heterogeneity was indicated [27]. If heterogeneity were found then the DerSimonian and Laird random effects model which incorporates between-study variability would be used [28]. For each study, the within-group mean change from baseline in homocysteine (μmol/L) was calculated, and then the between-group mean differences and sampling variances were calculated. The effect size reported represents the weighted mean difference (change from baseline) in homocysteine (μmol/L) with 95% confidence intervals. Statistical analysis was performed using the Metafor package [29] for R version 3.0.2 (Foundation for Statistical Computing, 2012). Meta-regression was used to test for moderating effects of study characteristics such as: total DHA and EPA dosage, duration and baseline homocysteine.

2.5. Sensitivity analysis

Pre-specified sensitivity analysis encompassed: leave-one-out sensitivity analysis for determining influential studies [29]; separately assessing studies where homocysteine-lowering was not a primary outcome; and removing studies with low precision or high individual study bias.

3. Results

3.1. Study characteristics

Forty-five studies were identified and assessed for inclusion and 26 were excluded (Fig. 1). The final dataset consisted of 19 studies with two having two trial arms. This yielded 13 trials for the omega-3 PUFAs trial arm, and 8 trials for the omega-3 PUFAs with folic acid and B-group vitamins trial arm (Table 1). The primary outcome for 10 studies was to measure changes