Review Article

Omega-3 polyunsaturated fatty acids and non-communicable diseases: meta-analysis based systematic review

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The aim of this updated systematic review is to summarize the evidence of the effect of omega-3 polyunsaturated fatty acids (n-3 PUFA) on non-communicable diseases (NCDs). Publications of meta-analysis up to August 2014 were systematically searched from PubMed, the Cochrane and EMBASE databases. N-3 PUFAs have the following beneficial effects; cardio-protective effects, reduce ischemic stroke risk in both men and women and total stroke risk in women, increase insulin sensitivity in Asians, decrease risk of breast cancer and colorectal cancer in men. However, n-3 PUFAs may have unfavourable effects on type 2 diabetes in Caucasians. In conclusion, n-3 PUFA plays a crucial role in the prevention of NCDs, however, unfavourable effects should be considered in subjects with certain clinical conditions. Cross-cultural studies on the effect of n-3 PUFA on type 2 diabetes are needed to verify why diabetic patients with different ancestries have a different response to n-3 PUFA.

Key Words: n-3 PUFA, non-communicable disease, meta-analysis, systematic review, mechanism

INTRODUCTION

Non-communicable diseases (NCDs), also known as chronic diseases, are those which cannot be passed from person to person, NCDs are generally slow-progressing and long-duration diseases. NCDs are the leading cause of death worldwide.[1] Based on WHO definition, there are four main types of NCDs: cardiovascular diseases, cancers, diabetes and chronic respiratory diseases.[2] The prevalence of NCDs is dramatically increasing in developing and transitional countries in recent years, which is associated with globalization of unhealthy lifestyles, rapid unplanned urbanization and the aging population.[3] Unhealthy lifestyles include unhealthy diets, physical inactivity, exposure to tobacco smoke and harmful use of alcohol. Unhealthy diets include increased intake of foods rich in total fat, saturated fat, n-6 polyunsaturated fatty acid (PUFA) and sugar, and decreased intake of dietary fibre, n-3 PUFA, fruits and vegetables.[4]

Essential fatty acids for humans are α-linolenic acid (ALA; C18:3n-3) and linoleic acid (LA; C18:2n-6). C18:2n-6 is the predominant PUFA in the global food chain, which is commonly found in vegetable seed oils and in most manufactured foods. C18:3n-3 is less abundant than C18:2n-6, and is the predominant n-3 PUFA found in plant food and commonly found in some vegetable oils such as flaxseed, perilla, canola, soybean and walnut oils. C18:3n-3 and C18:2n-6 can be converted in *vivo* to C20 and C22 long chain (LC) PUFA in humans.[5] Eicosapentaenoic acid (EPA, C20:5n-3) is a predominant LC n-3 PUFA in most fish and fish/marine oils, docosahexaenoic acid (DHA, C22:6n-3) is most abundant LC n-3 PUFA in tuna and tuna oil,[6] while docosapentaenoic acid (DPA, C22:5n-3) is a major LC n-3 PUFA in certain seafood such as abalone,[7] lean meat and meat products etc.[8] Stearidonic acid (SDA, 18:4n-3) is found in Ribesberries and Boraginaceae families.[9]

The effect of n-3 PUFA on NCDs has been extensively studied during the past three decades. The aim of the present review was to systematically review the effect of n-3 PUFA on NCDs based on the results of current meta-analysis, which use statistical methods to combine similar results of individual studies. Meta-analysis allows us to make the best use of all the information to improve the precision of our estimates of treatment effect and increase the power of the analysis.[10]

CARDIOVASCULAR DISEASES

N-3 PUFA & CHD

Meta-analysis of randomized controlled trials (RCTs), prospective cohort and biomarkers studies revealed that n-3 PUFA are inversely associated with mortality and

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morbidity from coronary heart disease (CHD). The two most recent meta-analyses published in 2014 reported that n-3 PUFA have a cardio-protective benefit. In the first meta-analysis, authors summarized the effect of n-3 PUFA supplementation on major cardiovascular events and mortality in patients with coronary heart disease. Fourteen randomized controlled trials (RCTs) met inclusion criteria, including 16,338 patients in the n-3 PUFA group and 16,318 patients in the placebo control group. All subjects had CHD such as CAD, AMI, post-MI and heart failure. Two of the 14 studies were conducted for less than 3 months, 3 of the studies for 6 months, and the other 9 studies for more than 1 year. LC n-3 PUFA EPA plus DHA intakes ranged from 400 mg to 4,800 mg/d/person. Odds Ratio (OR) for reduced risk from death of all causes was 0.92; 95% CI: 0.85-0.99; p=0.02; I^2=6%, from cardiac causes 0.88; 95% CI: 0.80-0.96; p=0.003; I^2=0% and sudden cardiac death was 0.86; 95% CI: 0.76-0.98; p=0.03; I^2=29%; respectively.[11]

In another meta-analysis, the authors summarized the association between fatty acids and coronary disease. Results indicated that dietary intake of total LC n-3 PUFA and circulating individual LC n-3 PUFAs were significantly associated with decreased coronary risk. The summary estimated relative risks (RRs) for coronary disease in prospective cohort studies of dietary intake of total LC n-3 PUFA was 0.87 (95% CI: 0.78 -0.97) based on 16 studies with 422,786 participants and 9,089 events. For the circulating individual n-3 PUFA composition in prospective cohort studies, combined RRs was 0.78 (95% CI: 0.65-0.94) for C20:5n-3 and 0.79 (95% CI: 0.67-0.93) for C22:6n-3 in 13 studies with 23,056 participants and 4,624 events, 0.75 (95% CI: 0.62-0.89) for C20:5n-3 + C22:6n-3 in 13 studies with 20,809 participants and 4,073 events, and 0.64 (95% CI: 0.47-0.89) for C22:5n-3 in 4 studies with 7,155 participants and 2,565 events, respectively. However, meta-analysis of RCTs reported that RRs for LC n-3 PUFA was 0.89 (95% CI: 0.71-1.12) in 27 RCTs, which included a total of 105,085 participants, among whom 6,229 had an incident coronary outcome with mean follow-up ranging from 0.1 to 8.0 years.[12] This result has been questioned due to inclusive criteria, in which 27 RCTs including 18 trials recruited participants with CVD at baseline, 8 recruited participants with elevated cardiovascular risk factors, and 1 involved initially healthy participants. The absence or presence (and type) of pre-existing CVD at baseline will cause substantial heterogeneity and bias.

N-3 PUFA & cerebrovascular disease

Evidence from the recent meta-analysis revealed that increased dietary intake of LC n-3 PUFA is inversely associated with cerebrovascular disease. There were two meta-analyses of LC n-3 PUFA and cerebrovascular disease published in 2012. The first meta-analysis included 26 prospective cohort studies and 12 RCTs with 794,000 participants and 34,817 cerebrovascular cases. In prospective cohort studies, RR for circulating biomarkers of LC n-3 PUFA was 1.04 (0.90-1.20) and for dietary intake was 0.90 (0.80-1.01) when comparing the top thirds with the bottom thirds. In the RCTs, RR was 0.98 (0.89-1.08) for primary prevention trials of cerebrovascular disease and 1.17 (0.99-1.38) for secondary prevention trials in LC n-3 PUFA supplementation group compared with control group. The authors concluded that there was a moderate inverse association of dietary intake of LC n-3 PUFA with cerebrovascular risk.[13]

Another meta-analysis included 8 prospective cohort studies with 242,076 participants and 5,238 stroke cases. Upon comparing the highest category of LC n-3PUFA intake versus lowest, RR was 0.90 (95% CI: 0.81-1.01) for total stroke without heterogeneity among studies (p=0.32), 0.82 (95% CI: 0.71-0.94) for ischemic stroke and 0.80 (95% CI: 0.55-1.15) for hemorrhagic stroke, and 0.80 (95% CI: 0.65-0.99) for total stroke risk in women. The authors suggested that women might benefit from a higher intake of these PUFAs for stroke prevention.[14]

CANCERS

N-3 PUFA may have different effects on different types of cancer. Meta-analysis of prospective cohort and biomarkers studies summarized that dietary intake of LC n-3 PUFA and ratio of n-3/n-6 PUFA are negatively associated with risk of breast cancer and colorectal cancer in men. Inconsistent outcomes from meta-analysis of n-3 PUFA and prostate cancer have been reported, therefore this disease as not been included in the systematic review.

N-3 PUFA & breast cancer

The most recent meta-analysis of dietary ratio of n-3/n-6 PUFAs and risk of breast cancer was published in 2014, which includes six prospective nested case-control and 5 cohort studies with 274,135 participants and 8,331 breast cancer cases. Higher dietary ratio of n-3/n-6 PUFAs was significantly inversely associated with decreased risk of breast cancer (RR=0.90, 95% CI: 0.82-0.99), and per 1/10 increment of dietary ratio of n-3/n-6 PUFAs was associated with a 6% reduction of breast cancer risk (RR=0.94, 95% CI: 0.90-0.99; p for linear trend =0.012). Higher ratio of n-3/n-6 in serum phospholipids (PL) was associated with significantly decreased risk of breast cancer (RR=0.62, 95% CI: 0.39-0.97; I^2=0.00%) in 3 studies from USA, and there was a 27% reduction of breast cancer risk with 1/10 increment of serum PL ratio of n-3/n-6 PUFA (RR=0.73, 95% CI: 0.59-0.91; p for linear trend =0.004).[15]

Another recent meta-analysis of n-3 PUFA and breast cancer was published in 2013, which included 26 publications with 883,585 participants and 20,905 cases of breast cancer from 21 independent prospective cohort studies. Marine n-3 PUFA were significantly negatively associated with breast cancer risk (RR=0.86, 95% CI: 0.78- 0.94; I^2=54%) in 17 publications from 16 independent cohort studies involving 527,392 participants and 16,178 breast cancer cases. Dose-response analysis showed a 5% reduction of breast cancer risk with 0.1 g/day (RR=0.95, 95% CI: 0.90-1.00, I^2=52%) or 0.1% energy/day (RR=0.95, 0.90-1.00, I^2=79%) increment of dietary intake of marine n-3 PUFA. Total n-3 PUFA intake was significantly negatively associated with risk of breast cancer (RR=0.77, 95% CI: 0.60-0.99) only in studies without adjustment for BMI. For individual marine n-3 PUFA, the significant inverse association with risk of breast cancer was observed only in studies with shorter follow-up, RR=0.82

(95% CI: 0.70-0.96) for C20:5n-3 and 0.74 (0.62-0.89) for C22:6n-3. These inverse associations with risk were more evident in studies that adjusted for BMI or education compared with studies without such adjustment, while it was not significant for C20:5n-3 or C22:6n-3 among studies with longer follow-up. There was no significant association between risk of breast cancer and dietary intake of fish in 11 articles with 687,770 participants and 13,323 breast cancer cases, and nor for C18:3n-3 in 12 publication with 405,592 participants and 14,284 breast cancer cases.[16] The possible explanations for why dietary intake of n-3 PUFA is negatively associated with breast cancer, but not for fish intake are that different species of fish contain different amounts of n-3 PUFA fatty acids,[17] and the cooking method (especially deep frying) and choice of cooking oil can also influence the overall fatty acid content of fish.[18]

N-3 PUFA & colorectal cancer

A recent meta-analysis of dietary intake of n-3 PUFA and colorectal cancer was published in 2002, including 7 prospective cohort studies with 489,465 participants and 4,656 colorectal cancer cases. The pooled RR of colorectal cancer in relation to dietary intake of n-3 fatty acids was 0.98 (95 % CI: 0.88-1.09). The results from subgroup analysis indicated a significant reduced risk of colorectal cancer in relation to dietary intake of n-3 fatty acids among men (RR 0.87, 95 % CI: 0.75-1.00).[19]

TYPE 2 DIABETES

A number of meta-analyses have been published in recent years, with the pooled RR indicating that dietary and circulating LC n-3 PUFA were either positively associated with type 2 diabetes (T2D), or there was no significant association. However, two recent meta-analyses which conducted a subgroup analysis based on the ethnic background revealed that Asian and Caucasian T2D patients have a different response to LC n-3 PUFA, i.e. LC n-3 PUFA have a beneficial effect on insulin sensitivity in Asian populations, but not in Caucasians. Therefore, a summary of the effect of n-3 PUFA on T2D based on the two meta-analyses with subgroup analysis in relation to genetic background was included in the present review. In the first meta-analysis, 24 prospective cohort studies (1 study from Australia, 1 from Cuba, 7 from Europe, 8 from Asia and 7 from the US) with total of 24,509 T2D patients and 545,275 participants were included. For cohort studies, the summary RR of T2D for the intake of highest vs lowest categories was 1.07 (95% CI: 0.95-1.20) for marine n-3 PUFA and 0.93 (95% CI: 0.81-1.07) for C18:3n-3, respectively. Subgroup analyses based on genetic background indicated that summary RR of T2D for the intake of highest vs lowest category of marine n-3 PUFA intake was 0.87 (95% CI: 0.79-0.96) for Asian populations and 1.16 (95% CI: 1.04-1.28) for Western populations. In Asians, compared with healthy subjects, T2D patients have a significantly lower tissue composition of C22:6n-3 (standardized mean difference (SMD): -1.43; 95% CI: -1.75, -1.12) and total n-3 PUFA (SMD: -1.41; 95% CI: -2.23, -0.59).[20]

Similar results were also reported in another meta-analysis published in 2012, whereby 16 prospective studies, 7 studies from USA, 4 from Europe, 4 from Asia, and 1 from Australia were included with a total of 527,441 participants and 24,082 diabetes cases. For each 0.30 g per day increment in dietary intake of LC n-3PUFA intake (corresponding to approximately one serving per week of fatty fish), the corresponding summary RR were 1.17 (95% CI: 1.09-1.26) for USA, 0.98 (95% CI: 0.70-1.37) for European and 0.90 (95% CI: 0.82-0.98) for Asian/Australian studies, respectively.[21]

RESPIRATORY TRACT DISEASES

There are only two meta-analyses in the literature in relation to respiratory disorders and n-3 PUFA. Enteral supplementation of n-3 PUFA only had no significant beneficial effects on acute respiratory distress syndrome, however, combined C20:5n-3 and gamma-linolenic acid (C18:3n-6) revealed a significant inverse association. The most recent meta-analysis of n-3 PUFA was published in 2014, which involved 7 RCTs with 955 adult acute respiratory distress syndrome patients. The authors stated that all the included trials were considered as at high risk of bias. RR of enteral n-3 PUFA supplementation on all-cause 28-day mortality of acute respiratory distress syndrome was 0.90; 95% CI: 0.68-1.18; p=0.44; I^2=31%;

Table 1. Summary of the effect of n-3 polyunsaturated fatty acids on non-communicable diseases from meta-analysis

	n-3 polyunsaturated fatty acid			
	n-3 PUFA source	Study design	Effect[†]	References
Coronary heart disease	LC n-3 PUFA	RCT	↓	11,12
Cerebrovascular disease	LC n-3 PUFA	RCT	↓ (moderate)	13
		Cohort	↓ (women)	14
Breast cancer	n-3:n-6	Cohort	↓	15
	LC n-3 PUFA	Cohort	↓	16
Colorectal cancer	LC n-3 PUFA	Cohort	↓ (men)	17
Type 2 diabetes	LC n-3 PUFA	Cohort	↓ (Asian)	18
		Cohort	↑ (Caucasian)	18
		Cohort	↓ (Asian)	19
		Cohort	↑ (USA)	19
Respiratory tract disease	C20:5n-3+C18:3n-6	RCT	↓	20
		RCT	↓	21

[†]↓ negative correlation, ↑ positive correlation

random effects. Ratio of partial pressure of arterial oxygen/ fraction of inspired oxygen (PaO_2/FiO_2) was significantly increased in the n-3 PUFA group on day 4, weighted mean difference (WMD) was 45.1; 95% CI: 16.8-73.5; p=0.002; I^2=86%; random effects, and on day 7 WMD was 33.1; 95% CI: 1.67-64.5; p=0.04; I^2=88%; random effects. There was no significant differences in ventilator-free days (VFD) (WMD, 2.47 days; 95% CI: -2.85-7.79; p=0.36; I^2=91%) or intensive care unit-free days (ICU) (WMD, 2.31 days; 95% CI: -2.34-6.97; p=0.33; I^2=89%) between the n-3 PUFA and control groups.[22]

Another meta-analysis was published in 2008, which involved 3 RCTs with 411 acute respiratory distress syndrome patients. Risk of mortality was significantly reduced with odds ratio (OR)=0.40 (95% CI: 0.24-0.68; p=0.001) and risk of developing new organ failure was also significantly reduced with OR=0.17 (95% CI: 0.08-0.34; p<0.0001) in C20:5n-3 + C18:3n-6 group compared with control group. Standardized mean difference [SMD]=0.56 (95% CI: 0.32-0.79; p<0.0001) for time on mechanical ventilation, and 0.51 (95% CI: 0.27-0.74; p<0.0001) for intensive care unit stay in C20:5n-3 + C18:3n-6 group compared with control group.[23]

HEAVY METAL IN FISH AND NON-COMMUNICABLE DISEASES

Fish is a good source of LC n-3 PUFA.[24] However, there has been increasing concern over safety from contaminants in some fishes such as heavy metal mercury, lead, chromium and cadmium, especially cultured freshwater species since it was directly affected by the heavy pollution of water resources, especially in some offshore areas.[25] The public is facing conflicting reports on the benefits and risks of fish intake, resulting in confusion over the role of fish consumption in a healthy diet. However, there are no data to show that certain clinical condition is caused by the fish consumption. In a US nested case-control study, toenail clippings were collected in 1987 from 33,737 male health professionals who were 40 to 75 years of age in 1986. The mercury level of toenail clippings was significantly correlated with fish consumption (r=0.42, p<0.001), however, it was not significantly correlated with the risk of coronary heart disease adjusted for age, smoking, and other risk factors of coronary heart disease.[26] In another study, 3,427 cases of coronary heart disease and stroke from two US prospective cohorts (51,529 men and 121,700 women) were participated the study. Toenail mercury concentration was measured by neutron-activation analysis. Results showed that mercury exposures was not significantly associated with neither coronary heart disease, stroke, nor total cardiovascular disease.[27] The report of the 2010 Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption summarized that there is an absence of probable or convincing evidence of risk of coronary heart disease associated with methylmercury. In addition, the report indicated that the potential cancer risks associated with dioxins are well below established coronary heart disease benefits from fish consumption.[28]

POSSIBLE MECHANISMS OF THE N-3 PUFA ON NON-COMMUNICABLE DISEASES

The beneficial effect of n-3 PUFAs on non-communicable diseases may be attributed to its anti-inflammatory activity.[29,30] Marine n-3 PUFA EPA, DHA and DPA are substrates for specialized proresolving lipid mediators resolvins, protectins and maresins, which are novel autacoids that resolve inflammation, protect organs, stimulate tissue regeneration and modulate immune function.[31] These novel lipid mediators have been recently identified in human plasma following increased consumption of marine oils and diets rich in n-3 PUFA.[32-34] Marine-derived n-3 PUFA supplementation had a significant lowering effect on serum levels of CRP, IL-6 and TNF-α.[35] Marine-derived n-3 PUFAs are antagonistic towards pro-inflammatory eicosanoids such as PGE_2 and LTB4, and pro-thrombotic eicosanoid thromboxane A_2 from arachidonic acid.[36] In addition to effects on inflammation, n-3 PUFA also have a beneficial effect on increased heart rate variability,[37] and decreased blood pressure in hypertension subjects[38] and serum triacylglycerol concentration,[39] and showed a prolonged relative refractory period by electrically stabilizing cardiac myocytes.[40]

CONCLUSION

Available evidence from recent published meta-analyses indicated that n-3 PUFA plays a crucial role in prevention of NCDs, such as cardiovascular disease, breast cancer, colorectal cancer in men, and diabetes in Asian populations. However, unfavourable effects should be accounted in subjects with certain clinical conditions, such as Caucasian type 2 diabetes. Cross-cultural studies on the effect of n-3 PUFA on type 2 diabetes are needed to verify why diabetes patients with different ancestries have different responses to n-3 PUFA.

AUTHOR DISCLOSURES

The Author has no conflict of interest in regards to this paper.

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Review Article

Omega-3 polyunsaturated fatty acids and non-communicable diseases: meta-analysis based systematic review

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N-3 多不饱和脂肪酸和非传染性疾病：基于荟萃分析的系统综述

此更新的系统综述的目的是总结 n-3 多不饱和脂肪酸对非传染性疾病影响的证据。从 PubMed、 the Cochrane 和 EMBASE 数据库系统检索了截止 2014 年 8 月底前发表的荟萃分析。 N-3 多不饱和脂肪酸具有以下有益效果：心脏保护作用，降低男性和女性缺血性脑卒中的风险以及女性总脑卒中风险，增加亚洲人对胰岛素的敏感性，降低男性患乳腺癌和结肠癌的风险。但是，n- 3 多不饱和脂肪酸对白种人的 2 型糖尿病会产生不利影响。总之， n-3 多不饱和脂肪酸在预防非传染性疾病方面起非常重要的作用。但是，对某些人群的临床情况应考虑他的不利影响。n-3 多不饱和脂肪酸对 2 型糖尿病的影响需要通过跨文化研究以验证为什么不同血统的糖尿病患者对 n-3 多不饱和脂肪酸的应答不同。

关键词：n-3 多不饱和脂肪酸、非传染性疾病、荟萃分析、系统综述、机制