Omega-6 fatty acids and risk of cardiovascular disease: insight from systematic review and meta-analysis of randomized controlled trials and a mendelian randomization study

Authors:
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Topic(s):
Risk Factors and Prevention – Epidemiology

Background: Omega-6 polyunsaturated fatty acids (PUFAs) represent almost 15% of the total energy intake in the Western countries. Their effects on several cardiovascular (CV) risk factors are still controversial.

Purpose: We performed a systematic review and meta-analysis of randomized control trials (RCTs) as well as a Mendelian randomization (MR) analysis to evaluate the links (or possible causality) between supplementation or serum levels of omega-6 PUFAs, CV disease (CVD) and cardiometabolic risk factors.

Methods: Selected databases were searched until 31 August 2019 to identify prospective studies investigating the effects of omega-6 PUFAs supplementation on CVD events/mortality. Random-effects model meta-analysis was performed for quantitative data synthesis. Trial sequential analysis (TSA) was used to evaluate the optimal sample size to detect a 20% reduction in outcomes after administration of omega-6 PUFAs. Inverse variance weighted method (IVW), weighted median-based method, MR-Egger and MR-Pleiotropy RESidual Sum and Outlier (PRESSO) were applied for MR.

Results: In the meta-analysis of 9 studies with 4,433 participants we showed that omega-6 PUFAs supplementation was not associated with CVD event risk - RR 0.94 (95% CI: 0.77-1.15, heterogeneity p=0.031; I²=66.2%, n=4 studies). The pooled estimate (RR) of the effect of omega-6 PUFAs supplementation on CVD death was 1.06 (95% CI: 1.07-1.55, heterogeneity p=0.011; I²=66.2%, n=6 studies), on CHD events 0.84 (95% CI: 0.61-1.16, heterogeneity p=0.001; I²=79.4%), on MI 0.87 (95% CI: 0.74-1.01, heterogeneity p=0.381; I²=2.3%) (Figure), and on stroke 1.36 (95% CI: 0.45-4.07, heterogeneity p=0.082; I²=55.3%). In MR analysis we showed that individuals with genetically higher serum adrenic acid (AA; 22:4:n-6) levels had a greater risk of CHD events (IVW=Beta: 0.526, p=0.007), MI (IVW=Beta: 0.606, p=0.017) and stroke (IVW=Beta: 1.694, p=0.009), as well as higher levels of FBG (IVW=Beta: 0.417, p= 1.0*10⁻³), LDL-C (IVW=Beta: 0.806, p= 4.9*10⁻⁵), HDL-C (IVW=Beta: -0.820, p= 4.3*10⁻¹⁷), whereas lower levels of TG (IVW=Beta: -1.064, p= 1.2*10⁻¹²) and TC (IVW=Beta: -1.064, p= 1.2*10⁻¹²).

Conclusions: In the pooled analysis different omega-6 PUFAs supplementation did not affect the risk of MI, stroke and CHD event/mortality or the serum concentration of cardiometabolic parameters (data not presented), however in MR analysis, higher AA levels significantly associated with the risk of CHD, MI and stroke, as well as with elevated levels of FBG, LDL-C and HDL-C and reduced levels of TC and TG. There is probably lack of class effect for omega-6 PUFAs, therefore further studies are needed to assess the effects of omega-6 PUFAs on cardiometabolic outcomes.
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### Meta Analysis

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris,1968</td>
<td>0.951</td>
<td>0.641</td>
<td>1.410</td>
<td>0.801</td>
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<tr>
<td>Houtsmuller,1979</td>
<td>0.077</td>
<td>0.004</td>
<td>1.331</td>
<td>0.078</td>
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<tr>
<td>Burr ML,1989</td>
<td>0.873</td>
<td>0.736</td>
<td>1.035</td>
<td>0.118</td>
</tr>
<tr>
<td>Daytos,1969</td>
<td>0.814</td>
<td>0.535</td>
<td>1.239</td>
<td>0.337</td>
</tr>
</tbody>
</table>

**Risk ratio and 95% CI**

Lower risk | Higher risk

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Meta Analysis