

## Randomised controlled trial

## Possible protective effect of prenatal omega-3 long-chain polyunsaturated fatty acids supplementation on persistent wheeze and asthma in early childhood

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## Context

The incidence of asthma and wheezing disorders in developed countries has increased in recent decades.<sup>1</sup> Profound changes in the type of fat consumed, particularly an increased intake of omega-6 ( $\omega$ -6) relative to omega-3 ( $\omega$ -3) fatty acids, parallel the increasing prevalence of asthma and other inflammatory diseases, leading to the hypothesis that imbalance of fats may be causally related. This randomised controlled trial (RCT) investigates the effect of prenatal  $\omega$ -3 long-chain polyunsaturated fatty acids (LCPUFA) fish oil supplementation compared with control on symptoms of wheeze or asthma in the offspring between birth and 3 to 5 years of age.

## Methods

In this double-blind, placebo-controlled, parallel group RCT, pregnant women were randomised to receive either 2.4 g/day of  $\omega$ -3 LCPUFA (55% eicosapentaenoic acid (EPA) and 37% docosahexaenoic acid (DHA)) or control in the form of olive oil (72%  $\omega$ -9 oleic acid and 12%  $\omega$ -6 linoleic acid) from 24 weeks' gestation until 1 week postpartum. A subset of women were concomitantly randomised to high-dose vitamin D<sub>3</sub> (2400 IU/day) versus normal recommended intake of vitamin D<sub>3</sub>. The primary outcome was persistent wheeze or asthma determined longitudinally by the documentation of five wheezy episodes (at least 3 consecutive days) within the preceding 6 months, symptoms of typical asthma and a trial of inhaled corticosteroids with improvement and relapse after stopping. Additional outcomes included lower respiratory tract infection(s), allergic rhinitis, rhinoconjunctivitis, eczema, allergic sensitisation (6 and 18 months) and lung function (5 years).

## Findings

There was a significant reduction in the cumulative risk of persistent wheeze or asthma from birth to 3–5 years (16.9% vs 23.7%, relative risk (RR)=0.69, 95% CI 0.49 to 0.97,  $p=0.035$ ) and birth to 5 years (17.5% vs 24.6%, RR=0.68, 95% CI 0.49 to 0.95,  $p=0.024$ ) in the intervention group. Secondary outcomes showed a significant reduction in the incidence of

lower respiratory tract infections in the  $\omega$ -3 LCPUFA group from birth to 3–5 years (31.7% vs 39.1%, RR=0.75, 95% CI 0.58 to 0.98,  $p=0.33$ ) and birth to 5 years (38.8% vs 45.5%, RR=0.77, 95% CI 0.61 to 0.99,  $p=0.041$ ), but no difference between groups for outcomes including risk of asthma exacerbations, eczema, allergic sensitisation, allergic rhinoconjunctivitis and lung function.

## Commentary

This large trial, with excellent follow up rates, reports a 31% reduction in persistent wheeze or asthma in 3- to 5-year-old offspring of mothers supplemented with  $\omega$ -3 LCPUFA in the third trimester of pregnancy. The authors found no significant effect of the intervention on eczema or allergic sensitisation, in contrast to another large, high-quality study from Australia that reported lower rates of atopic eczema and sensitisation but no significant effect on  $\omega$ -3 supplementation on wheezing or asthma (1–6 years of age).<sup>2–4</sup> Contrasting effects may be explained by several factors: the Bisgaard group used significantly higher doses of  $\omega$ -3 LCPUFA supplementation (2.4 g vs 900 mg) and supplements consisted predominantly of EPA as opposed to DHA. Variation in data collection and diagnosis of wheeze and asthma is often heterogeneous and may also account for differences as well as population diversity. The authors report no significant interaction with concomitant vitamin D<sub>3</sub> supplementation in this study, although the effects of  $\omega$ -3 LCPUFA were less evident in children randomised to the high-dose vitamin D<sub>3</sub> group. Of interest is the finding that protective effects of the intervention were driven by mothers whose fatty acid status (EPA and DHA) was in the lowest third of the population, suggesting a population with insufficient  $\omega$ -3 LCPUFA status may benefit most from supplementation.

## Implications for practice

Systematic reviews investigating the effects of prenatal  $\omega$ -3 LCPUFA in offspring have been somewhat unconvincing with regard to demonstrating beneficial effects on asthma and wheeze outcomes.<sup>5,6</sup> Although this study shows significant protective effects of prenatal  $\omega$ -3 LCPUFA supplementation on persistent wheeze and asthma from birth to 3–5 years of age, one study does not provide enough evidence for a change in practice. This study does however highlight the need for further research to see if results may be replicated in other populations.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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## Therapeutics/Prevention

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