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# Importance of adequate sample sizes in fatty acid intervention trials

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ABSTRACT

Randomised controlled trials are the ideal way to assess the effects of interventions. Small trials are useful for generating pilot data to determine samples sizes for larger trials, but can produce unreliable or biased results if they are considered in their own right. We investigate the impact of small sample sizes due to either inadequate recruitment targets or high attrition rates on the results of fatty acid intervention trials. Data from our large trial of DHA supplementation during pregnancy with minimal attrition are used for illustration. Our findings demonstrate that recruiting fewer participants or neglecting to follow up difficult participants can lead to substantially different results and alter conclusions about the effectiveness of the intervention. Developing strategies for overcoming these inadequacies should be a top priority in fatty acid intervention trials.

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## 1. Introduction

Randomised controlled trials (RCTs) are generally considered to be the gold standard for judging the effectiveness of an intervention [1]. However, it can be difficult to draw meaningful conclusions from RCTs when the number of participants in the trial (the sample size) is inadequate. Statisticians would describe such a trial as underpowered to detect clinically important treatment effects, if they are present. Underpowered trials are problematic as, despite the enthusiasm of many investigators, they are more likely to produce significant findings that are the result of chance, rather than a real effect of the intervention [2,3]. Underpowered trials have also been deemed unethical, as they expose participants to interventions with little chance of providing a clear answer regarding their effectiveness [4]. Trials that become underpowered due to high attrition rates (participant losses due to various causes) are even more problematic, since they can produce biased estimates of the treatment effect. Such bias is likely to occur when the participants who withdraw or are lost to follow up have different characteristics or outcomes than those participants who provide complete data, or when the attrition rate differs between treatment groups [5–7]. Attrition can also reduce the generalisability of the trial results [5]. It is therefore crucial to ensure that RCTs have adequate sample sizes with sufficient power to detect clinically important treatment effects, by choosing appropriate recruitment targets and minimising attrition rates.

Conducting adequately sized trials in fatty acid research can be especially challenging. Since background levels of the fatty acid of interest are present in the control group due to endogenous synthesis and background diet intake, the difference between treatment groups in the fatty acid of interest can be reduced [8]. As a result, the difference in outcomes that is achievable with a fatty acid intervention can be smaller than for other types of interventions, and hence a larger sample size may be needed. Despite this, many RCTs of fatty acid interventions suffer from small sample sizes due to inadequate recruitment targets and/or high attrition rates, as highlighted by systematic reviews of fatty acid interventions e.g. [9,10]. A reminder of the importance of conducting adequately sized trials in this setting is therefore warranted.

The aim of this article is to demonstrate how trials involving small numbers of participants can lead to questionable results, using data from

*Abbreviations:* RCTs, randomised controlled trials; DHA, docosahexaenoic acid; DOMInO, DHA to optimise mother infant outcome; EPDS, Edinburgh Postnatal Depression Scale.

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our large-scale Docosahexaenoic acid (DHA) to Optimise Mother Infant Outcome (DOMInO) trial with minimal attrition for illustration [11].

## 2. Patients and methods

### 2.1. The DOMInO trial

The DOMInO trial was a double-blind, multicenter RCT conducted in five maternity hospitals in Australia between 2005 and 2009 (Australian and New Zealand Clinical Trials Registry Identifier ACTRN126050005-69606; anzctr.org.au) and has been described in detail previously [11]. Briefly, women with a singleton pregnancy between 18 and 21 weeks' gestation who were not already taking a prenatal supplement containing DHA were eligible to participate. Women providing written informed consent were randomised to the DHA or control group and were asked to consume three DHA-rich fish oil capsules or vegetable oil capsules per day, respectively, from trial entry until delivery. All procedures were conducted in accordance with the approval of the relevant Human Research Ethics Committees at each maternity hospital.

The aim of the DOMInO trial was to determine the effect of DHA supplementation during pregnancy on postnatal depression in the women, and cognitive and language development in the infants. Postnatal depression was assessed at six weeks and six months postpartum using the Edinburgh Postnatal Depression Scale (EPDS) [12] and a score of 12 or more was used to indicate probable depression. Cognitive and language development were assessed at 18 months of age (corrected for premature birth) using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) [13]. The Bayley-III produces standardised scores with a mean of 100 and a standard deviation of 15, where lower scores represent poorer performance.

High recruitment targets were set for the DOMInO trial [11]. Sample size calculations indicated that 2280 women (1140 per group) should be recruited to detect a clinically important 4.2% absolute reduction in the prevalence of postnatal depression from 16.9% in the control group with 80% power. A 4.2% reduction was chosen on the basis of epidemiological data that suggested a 7–8% reduction [14] and the possibility that part of this effect may be due to residual confounding, while the control group prevalence of 16.9% was estimated from Australian population data [15]. Only 630 infants (315 per group) were required to detect a clinically meaningful 5 point improvement in the mean cognitive and language scores separately for boys and girls, based on 80% power and the known standard deviation of the Bayley-III standardised scores of 15 [13]. A 5 point improvement was of interest as previous studies showing differences of 4–5 points had prompted changes in health policy [16,17]. Developmental assessment was therefore planned for only a subset of infants to minimise both the cost of the trial and the burden on participants. A number of strategies for minimising attrition were implemented, including collecting up to four alternative contacts for participants at trial entry, and keeping in contact via mailing a regular newsletter that included a change of address slip.

### 2.2. Statistical methods

A post-hoc exploratory analysis of data from the DOMInO trial was performed to determine how the results might have changed if the sample size had been smaller due to recruiting fewer participants or neglecting to follow up difficult participants. Language scores at 18 months of age and postnatal depression at six months postpartum were used for illustration.

To investigate the potential impact of small sample sizes due to inadequate recruitment targets, we estimated the effect of DHA supplementation on language scores in three different groups of DOMInO participants: (i) all infants who completed the developmental assessment; (ii) 100 different random samples of 50 infants (25 per group) selected from the infants who completed the developmental assessment; and (iii) after every 50 infants had completed the developmental assessment. In each case, the mean language score was compared between the DHA and control groups using a two-sample *t*-test. The percentage of random samples of 50 infants where the estimated treatment effect was expected to exceed the clinically important difference of 5 points, just by chance, was calculated based on properties of the normal distribution.

To investigate the potential impact of small sample sizes due to high attrition rates, we estimated the effect of DHA supplementation on postnatal depression at six months postpartum in two different subsets of DOMInO participants: (i) all women who completed the EPDS; and (ii) after excluding women who were difficult to follow up, defined as completing the EPDS more than 30 days after it was due, or requiring telephone follow up based on incomplete responses to the questionnaire. For each of these subsets, the proportion of women who had probable depression (EPDS $>$ 12) was compared between the DHA and control groups using a chi-square test.

## 3. Results

Recruitment targets were exceeded for the DOMInO trial to ensure adequate sample sizes would remain after any attrition. A total of 2399 women (1197 DHA, 1202 control) were enroled in the trial and 726 infants (351 DHA, 375 control) were selected for the developmental assessment. Attrition rates for the trial were kept to a minimum. EPDS scores at six months postpartum were obtained from 2341 (97.6%) women, while 692 (95.3%) infants completed the language assessment at 18 months of age. The primary findings of the trial have been reported in detail elsewhere [11].

### 3.1. Impact of inadequate recruitment targets

Based on all 692 infants who completed the language assessment, the mean (SD) language score from the Bayley-III was 96.5 (13.6) for the DHA group and 98.2 (15.3) for the control group. The difference in means (DHA minus control) was $-1.7$ points (95% confidence interval, $-3.9$ to 0.5), indicating that there was insufficient evidence to support the hypothesis that the mean language score differed between the treatment groups ($P=0.13$). Similar results have been reported for this outcome elsewhere using more complex statistical methods [11]. A high degree of confidence can be placed in these results, due to the large sample size and minimal attrition rate.

In order to demonstrate the effect of inadequate recruitment targets on these results, we estimated the effect of DHA supplementation on language for 100 random samples of 50 infants (25 per group). Treatment effect estimates ranged from a reduction in the mean score of 8.4 points, to an increase in the mean score of 7.8 points, depending on the random sample chosen (Fig. 1). There was one random sample where DHA supplementation had a significant positive effect and three random samples where it had a significant negative effect on the mean language score. These small samples therefore could have led to conclusions that differed from the main trial findings when all infants were included in the analysis. None of the other random samples showed a statistically significant effect of DHA supplementation on language. For 20% of random samples, the estimated treatment effect exceeded the clinically important difference in mean language scores of 5 points. If DHA supplementation had no effect on language, a difference of 5 points or more would be expected just by chance in 24% of random samples. These findings are therefore consistent with the lack of effect of DHA supplementation on language seen among all infants.

Another way to demonstrate the effect of inadequate recruitment targets on the trial results is to examine the cumulative effect of DHA supplementation on language after every 50 infants completed the

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