We thank the Editors and Reviewers for their constructive comments, which we address individually below. We believe that the manuscript has been significantly improved through the additional analyses and manuscript corrections and hope that you now find it acceptable for publication in the British Medical Journal.

Reviewer: 1
Comments:
This is an interesting manuscript.
It is based on a well-conducted and comprehensive randomised controlled trial with fish oil vs olive oil supplementation during pregnancy. The study follows up children to the age of 6y with anthropometric measurements. The study is not the first of its kind, but it is relatively large, it has repeated measurements during follow up and has an extensive battery of measurements.
Generally, the manuscript is well written and overall it complies with the Consort Statement.
There are however a few general and some more specific comments.
Response: We thank the reviewer for the appreciation of our study. We have addressed the individual comments below.

General comments:
Attrition is generally low but there is some attrition in the study up to the age of 6y (particularly for the DEXA scans). Have the authors considered whether exchangeability between the two interventions groups is still present after 6 years? Did you consider adjusting for potential risk factors for the outcome?
Response 1: Since we had a successful randomization (refer to table 1), we follow the typical guidelines for reporting of randomized controlled trials, which is without confounder adjustment. We only adjust for sex and age, which is crucial for comparison of growth endpoints. Furthermore, the attrition in relation to DEXA scans at 3.5 and 6 years was similar for the two supplementation groups; please also see Response 9 and 10.

A number of sub-analyses are described in the result section, which have not been described in the method section (consort checklist 12b). This includes both stratified analyses, interaction analyses and also the sub-analysis concerning FADS. I suggest that these analyses also should be included in the method section.
Response 2: This has ben done as suggested, please refer to response 4 and 8 for details.

Specific comments:
pp6 line 9: Is "growth" the right word to use?
Response 3: We have now changed this to “anthropometry.”

pp8 line 33-38: It is unclear at this point what this information should be used for. I suggest that

either it is introduced as a secondary aim or that it is shortly explained here in the method section.
Response 4: We have added this sentence to the methods section.
Page 8, line 179: *"The FADS genotype was used to perform a genetic validation of our findings."*

pp9 line 28-29: Self-reported birth weight and length were validated against information from the Danish National Birth Register. How valid was the self-reported information? What did you do in case of discrepancy? What was the correlation? Generally it is unclear what this validation showed and what you used the information for.
Response 5: We have added this to the methods section:
Page 9, line 204-206: *"Furthermore, if there was a difference larger than 10g and 5cm, data were validated against the length and weight measures at 1 week from the research clinic."*

pp10 line 14: Twins were excluded. They usually come in pairs. How come three twins are excluded from the LCPUFA group?
Response 6: It was twin pregnancies which were excluded, the word "*pregnancies"* has been added to the text.

pp10 line 17 and 22. The use of "cross sectional" in this context is a bit confusing.
Response 7: We have rewritten the methods section:

Page 10, line 232-235: *"The effect of n-3 LCPUFA supplementation on cross-sectional anthropometric outcomes at 6 years of age (defined as the specific anthropometric measurement closest to 6 years ± 6 months) was analysed using Student's t-test for normally distributed continuous variables and chi-square tests for categorical variables."*

pp10 statistical analysis: A number of sub-analyses have been performed. They should be described in this section.
Response 8: We have added a methods section regarding sub-analyses:
Page 10, line 250-255: *"We analyzed for interaction in regards to sex, age, size for gestational age, FADS-genotype and maternal pre-intervention blood levels of EPA and DHA. A subgroup from this pregnancy cohort also participated in a nested; factorial designed, double-blind, RCT of 2,400IU/day of vitamin D3 supplementation (N=576). We performed a sub-analysis excluding children with asthma at age 6 years and/or with lower respiratory tract infections before age 3 years. In a sub analysis we adjusted our primary outcomes for size for gestational age and birth weight."*

pp11 line 19-21: The sentence is a bit unclear. Consider revising.
Response 9: We have changed the sentence to this:

Page 11, line 267-269: *"Adherence to the study supplementation defined as an intake of more than 80% of the prescribed dose based upon capsule count was estimated to be 71%, with no differences between the n-3 LCPUFA (N=242) and control group (N=245)."*

pp11 line 34: "Only" 76% of participants had DEXA scans performed. Was the attrition similar in the two groups? Could the attrition have affected the results? The problem might be even higher at 3.5 y. A short discussion about this could be included in the discussion
Response 10:
We have added this to the manuscript:
Page13 line 331-332: *"The number of participants completing the scans at 3.5 and 6 years was equal in the two supplementation groups (176 vs 180 and 263 vs 260 for 3.5 and 6 years, respectively)"*.

Furthermore, as shown below, drop out did not result in bias in terms of different risk factor profiles between randomization groups in those children who were day-scanned. Thus, there is no indication that attrition has affected our results.

Here we show a table (similar to the baseline table) with relevant exposures and relevant anthropometric outcomes on the 523 children, who had a dxa- scan at 6 years of age. Beside a higher maternal age for the children in the fish oil group, we did not find any exposure differences between the groups:

	n-3 LCPUFA	Control	p-value
	50% (263)	50% (260)	
Child			
Sex, male % (N)	47 (119)	53 (133)	0.21
Exclusive breastfeeding (days), mean (SD)	105 (58)	107 (59)	0.70
Marsál percentage*, mean differences (SD)	50 (28)	49 (28)	0.54
Born before week 37 % (N)	3 (8)	4 (10)	0.79
Parents			
Maternal age at Birth (years), mean (SD)	32.5 (4.4)	31.8 (4.9)	0.05
Social circumstances, mean (SD)	0.0 (1.0)	0.0 (1.0)	0.83

Maternal pre-pregnancy BMI (kg/m^2), mean (SD)	24.7 (4.2)	24.6 (4.6)	0.83
Father height (cm), mean (SD)	181 (6)	180 (7)	0.51
Daily fish intake before inclusion (g), mean (SD)	28 (16)	29 (19)	0.69
Maternal pre-treatment blood levels of EPA+DHA[#] (%), mean (SD)	4.9 (1.2)	5.0 (1.2)	0.52
Pregnancy			
Prim parity % (N)	45 (118)	48 (126)	0.46
Preeclampsia % (N)	4 (11)	4 (10)	1
Smoking in pregnancy % (N)	6 (15)	8 (21)	0.37
Antibiotics in pregnancy % (N)	35 (89)	36 (90)	0.8
Anthropometric at 6 years of age			
Weight mean (SD)	21.7 (2.87)	21.4 (2.88)	0.26
Waist mean (SD),cm	55.38 (3.63)	54.85 (3.60)	0.09
Weight/height mean (SD) kg/cm	0.18 (0.02)	0.18 (0.02)	0.14
ZBMI, mean, (SD)	0.08 (0.81)	-0.08 (0.83)	0.03

pp15 line 10: Z-scores were not used in ref 36.
Response 11: We have deleted the z-score part now. Thanks for pointing this out.

pp15 line 17. Could this be due to the effect decreasing over time?
Response 12: For the time being, we cannot answer this question, but we agree that this could indicate a decreasing n-3 LCPUFA effect over time and thereby highlights the importance of following these children through puberty.
We have added one sentence about this to the last part of the discussion:

Page 16, line 416-419: "*The cohort will be followed into adulthood to evaluate if the effects on growth and body composition induced by n-3 LCPUFA supplementation in pregnancy are sustained.*"

Table E3: Something goes wrong with the splitting of the text. In addition, why are only the significant p-values highlighted?
Response 13: Table E3 has been corrected. The significant p-values are not highlighted anymore, and the table now resembles the appearance of the other tables.

Reviewer: 2

Recommendation:
Comments:
This paper is well written and the study appears to have been well-conducted. My main concern is the potential impact of missing data on the findings – I would like some reassurance from the authors that this has been considered, and that it has not led to bias. Some indication of the extent of the missing data (i.e. numbers of children with missing data points at each time point of measurement) and whether this is equally balanced between the treatment groups would also be helpful. I also think the authors need to make a stronger case for the study, in particular highlighting how their study differs from other previous trials – since the argument could otherwise be made that this topic is done and dusted. My specific comments/questions are below:
Response: We thank the reviewer for this appreciation of our study and the feedback. We have addressed the concerns both in the answers above and below.

The potential impact of missing data on the findings:
Response 14: Please refer to response 10 and 20.

A stronger case for the study, in particular highlighting how their study differs from other previous trials:
Response 15: Please refer to response 17 and 18.

1. The introduction needs to make the point that the increase in birthweight in infants exposed to an increased supply of omega-3 during pregnancy is largely a consequence of the increase in gestation length
Response 16: We have added this to the introduction section as suggested:
Page 7, line 138-139: "*mainly explained by an increase in gestational age, but an increase in size for gestational age has not been excluded"*

2. The introduction should also make clear that the data from animal studies are not conclusive, since there is at least one study that shows that omega-3 LCPUFA supplementation during pregnancy/lactation actually increases body fat mass in the offspring, and many others do not isolate the omega-3 supplementation to the perinatal period.
Response 17: Thank you for your comment, we have now added this to the introduction:
Page 7, line 143-145: *"Despite these possible mechanisms a recent systematic review of animal studies concluded that the evidence is insufficient to draw any definite conclusions on the role of n-3 LCPUFA supplied during pregnancy and/or lactation on fat mass development in the offspring* (1).

3. Think the introduction would benefit from some additional detail/context regarding the

need for this study, especially given that much larger studies have shown null effect on body composition – perhaps highlighting the need to understand whether different fatty acids (i.e. EPA vs DHA) may have different effects?

Response 18: Thank you for the comment; we have added this to the discussion:

Page 7, line 147-151: *"Randomized controlled trials with n-3 LCPUFA supplementation in pregnancy and/or during lactation have shown diverging results but mainly no effects on anthropometric outcomes Recent reviews have concluded that there is no evidence of n-3 LCPUFA supplementation affecting BMI or growth development in childhood* (2–4). *However, there are large differences regarding the amount of n-3 LCPUFA supplied, as well as the combination of fatty acids used in these trials."*

4. Can the authors provide a rationale as to why they selected the rs1535 SNP for analysis in this cohort? Were other SNPs also analysed?

Response 19: We only analysed the rs1535 SNP. The FADS genes harbor several genetic variants, but the rs1535 SNP was chosen because it, and its proxies in close linkage disequilibrium, has been associated with n-3 LCPUFA levels in a genome-wide association study (5) and with blood levels of EPA and DHA during pregnancy(6).

We have added this to the result section:

Page 13, line 338-339: *"The maternal FADS gene variant rs1535 has been associated with blood levels of EPA and DHA during pregnancy."*

5. It would be interesting to know the number of children who had 1, 2,3,4,5 or complete sets of anthropometric measures, and whether this was equivalent between treatment groups. If the missing data weren't equally balanced between treatments, then would this lead to bias in the results? How did the authors ensure that this wasn't the case? Would it be possible to do a sensitivity analysis which included only children with complete sets of measures?

Response 20: The suggested table looks like this:

Number of visits	1	3	4	5	6	7	8	9	10	11	12	13
Children in the Fish oil group	22	2	2	2	3	5	13	12	29	63	185	22
Children in the control group	24	0	3	4	6	5	4	14	26	76	184	23

On the full dataset the results on BMI difference was found to be:

Mean z-score difference: 0.14, 95% confidence interval (CI) [0.04; 0.23], p=0.006.

When performing the requested sensitivity analysis on the 414 children with more than 11 growth measurements, we found this result:

Mean z-score difference: 0.18, 95% confidence interval (CI) [0.06; 0.31], p=0.004.

This has ben added to the results section:

Page 11 line 280-282: *"A sensitivity analysis restricted to children with more than 11 growth measurements (n=414) showed similar results (Mean z-score difference: 0.18, 95% confidence interval (CI) [0.06; 0.31], p=0.004.)".*

6. I am particularly interested by the finding that BMI z-scores weren't different between treatments between 1 week and 6 months, but were at all other time points – do the authors have an explanation for this?

Response 21: Several explanations could exist for this. First of all, it is important to note that BMI is a less sensitive measure in early infancy compared to later ages, because height is a more accurate measurement than length. Second, this non-difference in mean BMI at set ages in infancy could be caused by different growth patterns in the two intervention groups. In infancy the BMI peaks at a certain age, and the timing of this peak has been associated with later obesity outcomes - earlier peak has been positively associated to later obesity (7). If the n3 LCPUFA effect lead to a later infant BMI peak, this could explain the lack of BMI difference in the first year of life. This is of course speculative, as it would require more measurements to precisely establish the age of BMI peak.

As suggested below, we have tried to preform sitar analysis on this age span, however; we do not believe that this adds anything new to the conclusion, please refer to response 54.

7. In the results section, the authors need to make it clear whether they are referring to BMI or BMI z-scores – I assume that it is always BMI z-scores, but these terms seem to be used interchangeably in the text, which is confusing.

Response 22: Thank you for pointing this out. All the statistical analyses have been done on z-score BMI; however Figure 1, 2 and E3, illustrates BMI development. We have corrected the relevant parts of the text.

8. The finding of a higher BMI in the n-3 LCPUFA group at 6 years is certainly interesting. What happened if the analyses were adjusted for birth weight (as opposed to size for gestational age)? This is particularly important given that the children in the n-3 LCPUFA group were heavier at birth (as stated in the discussion)?

Response 23: Children in the n-3 LCPUFA group had both a higher gestational age, birth weight and size for gestational age. A part of the increase in birth weight is solely explained by higher gestational age, so the decision to use size for gestational age was to cover the potential increased intrauterine growth.

We have performed the adjusted analyses and they are stated below:

Weight:
Unadjusted: 0.36 kg (0.23) p-value: 0.12.

Adjusted: 0.24 kg (0.22); p-value: 0.28

zBMI:
Unadjusted: 0.19 (0.06) p-value: **0.005.**
Adjusted: 0.16 (0.06); p-value: **0.01**

Waist:
Unadjusted: 0.6 (0.30) p-value: **0.04.**
Adjusted: 0.5 (0.3); p-value: 0.10

Overall, we find a small decrease in the estimates for these relevant anthropometric outcomes at 6 years of age; however we still find a significant effect of fish oil on zBMI and trend of significant difference on waist.

We have expanded the result section to accommodate this:
Page 12, line 307-311: "*We did a sub analysis on the primary anthropometric outcomes, where we adjusted the analyses for size for gestational age, this yielded comparable results (data not shown). Furthermore, we adjusted the primary anthropometric outcomes for birth weight, and this also yielded comparable significant results, although however with a small reduction in the effect of n-3 LCPUFA supplementation (data not shown).*"

We did not add these data since they do not change the conclusion that the supplementation changes BMI – it is more of a mediation analysis showing to which extent the effect on BMI is mediated by changes in birth weight, and the results are largely unchanged indicating that the effect was mainly not mediated by changes in birth weight. On editor's discretion, we can add these data to the article.

9. It would also be helpful for the authors to add some additional context about this cohort – particularly whether the children were, on average, representative of the broader population, and what the rates of overweight/obesity were in this group.
Response 24: The rates for overweight and obesity are stated in the results in table 2. We had 30 (5%) children with an International Obesity Task Force grade above 0 at 6 years of age. The rate for overweight among Danish children ages 6-8 years of age is reported to be around 10% (Danish health ministry), so the study population has a lower rate compared with the broad population.
In our baseline article (8) regarding the cohort, we have described possible recruitment bias for the cohort and we found a higher amount of parents with atopic disease and they had higher income and education level than the broad population, while there was no apparent bias with respect to other suspected disease risk factors such as the mode of delivery, Mother pre-

pregnancy BMI, duration of solely breastfeeding, living with pets, smoking, or alcohol intake during pregnancy.
We have compared birth anthropometrics and gestational age from the cohort with those for the 63,000 born in Denmark in 2010 (year corresponding to our cohort's birth year) utilizing data from the Danish birth registers. We found a slightly higher birthweight in our cohort 3,552g vs. 3,468g and a slightly longer gestational age: 281 days vs. 280 days. .Analyzing solely in the control stratum we found no difference on gestational age 280 days vs 280 days, and more comparable birthweights 3,504g vs 3468g.
On editor's request, we can add information about this to the method section.

Reviewer: 3

Comments:

The study describes a double blind RCT of maternal pregnancy LCPUFA supplementation from week 24 to 1 week postnatally. The trial appears to be well done, and the results are both interesting and credible. The primary trial outcome was asthma, while this secondary analysis involved body composition outcomes at 6 years.

1. It looks odd that the title and Abstract outcomes do not mention BMI, yet the Abstract results and conclusions focus mainly on BMI z-score. This is odd because BMI is a crude measure of obesity that does not distinguish between lean mass and fat mass, yet the hypothesis relates to body composition, so that BMI is a particularly poor outcome to use. Framing the results and conclusions around BMI distorts both the trial findings and interpretation (incidentally the Abstract does not say how obesity was defined).
Response 25: In our final protocol, we had the following outcomes defined regarding growth. These were all added to the protocol before unblinding the RCT in March 2014:

- Body composition (fat mass and bone mineral density) assessed by DEXA scan at 3 years of age.
- Development of BMI from birth to 3 years assessed longitudinally in the research clinic.

Like the reviewer states below, we also believe that the effect on BMI is a result of a healthy somatic growth promotion and have been reluctant to add "BMI" to the title, since many readers could interpret this as an increased risk of obesity. The current title, reporting the findings on proportional increased lean, fat and bone mass, is in line with our interpretation of the data. However, as suggested by the reviewer, we have now tried to reduce the focus on BMI effects in the abstract, results and conclusion part and changed the conclusion to:
Page 5, line 126-129: *"Fish-oil supplementation from 24th week of pregnancy led to an increased BMI in the offspring from 0-6 years of age, but not an increased risk of obesity at age 6. The body composition at age 6 years in fish-oil supplemented children was characterized by a proportional increase in lean-, bone- and fat mass, suggesting a general growth stimulating effect of n-3 LCPUFAs."*

On editor's discretion, we could include BMI in the title, e.g.: *"Fish-Oil Supplementation in Pregnancy causes an increase in BMI through Childhood reflecting a Proportional Increase in Bone-, Lean- and Fat Mass at 6 Years: A Randomized Clinical Trial"*

We have furthermore added the definition of obesity to the abstract.

2. Weight, another secondary outcome but not mentioned in the Abstract, would be better than

BMI z-score as it is more transparently related to changes in lean mass and fat mass, and it is not directly associated with obesity. Weight should be adjusted for height to increase power, as it is in Table 3 for body mass and the DEXA outcomes, although the two groups did not differ in mean height. Maybe this was why BMI was added belatedly to the statistical analysis plan, to provide a form of weight adjusted for height.

Response 26: Please refer to response 23 regarding BMI and body composition in the original study protocol.

We have added mass from the DXA scans to the abstract to emphasize a larger focus on this.

As a post hoc analysis, we have further analyzed weight/height and found:

	n-3 LCPUFA N=304	Control N=301	P-value
Weight/height, mean (SD), g/cm	183,7 (19,1)	180,7 (18,7)	0.05

We have added this extra outcome to Table 2 and the result section both in the abstract and the main text.

Page 12, line 291-295: *"Children in the n-3 LCPUFA supplementation group had a significantly higher BMI z-score at age 6 years compared to the control group (sex and age adjusted): mean difference, 0.19, 95% CI [0.06; 0.32], p=0.004, a higher weight/height, 3.48g/cm, 95% CI [0.38;6.57], p=0.03 and a larger waist circumference, 0.6 cm, 95% CI [0.0; 1.2], p=0.04), while there were no differences in height or head circumference (Table 2)."*

3. But the focus on BMI gives quite the wrong impression – it implies that the research question involves obesity and that the intervention disproportionately affects fat mass, yet it doesn't. What changes is weight and lean mass and fat mass, as the title makes clear. And BMI as a z-score is in different units from every other outcome in Tables 2 and 3, again an anomaly. There should be more emphasis on the non-fat changes in the Abstract conclusion, which rather negatively says the intervention did not increase obesity.

Response 27: Please refer to response 25.

4. It is also disappointing that five of the six figures focus on BMI, by far and away the least interesting of the outcomes. The longitudinal analysis of BMI also adds little; the difference between arms is essentially constant from 1 year (Figure 2), and what matters is the difference at 6 years, so the longitudinal analysis can be omitted as it is a distraction.

Response 28: Since BMI development was in the predefined original study plan, we have kept a large focus on that. However, we have changed parts in the abstract (response 23) and added weight for height to the tables and text section (response 24).

In regards to the figures, we have merged figure 1+2 and removed the figure on 6 years z-score BMI. Instead, we have added a figure on the effects of n-3 LCPUFA on body composition at 6 years of age.

We have added this sentence:
Page 13, line 324-326: *"Figure 2 illustrates the proportional increase in lean, fat and bone mass for children in the n-3 LCPUFA supplementation group at 6 years of age".*

5. The Methods state that "A subgroup from the cohort also participated in a nested; factorial designed, double-blind, RCT of 2,400IU/day of vitamin D3 supplementation (N=576)." But nothing more is said about it, and there is no adjustment for the intervention in the analysis. It needs to be properly documented and adjusted for. Also the sample size of 756 is unhelpful at this point as the sample size of the main study has not yet been given.
Response 29: We have moved this description from the trial intervention section to a section about sub analyses. Furthermore, we have added the number of mother-child pairs to the trial design section.
Finally, we have added this interaction analysis to the result section:
Page 12, line 305-306: *"Furthermore, there were no interaction between the intervention with n-3 LCPUFA and the intervention with high dose vitamin-D (data not shown)."*

6. Maternal FADS genotype first appears in the Methods, with no mention in the Abstract or Introduction. How did it feature in the research question? – It needs properly framing. Why was FADS, given its association with BMI, included in the original protocol which focused on asthma?
Response 30: The analysis regarding FADS genotype is a sub analysis and is therefore not mentioned in the abstract.
The FADS genotype is a usable genetic proxy for the maternal n-3 LCPUFA blood levels (please refer to response 19).
Since the finding supports our primary finding, we believe that it is a relevant sub-analysis to include in the present study.

7. The term is Anthropometry not Anthropometrics (Methods).
Response 31: We have changed this as suggested

8. Why was birth weight adjusted against Marsal's intrauterine growth curves rather than using a birthweight reference to generate z-scores, as is usually done?
Response 32: Marsal's intrauterine growth curves are used to state size for gestational age in the Danish neonatal departments. Since we also included preterm children in our analysis, we decided to use these curves.
Please refer to response 23 for the other adjustments.

9. Statistical analysis: including children with at least one measurement at age 0-6 years only

applies to the longitudinal anthropometry. The DEXA outcomes were at 3.5 and 6 years, so a measurement at 6 years should define the analysis group.
Response 33: As mentioned in response 25 our primary outcome was BMI from 0-3 years of age, we therefore find it relevant to include all children with a BMI measurement at least one time point. Please refer to response 20 for a sensitivity analysis on the children with more than 11 BMI measurements.

The study would endure an unnecessary loss of power, if we restricted the entire study population to only include children, who had a DXA scan at 6 years of age.
However, we have added data on the difference in relevant anthropometry outcomes between the intervention groups to the table in response 10, which contain baseline and anthropometric data on the 523 children, who had a DXA scan performed at 6 years of age.
Similar effects exist regarding the intervention's effect on zBMI, waist, weight/height and weight. However, the findings loose power, and only remain significant for zBMI.

10. And why exclude twins? – they could easily be adjusted for in the analysis.
Response 34: This was an á priori decision, since twins often have different growth patterns and it would be difficult to say anything about the amount of supplementation they would have received.

11. What is the value of a post hoc power analysis, particularly using an outcome which was added only retrospectively to the analysis plan? The study size was defined by the primary outcome, and a post hoc analysis does not alter the study size.
Response 35: We performed the post hoc power calculation to see, if the study was powered to detect a difference in the size as we have revealed. Our sample size was decided according the primary study outcome, but often journals require such a post-hoc power calculation to be included with reporting of a RCT.
We will of course remove the post hoc power analysis by request of the editor.

12. There are anthropometry results for 605 children in Table 2, but for DEXA in Table 3 there are only 523. Out of 736 women recruited these correspond to 82% and 71% respectively, yet nothing is said about how representative they are.
Response 36: Please refer to response 21.

13. Table 1 should not be tested for significance (see text page 11).
Response 37: We have deleted the sentence as suggested.

14. Table E2 needs to test for a sex interaction, otherwise it is uninformative.
Response 38: We believe it is Table E1, which the reviewer refers to:

We have now added a column with the interaction p-values to the table.

15. Sub-analyses mentioned in the Results should first appear in the Methods with a statement as to whether or not they were pre-specified. If they were not pre-specified they should be omitted.
Response 39: Please refer to response 8

16. In the body composition section the adjustment for height (and apparently height squared, according to the footnote) of body mass and the other outcomes in Table 3 was not stated in the Statistical Analysis section.
Response 40:
This section has been added to the statistical section:
Page 9, line 219-221: *"All analyses on body composition from DXA scans were adjusted for height+height^2 with regards to fat- and lean mass and adjusted for height with regards to BMC and BMD."*

17. The FADS analysis results on page 13 are unclear. There was said to be a FADS effect in the control group but not the supplemented group, yet there was no significant FADS interaction. Is this correct? Table E3 should include the significance of the interaction terms. Also please remove the bold emphasis from the significant p-values in Table E3.
Response 40: Please refer to response 19.
It is correct that there is no statistically significant interaction.
We have added a sentence about the rationale behind FADS genotype.
We have added a column with the interaction p-values.
We have removed the bolded p-values.

18. The numerical presentation is very uneven. The DEXA results are given in grams to 5 or 6 significant digits whereas fat % has 3 significant digits (see Table 3). The results should be rounded to a maximum of 3 significant digits –
see http://adc.bmj.com/cgi/content/full/archdischild-2014-307149.
Response 42: We thank the reviewer for pointing this out. It has now been corrected.

19. In summary I feel that the main outcomes should be those at 6 years, excluding (or at least toning down) BMI, and including height adjustments. I'm not convinced that the FADS analysis adds anything useful to the trial results, so that it and the longitudinal results can be omitted. What remains is useful evidence that LCPUFAs in the third trimester of pregnancy stimulate healthy somatic growth to age 6.
Response 43: As mentioned above, mainly in response 25, we believe that since BMI development was the main growth outcome of the predefined study protocol, it is required to present it like this in the results section.
We have added weight for height to Table 2.

We believe that the FADS analysis is an important sub-analysis, which contributes with valuable observational genetic support of our study findings.
However, we are willing to remove the FADS analysis on editor's discretion.

Manuscript meeting 18.04.2018

The committee was interested in the topic of your research. The following concerns were mentioned:

• Why do you report just one secondary outcome of a Fish oil asthma study published in the NEJM in 2016?
Response 44: The $COPSAC_{2010}$ is a large and deeply characterized cohort and the secondary outcomes spans wide. We have chosen to focus independent studies on different secondary outcomes such as growth and neurology to be able to provide sufficient depth in details and interpretation for these very different outcomes.

• The RCT appears to be competently done, and the results are both interesting and credible.
Response: We thank the committee for the appreciation of our study

• It's odd that the title and abstract outcomes do not mention BMI, yet the abstract results and conclusions focus mainly on BMI. This to my mind is wrong as it distorts both the trials findings and interpretation.
Response 45: Please refer to response 25-28.

• The focus on BMI implies that the intervention affects fat mass, yet it doesn't. What changes is weight and lean mass, as the title makes clear. There should be more emphasis on the non-fat changes in the abstract conclusion, which rather negatively says the intervention does not increase obesity.
Response 46: Please refer to response 25-28.

• Note too that BMI was added to the statistical plan only as an afterthought.
Response 47: Please refer to response 25.

• The abstract does not say how obesity was defined (they used IOTF cut-offs).
Response 48: We have added this information to the abstract now.

• Marsal's growth curves for birthweight centile sound odd and need better explanation.
Response 49: We have changed the text accordingly:
Page 9, line 206-210: *"Size for gestational age was derived from Marsal's ultrasound-based intrauterine growth curves. This standardized fetal growth curve was used to find the difference between each child's birth weight and expected birth weight given their gestational age and afterwards calculate the percentage of expected birth weight. Percentage for gestational age is a sensitive measure for all ages."*

• Table 1 does not need significance tests (see text page 11).
Response 50: Please refer to response 37.

• Sub-analyses mentioned in the Results should first appear in the Methods and should be pre-specified.
Response 51: Please refer to response 8.

• The numerical presentation is very uneven. DXA results are given in grams to 5 or 6 significant digits whereas fat % has 3 significant digits (see Table 3). DXA should be in kg to match weight.
Response 52: Please refer to response 42.

• Not sure how useful the longitudinal BMI measures are if they are not modelled – see Figures 1 and 2. The dip at 1-6 months in Figure 2 may reflect a difference in growth timing, which could be detected with SITAR modelling.
Response 53: We thank the reviewer for this suggestion. We have tried to use sitar for modelling the infant growth (~0-1½ year) in relation to n-3 LCPUFA supplementation. Please see the attached html-file for our results. We find significant differences in timing and velocity. n-3 LCPUFA supplemented children have a later infancy BMI peak, and the peak is more "prolonged". Note the 0.00631 years later peak is around 2.3 days - but statistically significant. However when n-3 LCPUFA is added as fixed effects to the model there are no significant differences. Since Tim Cole acts as a reviewer on our manuscript, maybe he can help us interpret this apparent discrepancy -- if a discrepancy at all?
When plotting mean curves for BMI growth for each trial arm we see the same picture as for the estimate plot: the growth is similar until after 6 months where they separate.
We have tried to adjust the anthropometry outcomes at 6 years of age for each growth value in the sitar model (a,b,c) and this did not yield any difference regarding the effects of n-3 LCPUFA. Since we, for now, do not think that the sitar analysis on infant growth adds anything to the manuscript, we have chosen not to include it, but we will do this on editor's request.

• Reviewers concerned about missing data, particularly BMI.
Response 54: Please refer to response 10 and 21.

• Why do you call it a "study" and not a "trial". It is misleading.
Response 55: We have replaced the word "study" with "trial" at all relevant places.

• Reporting could be improved. The methods include some results (but some are only listed as "see supplementary…"

Response 56: This is due to the word limitation, if more space is granted, we can expand these sections on editor's request.

• Sample size calculated post hoc based on how many children they had. As we understand it, you tell us what difference you could find. But is this clinically meaningful? Why? The difference you found was less than what you had identified…
Response 57: Please refer to response 35.

• It is an interesting finding, contradicting earlier research. The clinical significance of a 0.14 difference in BMI Z-score is not clear.
Response 58: It is difficult to interpret on a potential clinical significance of a 0.14 difference in BMI Z-score before the children have been through puberty, since associations between BMI and later health/disease outcomes have only been established in adulthood.
As mentioned in the reviewer comments, we also believe that this increase in z-score BMI does not lead to an increased risk of obesity, but should be seen as a proxy for a healthy growth promotion in the children from the n-3 LCPUFA supplementation group.
We do not believe that the difference on 0.14 BMI score points have any clinical significance for the individual, but on a population level this could have large impact and therefore be relevant in relation to nutritional supplementation that might potentially be implemented as a general recommendation to all pregnant women.
We have added this part to the discussion:
Page 16, line 416-419: *"Finally, we interpret the effect on z-score BMI through childhood as a consequence of a healthy somatic growth stimulation to age 6.*

• Clinically 0.4kg doesn't seem like much.
Response 59: Please refer to response 56.

• We don't think that BMI is not a great measure to use in children.
Response 60: Please refer to response 25-28.

• If you look at the actual effects of the fish oil it seems to have led to an increase in lean mass and possibly bone density but not an increase in body fat. Aren't those "good" outcomes?
Response 61: Please refer to response 42.

• It was concerning to see no patient and public involvement (PPI) declaration with this RCT of pregnant women and no dissemination plan of the findings for pregnant women given the country of Denmark's focus on the importance of PPI in healthcare and research. The PPI declaration is mandatory for The BMJ; perhaps somehow this was missed (https://www.bmj.com/campaign/patient-partnership).
Response 62: The PPI was launched in 2014 and the planning of this trial started in 2005.

However, we have had very close follow-up and contact with our participants and their parents. The $COPSAC_{2010}$ is built on the knowledge from our existing older birth cohort $COPSAC_{2000.}$ In this cohort, we conducted semi-structured qualitative interviews with parents and children to assess ethical questions pertaining to such comprehensive and invasive clinical research. It was the consistent conclusion that it is possible to conduct invasive clinical research on infants and young children in a manner that parents find ethically sound. Altruism was their primary motivation and secondly the comfort of close and easy access to paediatricians and other specialists.
Furthermore, we have had several information meetings for the parents in the cohort, three times a year, we send out a newsletter regarding the findings from the cohort, and we have an updated homepage. This is all reflected in very high follow-up rates.

We hope that these explanations fulfill the PPI, on editor request we can include these information's on editor's discretion.