Author's response to reviews

Title: Early life factors and being overweight at 4 years of age among children in Malmo, Sweden

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Author's response to reviews:

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Dear Sir/Madame:

We greatly appreciate the insightful comments and constructive criticism from the two referees. We have now incorporated the suggestions of changes by the referees into our manuscript with the title: “Early life factors and being overweight at 4 years of age among children in Malmo, Sweden” (MS: 9038428234025367). With the revised version is included a description of the changes made where we respond point by point to the comments of the referees.

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Sincerely,

Maria Rosvall
Description and Motivation of the changes made to our manuscript with the name “Early life factors and being overweight at 4 years of age among children in Malmo, Sweden” (MS: 9038428234025367) after consideration of the suggestions of changes proposed by the referees.

Referee #1:

Major compulsory revisions:

The authors should state the proposed hypothesis between the range of factors examined and overweight/obesity in this age group.

Answer: We have now incorporated more information on the present hypotheses regarding the associations between early life factors and overweight/obesity in small children in the Introduction section on p. 3: “More recent research has also shown that an unfavourable environment early in life might elicit a range of physiological and cellular adaptive responses in key organ systems, which in turn might lead to pathology in later life [9]. Earlier studies have shown associations between early life factors such as maternal smoking during pregnancy [5,10,11,12, 13], impaired fetal growth [9,10,14], breastfeeding [1, 15], and high birth weight [10, 16] in relation to overweight in children..” and in the Discussion section on p.13-14: “Early life has been seen as a critical period for the development of obesity. (...) In a review by Gluckman and Hanson published in 2004, it was concluded that early development make important echoes in disease risk throughout life, and that this is important to bear in mind when forming interventional strategies [34]. An unfavourable environment in early life is thought to elicit a range of physiological and cellular adaptive responses in key organ systems. These adaptive changes result in permanent alterations and might lead to pathology in later life. However, the mechanisms underlying the developmental origins of disease remain poorly defined [9]. Environmentally induced changes in epigenetic states could lead to dysfunctional organ growth and differentiation that is detrimental in the long term [9]. There are theories involving an altered glucose-insulin metabolism in utero leading to an increased risk for obesity later in life. Many studies have shown an association between high birth weight and increased childhood as well as adult BMI [16, 35, 36, 37, 38]. Most of the studies on potential mechanisms between high birth weight and later adiposity come from studies of diabetes during pregnancy. Here the fetal pancreas responds to the elevated glucose levels by producing additional insulin. As insulin may act as a fetal growth hormone, this may produce fetal adiposity. [24] Breastfeeding has been shown to protect against obesity in childhood and in adolescence [15, 39, 40]. One mechanism is related to the fact that there are lower concentrations of serum insulin in infants fed breast milk than those fed with infant formula [16]. Furthermore, breast milk contains less protein than milk from bottles which decreases the risk of overweight [41]. According to Balaban
and Silva [41], the mechanism behind lack of breastfeeding and obesity might be related to metabolic imprinting which causes the early nutritional experience to result in long lasting effect that predisposes to certain diseases. Long-term effects of maternal smoking in pregnancy on the risk of overweight might be related to long-term effects of nicotine exposure on neurobehavioural impulse control as shown in animal and human studies [42] as well as through poor nutrition in the uterus [43,44]. The process which link reduced fetal growth with overweight/obesity has been suggested to stem from adrenal overactivity initiated by early growth restraint [45] and by early postnatal catch-up growth [43]. Secondhand tobacco smoke could also be related to overweight/obesity via low parental education and less healthy food patterns [46]. However, the association in the present study between secondhand tobacco smoke and overweight persisted even after adjustment for the mother’s educational level.

The introduction states that no known studies have examined the potential role of a range of exposures stratified by parental weight status. However, the authors do not state why this would be important.

Answer: We agree with the reviewer that this should be mentioned in the introduction section and have now incorporated some sentences stating why this is important in the Introduction section on p. 4: “To the best of our knowledge, however, there are no studies that investigate the importance of early life factors in relation to presence or absence of parental overweight. This is important due to the fact that parental obesity might reflect adverse eating and physical activity patterns, and might be related to both early life factors and later obesity. Furthermore, genes shared between the parents and child is associated with both early life factors and later obesity [24]. “ and in the Discussion section on p. 14.

In the Methods section the reliability of the measures is mentioned. Please specify the variables this relates to, how reliability was tested and what were the findings of the reliability study. This would enable more confidence in the measures employed in the study.

Answer: We thank the reviewer for this remark and have now clarified and re-written this section in the Methods section on p. 5.

The Methods section do not detail how children´s or parents´ overweight/obesity was assessed (i.e. by self-reported measures or by physical measures, or a combination of both?) Please be explicit about whether each of these measures were measured or self-reported.

Answer: Thanks you for bringing these issues to our attention. Children’s height and weight were measured by the CHC nurse at a physical examination of the child at the CHC visit at 4 years. The parents’ height and weight were self-reported. This is now clarified in the Methods section on p.5-6: “Children’s height (cm) and weight (kg) was measured by the CHC nurse at the physical examination of the child at the CHC visit at 4 years. Overweight and obesity were
assessed via iso-BMI according to the classification by Cole et al. based on six large nationally representative cross-sectional growth studies with cut-offs of 17.55 (boys) and 17.28 (girls) for overweight and 19.29 (boys) and 19.15 (girls) for obesity [29]. The parents’ height and weight were self-reported in the questionnaire and overweight was defined as BMI > 25 kg/m² and obesity as BMI > 30 kg/m².

A range of co-variates are included in the model, however there was no rationale as to why they were included. Were they included on statistical grounds (If so, what criteria was applied?) or theoretical grounds (if so, what were the hypothesised relationships? Given the large number of co-variates and small prevalence of obesity, this would have had implications for the power. Further, no rationale is provided as to the sequential modelling applied.

Answer: We thank the reviewer for this important comment. The potential confounders were included on theoretical grounds. For example, parental low educational level has been shown to be correlated with early life factors such as maternal smoking during pregnancy and secondhand tobacco smoke and has also been shown to be associated with child overweight/obesity. This information has now been added to the Statistical methods section on p. 7. We have now reduced the number of potential confounders included in the models from 12 to 9 not to risk any problems with the power.

Minor comments

The introduction needs to state the case why overweight/obesity in childhood is a significant public health issue.

Answer: In the Introduction section on p. 3 we state why obesity/overweight is a significant public health issue: “Rising rates of obesity and overweight is an increasing public health problem all over the world [1,2,3]. In Sweden, about 15-20 % of the children are overweight and 3-5 % obese. During the past twenty years the prevalence of overweight children has doubled, while that of obese children has increased 4-5 times, even though the increase has started to level out during later years [4]. Throughout the world, overweight and obesity are occurring at continually younger ages [5] and children who are obese tend to be obese as adults [4]. This has vast implications for future public health, since it is well-known that obesity is associated with an increased risk of arteriosclerosis, pulmonary hypertension, ischemic heart disease, congestive heart failure [6], and asthma [7].”

Please specify what drinks were included in sweetened beverages.

Answer: We thank the reviewer for this comment. The drinks included were soft drinks, syrup or Coca-cola. This is now clarified in the Methods section on p. 7.

Minor English corrections are required.

Answer: We have read the manuscript carefully and made linguistic revisions
were needed also including the tables.

Referee #2:

Major compulsory revisions:

The authors should in the introduction part more clearly justify why they include smoking, overweight at birth and breastfeeding as early life factors in this study on being overweight at four years. Why is not low birth weight included as an early life factor in the introduction and in the aims?

Answer: We thank the reviewer for this comment. We have now extended the introduction section on p 3 discussing the issue of early life factors in relation to overweight/obesity: “More recent research has also shown that an unfavourable environment early in life might elicit a range of physiological and cellular adaptive responses in key organ systems, which in turn might lead to pathology in later life [9]. Earlier studies have shown associations between early life factors such as maternal smoking during pregnancy [5,10,11,12, 13], impaired fetal growth [9,10,14], breastfeeding [1, 15], and high birth weight [10, 16] in relation to overweight in children.” We have also added a large section in the Discussion on p 13-14 on this issue. “Early life has been seen as a critical period for the development of obesity. Early life factors such as secondhand tobacco smoke [1,10,11], maternal smoking [5,10,11,12,13], high birth weight [10, 16] and low levels of breast feeding [1,15] have previously been shown to be associated with child overweight. In a review by Gluckman and Hanson published in 2004, it was concluded that early development make important echoes in disease risk throughout life, and that this is important to bear in mind when forming interventional strategies [34]. An unfavourable environment in early life is thought to elicit a range of physiological and cellular adaptive responses in key organ systems. These adaptive changes result in permanent alterations and might lead to pathology in later life. However, the mechanisms underlying the developmental origins of disease remain poorly defined [9]. Environmentally induced changes in epigenetic states could lead to dysfunctional organ growth and differentiation that is detrimental in the long term [9]. There are theories involving an altered glucose-insulin metabolism in utero leading to an increased risk for obesity later in life. Many studies have shown an association between high birth weight and increased childhood as well as adult BMI [16, 35, 36, 37, 38]. Most of the studies on potential mechanisms between high birth weight and later adiposity come from studies of diabetes during pregnancy. Here the fetal pancreas responds to the elevated glucose levels by producing additional insulin. As insulin may act as a fetal growth hormone, this may produce fetal adiposity. [24] Breastfeeding has been shown to protect against obesity in childhood and in adolescence [15, 39, 40]. One mechanism is related to the fact that there are lower concentrations of serum insulin in infants fed breast milk than those fed with infant formula [16]. Furthermore, breast milk contains less protein than milk from bottles which decreases the risk of overweight [41]. According to Balaban and Silva [41], the mechanism behind lack of breastfeeding and obesity might be related to metabolic imprinting which causes the early nutritional experience to result in
long lasting effect that predisposes to certain diseases. Long-term effects of maternal smoking in pregnancy on the risk of overweight might be related to long-term effects of nicotine exposure on neurobehavioural impulse control as shown in animal and human studies [42] as well as through poor nutrition in the uterus [43,44]. The process which link reduced fetal growth with overweight/obesity has been suggested to stem from adrenal overactivity initiated by early growth restraint [45] and by early postnatal catch-up growth [43]. Secondhand tobacco smoke could be related to overweight/obesity via low parental education and less healthy food patterns [46]. However, the association in the present study between secondhand tobacco smoke and overweight persisted even after adjustment for the mother’s educational level."

If we would have information on SGA (small for gestational age), we would have studied this in relation to child overweight/obesity. However, as it is now, we only have information on birth weight without being able to relate this to abnormal growth. We do, however, mention the results from other studies on this important issue of impaired fetal growth on overweight/obesity in the Introduction section on p.3 and in the Discussion section on p.13-14.

Data collection and covariates should be described more in detail. What is the response rate for parents answering the questionnaire? Which data was taken from the questionnaire and which from the CHC journals? Is parental overweight based on weighted data or self-reported data from the parents? Who answered the questionnaire? Participation in parental education program was not in detail described in the paragraph of covariates. Passive smoking was not in detail described in the paragraph of early life factors. It was unclear to the reader whether behavioural factors were described for the child or the parent.

Answers: We thank the reviewer for bringing these gaps in the Methods section to our attention. These issues have now all been clarified. The response rate was 68% and this information has now been added to the Methods section on p.4. under the heading: "Study population". Where different data were taken from (CHC journals or questionnaire) has now been clarified in the Methods section on p. 5 under the same heading. Parental overweight was assessed through self-reported data in the questionnaire. This has been clarified in the Methods section on p.6: “The parents’ height and weight were self-reported in the questionnaire and overweight was defined as BMI > 25 kg/m2 and obesity as BMI >30 kg/m2.” The questionnaire was answered mostly by both mother and father (55 %), by mother only (34 %) and by father only (5 %). Parental training was assessed through CHC journals where the nurse filled in whether the parents had taken part of parental educational program or not. This has been added to the Methods section on p.7. Secondhand smoking is now more in detail described in the paragraph of early life factors on p.7: “Secondhand tobacco smoke during early life was assessed by the question: Did anyone in the family smoke when the child was 0-4 weeks of age? The answering alternatives were: No, yes - mother/stepmother smoked on a daily basis (also including outdoor smoking), or yes-father/stepfather smoked on a daily basis (including outdoor smoking), or yes-siblings or other person smoked on a daily basis (including
outdoor smoking). Secondhand smoking at 0-4 weeks of age was divided into no (no secondhand smoking at all) and yes (daily secondhand tobacco smoke, including smoking outside). An identical question was used to assess secondhand smoking at 8 months of age.”

The paragraph under the heading behavioural factors (p.7) has now been rewritten to clarify that this applies to the child: “Child behavioural factors. The child’s drinking of sweetened beverages (i.e., soft drinks, syrup or Coca-cola) was dichotomized into daily drinking of sweetened beverages versus no daily drinking of these beverages.”

Analyses were not so easy to follow and interpret. Interaction-analyses would have given a better picture of whether the association between early life factors and being overweight at 4 years, differ between children with normal weight and children with at least one parent overweight. I would recommend that the authors also carry out interaction analyses with logistic regression. What kind of test is carried out in Table 3 for testing whether overweight children differ from normal weight children?

Answer: We have chosen to measure interaction by using the Rothman model. Rothman’s model of synergism used in the present study is based on the theory of two causes being component causes in the same sufficient cause sense [Hallqvist J, Ahlbom A, Diderichsen F, Reuterwall C. How to evaluate interaction between causes: a review of practices in cardiovascular epidemiology. J Intern Med. 1997;241:535-6]. The criterion for interaction is departure from additivity and the reference group for the comparisons is the group unexposed to either factor.

Assessment of interaction is sometimes performed by introducing product terms into logistic risk models. This practice has been criticized (Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins, 1998, Koopman JS. Interaction between discrete causes. Am J Epidemiol 1981;113:716–24), with arguments that assessment of interaction should mainly be based on additive models. An article by A Skrondal assessing measures of interaction as departure from additivity concluded that of three measures of interaction, i.e., attributable proportion (AP), the relative excess risk due to interaction (RERI) and synergy index (S), the S is the matter of choice with additional covariates are to be included (Skrondal A. Interaction as Departure from Additivity in Case-Control Studies: A Cautionary Note. Am J of Epidemiol 2003;158:251-58). Rothman’s model of synergism is also recommended in a review by Hallqvist et al. (Hallqvist J, Ahlbom A, Diderichsen F, Reuterwall C. How to evaluate interaction between causes: a review of practices in cardiovascular epidemiology. J Intern Med. 1997;241:535-6) and has also been used in clinical trials to measure synergistic effects between various drugs (Nguyen K, Aursnes I, Kjekshus J. Interaction between Enalapril and Aspirin on mortality after acute myocardial infarction: subgroup analysis of the cooperative new scandinavian enalapril survival study II (CONSENSUS II). The American J of cardiology 1997:79;115-119; Etminan M. Quantifying the
interaction between angiotensin-converting enzyme inhibitors and aspirin: are we using the right method? Pharmacotherapy. 2001:10;1247-9). We have now re-written part of the Discussion section on p14, where we clearly point out that there are other methods of measuring interaction than the method used (Rothman) and also give some information on the theoretical background for the use of the Rothman´s synergi index and have also re-written and clarified the results sections regarding the results from tables 4 and 5.

I think it would also be interesting to explore whether early life factors are related to overweight if parents are obese. I suggest that the analyses should also be stratified by parental obesity. Another interesting aspect would be to stratify analyses for both parents being overweight.

Answer: We thank for this comment. We have now performed analyses stratified by parental obesity and added information on these results on p.11 and 12 in the Results section. For example, there was a synergi index of 4.95 (95% CI: 2.03, 12.04) for maternal smoking during pregnancy and a synergi index of 2.63 (95% CI: 1.13, 6.10) for high birth weight on child obesity. We did not perform analyses for both parents being overweight or obese due to few cases in some of the groups.

I don´t find anywhere in the text how many of the children had parents with normal weight or overweight.

Answer: This information has now been added in the Results section on p. 9.

In the discussion part the authors concluded that there was a synergistic effect of early life factors in relation to presence or absence of parental overweight. Do the authors have any suggestions for explanations of why there is a synergistic effect. It was also concluded that there is an association between smoking and the development of child overweight. The authors should discuss what could explain these associations. Are they real associations with a logic explanation or are they false associations.

Answer: These issues are now thoroughly discussed on p.13-14.

Minor essential revisions

The last sentence in statistical methods about ethical considerations should be moved to the paragraph of study population.

Answer: This sentence has now been moved to the paragraph of study population.

Second paragraph in results part. Second sentence the last words should be …economic stress compared to children with no overweight.

Answer: This has now been clarified.
In table 2 I think the answer alternatives for breastfed should be changed. Now the results show that those who are not breastfed are more likely to be obese but in the text the authors conclude the opposite.

Answer: We thank the reviewer for this comment and have now corrected this in the table.

Many numbers are repeated in the text, that are already shown in the Table 4 and Table 5.

Answer: We thank the reviewer for bringing this to our attention. These texts have now been re-written and some of the numbers were taken out.