Author's response to reviews

Title: Joint association between birth weight at term and later life adherence to a healthy lifestyle with risk of hypertension: A prospective cohort study

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Author's response to reviews: see over
Response to Reviewer #1: Dr. Karien Stronks

This is an interesting paper on the joined influence of low birth weight and unhealthy lifestyle in adult life, on risk of hypertension in later life. Based on data from the Nurses’ Health Study II, the authors show that the combined risk of hypertension due to a low birth weight at term and unhealthy lifestyle factors is larger than the sum of the parts, indicating an interaction on an additive scale.

1. Is the question posed by the authors new and well defined?
   Yes
   
   Response: Thank you for the supportive comment.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   Yes, with a few questions:
   - Why have the authors made a contrast, in Table 4, between birth weight \( \geq 2.5 \) kg, and all other categories, including the category \( \geq 4.5 \) kg? The latter category has a reduced risk of hypertension according to Table 2, so would it not be logical to exclude that category from the reference group?

   Response: Thank you for the suggestion. We have changed the reference group to \( 2.5-4.49 \) kg (Page 30, Table 4) and revised the manuscript accordingly.

   - I was surprised to see use of nonnarcotic analgesics as a lifestyle factor – could the authors clarify this? I could also be an indicator of health problems.

   Response: We included use of nonnarcotic analgesics as a lifestyle factor because previous studies have documented that even a low frequency of nonnarcotic analgesic use might increase risk of incident hypertension \(^{1-3}\). We did not deny that use of nonnarcotic analgesics may be an indicator of health or sub-health status. So we have moved use of nonnarcotic analgesics to the final model when we reported the population-attributable risk (PAR) in Table 4. Then both PARs, with and without use of nonnarcotic analgesics, have been presented (Table 4, page 30).

   - What is the rationale for the categories in Table 4: why are the 3 healthy lifestyles DASH, exercise and analgesic use taken together, and alcohol and BMI added successively?

   Response: We now included DASH, exercise and alcohol, which are ‘lifestyle’ factors, in the basic model. We added BMI and use of nonnarcotic analgesics in the subsequent models as these two factors might reflect health conditions, as suggested in the previous comment. (Table 4, page 30).

3. Are the data sound and well controlled?
   - The role of smoking is unclear to me. I agree with not including it as a lifestyle factor, but I do not understand why it is sometimes included as a confounder (Table 2 and 4), and sometimes not (Figure 1). In addition, I do not understand why it is mentioned as a lifestyle factor in the legenda for Table 3.

   Response: Thanks for pointing out this inconsistency. Smoking was included in all models as a confounder. We have revised the manuscript accordingly.
- I was surprised to see that educational level (or another indicator of socio-economic position) had not been included as a confounder. See also comment below on unmeasured confounding.

Response: Information of educational level and other detailed socio-economic status was not collected in our cohort. As our study population was all registered nurses with a relatively high homogeneity in educational attainment and socioeconomic status, the potential confounding effects of socio-economic status should be minor. In the 2001 cycle of the NHSII study, the nurses had ranked their feeling about their standing in US society in 10 levels: “at the top are the people who are the best off — those who have the most money, the most education, and the most respectable jobs, while at the bottom are the people who are the worst off — those who have the least money, the least education, and the least respectable jobs or no job.”. After further adjustment for this evaluation as a surrogate indicator of socio-economic status (SES), the results did not appreciably change.

“In order to examine potential confounding of socioeconomic status (SES), we added self-ranking of their standing in US society, comprehensively presenting their money, their education, and their jobs, as a surrogate of their SES to the multivariable-adjusted model. The SES adjusted RRs of hypertension were 1.22 (95% CI: 1.10-1.35), and per 1-kg lower birth weight at term, 1.59 (95%CI: 1.49-1.69) per 1-point higher unhealthy lifestyle score, and 1.93 (95%CI: 1.81-2.05) of their joint effect, with a RERI of 0.12 (95%CI: 0.09-0.14), P for additive interaction < 0.0001.” (page 11 the last paragraph).

- Missing data: for a large number of women, data on lifestyle and birth weight was missing. How could this have affected the conclusions?

Response: If the missing randomly happened, it would unlikely have affected the associations we observed artefactually. To invoke missing data to explain the observed association requires a scenario in which we were disproportionately missing women who both had a low birth weight, unhealthy lifestyles and did not have hypertension as well as women who had a high birth weight, healthy lifestyles and did have hypertension. Such a pattern of selectively missing data seems unlikely. We have added the comparison of BMI and age between women with and without missing data at baseline, and also revised the discussion to address this issue.

“Participants who did not report birth weight or missed lifestyle factors had similar age (mean 36.3±4.7 vs 36.0±4.7 years) and BMI (24.9±5.5 vs 24.6±5.3 kg/m2) as those with the information.” (Page 5 the second paragraph)

“This study was also limited by its reliance on self-reported birth weight and lifestyle factors. As discussed previously, missing birth weight or lifestyle factors was likely to be random in our cohort, and therefore unlikely to affect the associations we observed artefactually.” (Page 15 the last paragraph).

- I did not feel competent to judge the statistical analyses used to test for (additive) interaction. This needs to be checked by a statistician.

4. Do the figures appear to be genuine, i.e. without evidence of manipulation?

Yes

5. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes
Response: Thanks for the comments.

6. Are the discussion and conclusions well balanced and adequately supported by the data?
   - In the discussion and conclusions, the authors interpret low birth weight as a marker of fetal growth restriction. It seems to me, however, that it cannot be ruled out that the influence of low birth weight might also reflect other explanations, including a genetic risk of HT (in case low birth weight is driven by HT of the mother – probably not completely covered by family history of HT), shared environment (both mother of those with low birth weight as the women with low birth weight at adult aged exposed to e.g. stress, e.g. as a result of unemployment), or unmeasured confounding (see also previous comment on educational level). I would expect the authors to discuss these alternative explanations in the discussion section.
   Response: Thank you for the comments. We have revised the discussion.

   “Although we have adjusted for family history of hypertension, residual confounding from genetic effect still could not be totally ruled out. Recent genome-wide association meta-analysis identified 7 loci associated with birth weight, and one (ADRB1) of the 7 loci were also associated with adult blood pressure.” (Page 15 the last sentence of the last paragraph)

   “Unmeasured confounding might also exist even though we have controlled for a wide range of risk factors for hypertension. However, only a very strong unmeasured risk factor for hypertension together with a very large prevalence imbalance among exposure groups could explain our findings.” (Page 16 the first paragraph)

   - The group of people with the lowest risk of HT is extremely small (Table 4: birth weight >= 2.5 kg, and adherent to all healthy lifestyle factors). This raises doubts as to how realistic the estimated PARs are. In my view, the authors need to comment on this in the discussion section, in particular in view of their conclusion that the majority of cases of hypertension could be prevented by the adoption of a healthier lifestyle.
   Response: We agree with the reviewer that the group of people with the lowest risk of hypertension was extremely small, and this might limit the statistic power for PAR estimation particularly in the category with all healthy lifestyle factors and birth weight within 2.5-4.49kg. However, the other categories (with less # of healthy lifestyle factors) had relatively larger sample sizes. Therefore the PAR% calculated for the other categories is more stable.

   From the public health perspective, the small size of people with the lowest risk of hypertension indicates that the group of people without the lowest risk of hypertension is large, providing considerable room for improvement of hypertension, including promoting healthy dietary pattern, increasing physical activity, limiting use of nonnarcotic analgesic drugs, drinking moderate alcohol and keeping a healthy BMI, as well as promoting women’ health during pregnancy.

   - Generalizability: how generalizable are the results to the population as a whole, given changing percentages of children with low birth weight over time? I would expect the authors to discuss this.
   Response: We have added the discussion regarding the generalizability.
Our study has several limitations. First, our cohorts included mostly Caucasian women and the population-attributable risk was population-specific, which limited the generalizability to men or other ethnic groups of women. However, the relative homogeneity of the study populations in educational attainment and socioeconomic status enhances the internal validity. The prevalence of low-risk factors in the NHSII women is much higher than that among black and Hispanic women, and the percentage of low birth weight is greater in the general US population than that in our cohorts. Therefore, the impact of unhealthy lifestyle and low birth weight would be greater in more racially diverse populations.” (Page 15 the second paragraph)
Response to Reviewer #2: Dr. Takanari Kitazono
This is an interesting study; however, it needs much more work.
The reviewer's specific comments are as follows.
Major
1. The authors excluded 31,369 participants who had factors potentially affecting outcome (incidence of hypertension). However, more than 10,000 participants were additionally excluded from the final analysis due to missing data. Is there any possibility that excluded subjects biased the results?
Response: Thank you for the comments.
Yes, we excluded 31,369 participants with pre-hypertension, hypertension, diabetes, cardiovascular disease and cancer at baseline. The purpose of excluding people with physician-diagnosed hypertension at baseline was to minimize the potential reverse causality between lifestyles and hypertension, which was hard to be avoided in a cross-sectional study. We also excluded the people with pre-hypertension at the baseline because prehypertension is one of the strongest risk factors for incident hypertension and many of the modifiable risk factors may be related to prehypertension. We also excluded women who had been ever diagnosed of diabetes, cardiovascular disease and cancer at baseline and during the follow-up period, to minimize the potential confounding effect and to exclude the influence of secondary hypertension of these diseases.

“We also did analysis of the main research questions based on the cross-sectional data at baseline including these 31,369 participants. The odds ratios of hypertension were 1.09 (95% CI: 0.93-1.28) per 1-kg lower birth weight at term, 1.62 (95%CI: 1.51-1.75) per 1-point higher unhealthy lifestyle score, and 1.78 (95%CI: 1.60-1.97) for their joint effect, with a Relative Excess Risk due to Interaction (RERI) of 0.07 (95%CI: 0.02-0.13) and P for additive interaction of 0.005).” (Page 12 the first paragraph)

The estimations based on the baseline cross-sectional dataset with all available data were attenuated as compared to the prospective estimation.

For the exclusion of participants with missing value of birth weight and lifestyle factors, if the missing was random, it would unlikely have affected the associations we observed artefactually. To invoke missing data to explain the observed association requires a scenario in which we were disproportionately missing women who both had a low birth weight, unhealthy lifestyles and did not have hypertension as well as women who had a high birth weight, healthy lifestyles and did have hypertension. Such a pattern of selectively missing data seems unlikely. We have added the comparison of BMI and age between women with and without missing data at baseline, and also revised the discussion to address this issue.

“Participants who did not report birth weight or missed lifestyle factors had similar age (mean 36.3±4.7 vs 36.0±4.7 years) and BMI (24.9±5.5 vs 24.6±5.3 kg/m2) as those with the information.” (Page 5 the second paragraph)

“This study was also limited by its reliance on self-reported birth weight and lifestyle factors. As discussed previously, missing birth weight or lifestyle factors was likely to be random in our
2. Were participants really free of hypertension at baseline? Blood pressure should have been measured at baseline. How did the authors validate the baseline data?

**Response:** We have excluded the nurses with self-reported physician-diagnosed hypertension and the nurses whose reported systolic blood pressure was higher than 120 mm Hg or diastolic blood pressure was higher than 80 mm Hg. Therefore, the population under study had a normal blood pressure at baseline. In our study, “self-reported hypertension was validated in a subset of this cohort using medical record review.” Of 51 women who reported hypertension and for whom records of blood pressure were available, the initial report was confirmed in all cases (BP >140/90 mmHg). In a second survey, blood pressure was measured in a sample of Boston-area participants who were part of the diet validation study. Among the 161 participants sampled who did not report high blood pressure, none had a blood pressure greater than 160/95 mmHg and 6.8% had values between 140/90 and 160/95 mmHg. This confirms a low rate of false negative reporting” (page 5 the last paragraph). The potential reason for high validation of reporting hypertension and low rate of false negative reporting of blood pressure was that our participants were all registered nurses, who had easy access to instruments for measuring blood pressure and physicians for clinical diagnosis.

3. The authors diagnosed hypertension by means of questionnaires. However, the severity of hypertension is unknown. Do the authors consider whether hypertension is severe or not?

**Response:** Hypertension cases were self-reported by the nurses, based on diagnosis by clinical physicians. As the information of systolic and diastolic blood pressure was not reported, we did not evaluate severity levels in our analysis.

4. In the assessment of healthy life score, each factor has equal weight, 1 point. Do these five factors have the same importance as adult hypertension risk?

**Response:** Yes, in our main analysis, each factor has equal weight, 1 point, which would be easily interpreted, especially for the readers without statistic background. We have also added secondary analysis using an expanded low-risk lifestyle score, and the results were similar.

“In sensitivity analysis, we also assigned weights to each low-risk factor based on the beta coefficients from the multivariable-adjusted Cox model with incident hypertension as the outcome. We then summed up the products, divided it by the sum of all beta coefficient value, and then multiplied by 5 to make the low-risk lifestyle score easier to interpret, e.g. each unit of low-risk lifestyle score presented one risk factor.” (Page 6 the last paragraph)

“When we applied the expanded low-risk lifestyle score, the RRs of hypertension were 1.28 (95% CI: 1.17-1.40) per 1-kg lower birth weight at term, 1.46 (95%CI: 1.40-1.51) per 1-point higher unhealthy lifestyle score (5- expanded low-risk lifestyle score), and 1.84 (95%CI: 1.74-1.94) of their joint effect, with a Relative Excess Risk due to Interaction (RERI) of 0.10 (95%CI: 0.08-0.13) and P for additive interaction < 0.0001”. (Page 12 the first paragraph)
5. The use of nonnarcotic analgesics does not appear to be associated with the incidence of hypertension. Is it necessary to adjust for this factor? What were the reasons for the participants to use such nonnarcotic analgesics?
Response: We included use of nonnarcotic analgesics as a lifestyle factor because previous studies have documented that even a low frequency of nonnarcotic analgesic use might increase risk of incident hypertension\textsuperscript{1-3}. We did not record the reason why the nurses had used the nonnarcotic analgesics medications in our cohort. Based on the previous report\textsuperscript{2}, nonnarcotic analgesic drugs are frequently used to alleviate pain of patients who suffer from inflammatory conditions. We did not deny that use of nonnarcotic analgesics may be an indicator of health or sub-health status. So we have moved use of nonnarcotic analgesics to the final model when we reported the population-attributable risk (PAR) in Table 4. Then both PARs, with and without use of nonnarcotic analgesics, have been presented (Table 4, page 28).

6. Salt intake has the most significant impact on the incidence of hypertension. Therefore, the amount of salt intake should be assessed separately from the diet score.
Response: We agree with the reviewer that salt intake has significant impact on the incidence of hypertension. Indeed, the foods used in deriving the DASH score reflected most of the variance of salt intake. Considering this situation, we only included salt as one factor in calculating DASH score. We have conducted secondary analysis with separating salt from DASH score and defining the low-risk lifestyle score with 6 lifestyle factors including sodium intake less than 1500mg and high non-sodium DASH score. The PAR\% estimation with 5 or 6 low-risk lifestyle factors plus healthy birth weight was 66.0\% (95\%CI: 59.2-71.8), which did not materially improve the estimation of the original 5 low-risk lifestyle factors plus healthy birth weight. So we have kept our original coding of low-risk lifestyle score.

7. When was BMI measured? How much is the correlation coefficient between birth weight and BMI? The proportion of obesity increases with age. In case of adjusting for BMI, the value at the timing of incidental hypertension would be better than baseline value.
Response: The BMI was recorded biennially. The correlation coefficient between birth weight and BMI at baseline was only 0.02 as the association between birth weight and BMI was in a U shape in our cohort\textsuperscript{4}. We agree with the reviewer that the proportion of obesity increases with age. So in our analysis, we used updated lifestyle factors including BMI, which were reported every two years, as covariates.

“We updated information during follow-up period by using the most recently available information” (page 8 the end of the first paragraph)

Minor
Is secondary hypertension excluded from the diagnosis of hypertension?
Response: We did not record the reason for hypertension, so the secondary hypertension was not specifically excluded from the analysis. However, we did exclude women with diabetes, cardiovascular disease and cancer at the baseline (page 4 the second paragraph), and at the beginning of each cycle (Page 6 the fourth paragraph). This minimized the potential influence of hypertension secondary to these conditions.
Response to Reviewer #3: Dr. George Zhang

Reviewer's report:
Excellent manuscript.

---------- Minor Essential Revisions -------------------
(The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.)

1. Page 5, Methods/Definition of Unhealthy and Healthy Lifestyle
1a. “we classified low risk as #30 min/d of moderate or vigorous activity.” The cut-off here is >=30 min/d – why not use the same unit as Table 1 or 2 (hours/week)?
Response:
Thanks for the suggestion. We have unified the unit of exercise to hours/week.

1b. “moderate alcohol consumption as greater than zero but not exceeding 10 g/d”; The cut-off “10 g/d” falls in the middle of the alcohol drinking group 5.0-14.9 – Is it odd?
Response:
Thanks for the suggestion. It was a typo. The category of alcohol consumption was “alcohol drinking (g/d: 0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥30)”.

2. Page 5, Statistical Analysis
This section did not mention a brief description of the definition and calculation method for so-called “Age-Adjusted Characteristics of Participants” in Table 1 – what exactly did “age-adjusted” mean? Age is the only covariate adjusted in the model? We need some clarifications.
Response:
Yes, for Table 1, we used indirect standardization, and the variables were standardized by age distribution of the study population.

“We presented the baseline characteristics of the study population according to the category of term birth weight in Table 1. Values were means ± standard deviation (SD) or percentages and were standardized to the age distribution of the study population.” (Page 7 the third paragraph and page 27 footnote of Table 1).

3. Page 9, Results/Table 3 Consistently to report decimal points? “additive interaction were 15.9%(95%CI: 8.9-22.9) for age #30 years, 12.9% (95% CI: 8.59-17.1) for 31-35 years,”; “additive interaction were 15.9%(95% CI: 8.90-22.9) for age #30 years, 12.9% (95% CI: 8.59-17.1) for 31-35 years,” That is, 8.9 becomes 8.90.
Response:
Thanks for the suggestion. We have revised the numbers to one decimal point (page 10 the first paragraph and page 29 Table 3).

4. Table 2, footnote The cut-offs of levels appear somehow arbitrary. Any material impact of different numbers of categories and/or cut-offs on the model results? Also, “supplemental folic acid intake (no, <400, 400-800 or >800 ug/d).” vs. However, mean values of “supplemental folic acid intake, ug/d” in Table 1, just 147 to 166 – much lower than the lower cut-offs in Table 2 (“<400”). Very skewed distribution or other explanation/correction?
Response:
The unit of categories of supplemental folic acid intake was based on the Recommended Dietary Allowances (RDAs) for Folate for women above 18 years (400 ug/d)) and frequently used dose of supplemental folic acid (400 ug/d). As the reviewer noted, the low average value was resulted from the skewed distribution of supplemental folic acid intake in the study population. Around 57% of the study population did not use supplemental folic acid. We have added the frequency of “Using supplemental folic acid” in Table 1 (Page 27 Table 1).

5. Table 3, Please report the sample size under each of three categories of baseline age groups.
Response:
Thanks for the suggestion. We have added the baseline sample size according to age groups in Table 3 (Page 29).
Response to Editor’s Comment

We have revised the manuscript according to the style of BMC medicine, including (1) Provide email addresses of all coauthors; (2) Provide Ethical Approval of the study in Method; (3) Informed consent had been documented; (4) Add an abbreviation section after Abstract; (5) Reformate the author contributions in BMC medicine style.
REFERENCE