Prenatal exposure to the Dutch famine and health in later life
Roseboom, T.J.

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Maternal nutrition during gestation
and adult blood pressure

Tessa J. Roseboom, Jan H.P. van der Meulen, Gert A. van Montfrans,
Anita C.J. Ravelli, Clive Osmond, David J.P. Barker, Otto P. Bleker

Late gestation might be a critical period
for the nutritional programming of blood pressure.

submitted for publication
Summary

**Objective:** To assess the link between maternal diet during pregnancy and blood pressure of the offspring.

**Methods:** We measured blood pressures of people born at term as singletons between November 1943 and February 1947 in a university hospital in Amsterdam, the Netherlands. We used information on the official rations provided to adults in Amsterdam as a proxy for maternal nutritional intake during pregnancy.

**Results:** Adult blood pressure was not associated with protein, carbohydrate or fat intake during any period of gestation. We found, however, after adjustment for sex that the systolic blood pressure decreased by 0.6 mmHg (95% confidence interval 0.1 to 1.1) for every one percent increase in protein/carbohydrate ratio in the third trimester. This association was present both in people who had been exposed to the famine during gestation as well as in those who had not been exposed. The association between protein/carbohydrate ratio in the third trimester and adult blood pressure was furthermore independent of maternal weight gain and final weight, and birth weight (increase for every one percent increase in protein/carbohydrate ratio 0.6 mmHg (95% confidence interval 0.0 to 1.2)). Adjustment for adult characteristics such as BMI, smoking and socio-economic status did not affect the observed association appreciably (adjusted increase 0.5 mmHg (95% confidence interval 0.0 to 1.0))

**Conclusion:** Adult blood pressure seems to be affected by small variations in the balance of macro-nutrients in the maternal diet during gestation rather than by relatively large variations in the absolute amounts.
Introduction

Studies performed in Europe, America and Asia have shown that small size at birth is associated with raised blood pressure in adult life. It is thought that this association is the result of adaptations made by the fetus in response to undernutrition in late gestation. Recently, we studied the effects of prenatal exposure to maternal malnutrition in 50-year-old men and women born in Amsterdam around the time of the Dutch famine, a 5 – 6 month period of severe food shortage during which the caloric intake from protein, carbohydrate and fat was more or less proportionately reduced. We found that people who had been exposed to famine in late gestation had only slightly and non-significantly increased blood pressures compared to those who had not been exposed to famine in utero. However, animal experiments have shown that undernutrition of pregnant rats permanently raises blood pressure in the offspring. These experiments have demonstrated that the size of the effect on blood pressure depends upon the type of undernutrition. The effects of protein restriction are up to three times larger than those of caloric restriction. Moreover, there is now also evidence in humans that the balance of macronutrients in the maternal diet during pregnancy is linked to the blood pressure of the offspring in humans. A study performed in Aberdeen showed that the blood pressure of 40-year-old men and women was related to the balance of animal protein and carbohydrate in their mothers’ diet during late pregnancy. An imbalance in either direction was associated with raised systolic and diastolic blood pressure. Most mothers in that study ate less than 50 g animal protein a day. Among them, carbohydrate intake in late pregnancy was positively associated with their offspring’s blood pressure. On the other hand, in women who ate more than 50 g animal protein daily, the blood pressure of their offspring decreased with increasing carbohydrate intake in late pregnancy. Furthermore, a randomised trial of calcium supplementation in the second half of pregnancy showed that the children of mothers who received the supplement had lower blood pressures than the control group.

These animal and human studies suggest that blood pressure is more strongly linked with the composition rather than the quantity of the maternal diet during pregnancy. Therefore, we assessed to what extent variations in the composition of the maternal diet during different periods of gestation are associated with blood pressure in adult life in the Dutch famine birth cohort. We examined the associations between maternal nutritional intake of macro-
nutrients and the balance of macro-nutrients in the maternal diet during different periods of gestation and blood pressure in adult life.

Methods

Subjects

The selection procedures of this study have been described in detail elsewhere. All singleton babies born alive in the Wilhelmina Gasthuis in Amsterdam between 1 November 1943 and 28 February 1947 were candidates to be included. We excluded those whose birth records were not available (1.0%) or those who were born prematurely (8.9%, gestational age below 259 days). In all, 2414 liveborn singletons were included.

The ‘Bevolkingsregister’ of Amsterdam (population registry) traced 2155 (89%) of the 2414 included babies. Of these, 265 had died, 199 had emigrated from the Netherlands, and 164 did not allow the population registry to give us their address. Of the remaining 1527, we interviewed 912 people (who lived in or close to Amsterdam) at home and asked them to attend the clinic; 741 attended the clinic, and we measured blood pressure successfully in 739. Birth weights according to prenatal exposure to famine in this group of 739 subjects were not different from the 1675 who were not included (difference in birth weight adjusted for exposure was 28 g, p = 0.23).

Maternal nutritional intake

For the purpose of our analyses we used the official daily rations for people over 21 years of age. These rations accurately reflect the variation over time in the total amount of food available in the west of the Netherlands. In addition to these official rations, food also came from other sources (e.g. church organisations, central kitchens, and the ‘black market’), and the actual caloric intake was roughly twice as high. The rations should therefore only be taken as a relative measure of nutritional intake for the population as a whole.

The official rations were determined weekly by the National Bureau for Food Distribution during War Time. We used weekly protein, carbohydrate and fat intake to calculate the percentage of energy derived from protein, carbohydrate and fat during each week, and also to calculate the
protein/carbohydrate ratio. We assumed that birth took place in the 40th week of gestation and estimated the intakes in the first, second and third trimester as the average intake during week 1 to 13, week 14 to 26, and week 27 to 39, respectively. We considered a baby to be exposed to famine in utero if the average maternal daily ration during any 13-week period of gestation was below 1000 calories. Babies born between 7 January 1945 and 8 December 1945 were thus exposed in utero.

Study parameters

The medical birth records provided information about the mother, the course of the pregnancy and the size of the baby at birth. Maternal weight gain in the third trimester was calculated from the difference in weight at the beginning and end of the third trimester divided by the duration of the time interval between the 2 measurements and multiplied by the duration of the trimester (13 weeks).

Socio-economic status at birth was derived from the occupation of the head of the family, which was dichotomised into manual and non-manual class. Socio-economic status at age 50 was determined from the subject's or partner's occupation, whichever was highest, according to the socio-economic index (ISEI-92) with a scale ranging from 16 for the lowest to 87 for the highest status. 10

Statistical methods

We used multiple linear regression analyses to assess the association between nutritional intake and blood pressure in adult life. We always adjusted for sex. Secondly, we adjusted for adult characteristics BMI, smoking, socio-economic status and age. Finally, we also adjusted for maternal weight gain and weight at the end of pregnancy and size of the baby at birth. Information on maternal weight at the end of pregnancy and weight gain was missing for a relatively large number of participants. Therefore, when adjusting for these variables, we imputed the mean value for that variable if information was missing and added a separate variable indicating missing information.

Maternal nutritional intake and age of the participant at blood pressure measurement were both directly derived from the date of birth of the participant, and found to be strongly related (for example the correlation
coefficient of the protein/carbohydrate ratio in the third trimester and age was -0.62). Blood pressure increased with age (systolic blood pressure increased by 1.8 mmHg (95% confidence interval 0.5 to 3.0) per year of life). This is considerably higher than the increase of 0.8 mmHg per year reported in a study assessing age-related changes in blood pressure in healthy men and women. Because of the strong correlation between nutritional intake and age we compared effects of two different approaches to adjust for age. First, we standardised the blood pressure to the age of 50 by using the reported annual 0.8 mmHg increase in systolic blood pressure. Second, we adjusted for age by adding the age of the participant into the linear regression model.

Results

Figure 1 shows the total caloric content of the official rations for adults in Amsterdam as well as the amount of protein, carbohydrate and fat per week as a function of time. The caloric content of the official rations was about 1700 calories per day from April 1941 to January 1944. Around 70% of energy came from carbohydrate, 12% from protein, and 18% from fat. The caloric content gradually decreased to about 1400 calories in October 1944, and fell below 1000 calories on 26 November 1944. The rations varied between 400 calories and 850 calories from December 1944 to April 1945. During the famine period, between 61% and 86% of energy came from carbohydrate, between 5% and 14% from protein, and between 4% and 26% came from fat. On May 12, 1945, one week after the final surrender of the German forces in the West of the Netherlands, the official daily rations rose above 1000 calories. In June 1945, rations were over 2000 calories and around 65% of energy came from carbohydrate, 13% from protein and 22% from fat.

Adult blood pressure

Adult blood pressure was not significantly associated with total caloric, protein, carbohydrate or fat intake during any week of gestation (table 1 and 2). It was, however, negatively associated with the protein/carbohydrate ratio in weeks 32-38. After adjustment for sex, the decrease in blood pressure for
Figure 1. Calories, carbohydrate, fat and protein in official weekly rations for adults between April 1941 and April 1947.

Figure 2. Protein/carbohydrate ratio in the official weekly rations for adult between April 1941 and April 1947.

every percent increase in the protein/carbohydrate ratio varied from 0.4 mmHg (95% confidence interval 0.0 to 0.9) in week 33 of gestation to 0.6 mmHg (95% confidence interval 0.1 to 1.0) in week 37 of gestation.

Consequently, we found that adult blood pressure was inversely related to the average protein/carbohydrate ratio in the third trimester, but not in the
decreased by 0.6 mmHg (95% confidence interval 0.1 to 1.1) for every one percent increase in protein/carbohydrate ratio in the third trimester. The association between protein/carbohydrate ratio in the third trimester and blood pressure was present both in people who had been exposed to the famine during gestation as well as in those who had not been exposed to famine in utero (those born before or conceived after the famine), which indicates that this association is independent of starvation. After adjustment for sex, systolic blood pressure decreased by 0.6 mmHg (95% confidence interval −0.1 to 1.3) for every one percent increase in protein/carbohydrate ratio in people who had been exposed to famine in utero, and 0.7 mmHg (95% confidence interval −0.1 to 1.5) in the unexposed.

Using an 0.8 mmHg increase in systolic blood pressure per year to adjust for age (see methods), we found that systolic blood pressure decreased by 0.4 mmHg (95% confidence interval −0.1 to 0.9) for every one percent increase in the protein/carbohydrate ratio in the third trimester. Adding age into the linear regression model, we found a 0.3 mmHg (95% confidence interval −0.4 to 1.0) decrease in blood pressure for every one percent increase in protein/carbohydrate ratio.

The association between protein/carbohydrate ratio in the third trimester and systolic blood pressure was largely independent of adult characteristics. For example, using an 0.8 mmHg increase in blood pressure per year we found that blood pressure decreased by 0.5 mmHg (95% confidence interval 0.0 to 1.0) for every one percent increase in the protein/carbohydrate ratio after adjustment for BMI, smoking and socioeconomic status at adult age.

Maternal weight gain, maternal weight and size of the baby at birth

Maternal weight gain in the third trimester and weight at the end of pregnancy increased with increasing protein/carbohydrate ratio in the third trimester (table 2). Weight gain increased by 0.7 kg (95% confidence interval 0.6 to 0.8), and maternal weight 0.6 kg (95% confidence interval 0.3 to 0.9) for every one percent increase in protein/carbohydrate ratio in the third trimester. The protein/carbohydrate ratio in the third trimester was also positively associated birth weight. After adjustment for sex, birth weight increased by
Table 1. Adult systolic and diastolic blood pressure and BMI according to maternal caloric intake in the third trimester.

<table>
<thead>
<tr>
<th>Caloric intake in 3rd trimester (n)</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 (168)</td>
<td>126.4</td>
<td>85.5</td>
<td>26.6</td>
</tr>
<tr>
<td>1000-1250 (39)</td>
<td>122.5</td>
<td>82.4</td>
<td>26.8</td>
</tr>
<tr>
<td>1250-1500 (89)</td>
<td>126.4</td>
<td>86.4</td>
<td>26.8</td>
</tr>
<tr>
<td>1500-1750 (127)</td>
<td>123.6</td>
<td>84.6</td>
<td>26.7</td>
</tr>
<tr>
<td>1750-2000 (71)</td>
<td>124.7</td>
<td>85.0</td>
<td>27.2</td>
</tr>
<tr>
<td>&gt;2000 (245)</td>
<td>125.2</td>
<td>85.5</td>
<td>27.4</td>
</tr>
<tr>
<td>p for trend adjusted for sex</td>
<td>0.14</td>
<td>0.41</td>
<td>0.05</td>
</tr>
</tbody>
</table>

35 g (95% confidence interval 19 to 51) for every one percent increase in the protein/carbohydrate ratio in the third trimester. Similar associations were found for birth length, head circumference and ponderal index.

Maternal weight gain and weight at the end of pregnancy were not significantly associated with blood pressure (p always > 0.1). Size at birth was inversely associated with blood pressure. For example, after adjustment for sex, systolic blood pressure decreased by 2.6 mmHg (95% confidence interval 0.2 to 5.0) for every kg increase in birth weight.

The association between protein/carbohydrate ratio in the third trimester and adult blood pressure was independent of maternal weight gain,
weight and birth weight. Using an 0.8 mmHg increase in blood pressure per year, we found that after adjustment for these variables blood pressure decreased by 0.6 mmHg (95% confidence interval 0.0 to 1.2) for every one percent increase in protein/carbohydrate ratio.

Discussion

We found that adult blood pressure was higher in people whose mothers had a low protein intake in relation to carbohydrate intake during the third trimester. This was found both in those exposed to maternal malnutrition during gestation and those not exposed, which indicates that effects of variations in the balance of protein and carbohydrate were independent of maternal starvation. We have previously reported that prenatal exposure to the Dutch famine had only a slight, if any, effect on adult blood pressure. The present findings suggest that blood pressure of the offspring is more strongly affected by small variations in the balance of macro-nutrients than by relatively large changes in absolute amounts of nutrients in the maternal diet during pregnancy.

We used the official daily rations for adults as a proxy for actual nutritional intake. However, in addition to the official rations, food also came from church organisations, central kitchens, and the ‘black market’. The rations should be regarded as a relative measure of the availability of food, as the amount of food actually available were almost twice as high as the official rations. However, the official rations rather accurately reflected the variation over time in the total amount of food available in the west of the Netherlands. It is therefore likely that the protein/carbohydrate ratio derived from the official rations represents more accurately the actual intake than the absolute measures of nutritional intake. We consider it unlikely, however, that our finding that blood pressure was linked with the balance but not with any absolute measure of intake is merely the result of the fact that the rations more accurately reflect the balance of macro-nutrients than the absolute amounts of nutrients in the maternal diet.

Maternal nutritional intake and age were highly correlated, which implies that adjusting for age by adding it into the regression model might affect the accuracy of the coefficient representing the association of the protein/carbohydrate ratio in the third trimester and blood pressure. To
Table 3. Maternal characteristics and size of the baby and the placenta at birth according to maternal nutrition in the third trimester.

<table>
<thead>
<tr>
<th>Caloric intake in 3rd trimester (n)</th>
<th>maternal weight gain (kg)</th>
<th>maternal weight (kg)</th>
<th>birth weight (g)</th>
<th>birth length (cm)</th>
<th>head circumference (cm)</th>
<th>ponderal index (kg/m^2)</th>
<th>placental diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 (168)</td>
<td>0.5</td>
<td>62.8</td>
<td>3146</td>
<td>49.6</td>
<td>32.4</td>
<td>25.7</td>
<td>19.6</td>
</tr>
<tr>
<td>1000-1250 (39)</td>
<td>2.8</td>
<td>65.5</td>
<td>3252</td>
<td>49.9</td>
<td>32.1</td>
<td>26.1</td>
<td>20.2</td>
</tr>
<tr>
<td>1250-1500 (89)</td>
<td>3.4</td>
<td>66.5</td>
<td>3426</td>
<td>50.7</td>
<td>33.0</td>
<td>26.2</td>
<td>21.0</td>
</tr>
<tr>
<td>1500-1750 (127)</td>
<td>4.4</td>
<td>65.4</td>
<td>3346</td>
<td>50.3</td>
<td>32.8</td>
<td>26.3</td>
<td>20.3</td>
</tr>
<tr>
<td>1750-2000 (71)</td>
<td>5.8</td>
<td>67.4</td>
<td>3476</td>
<td>51.0</td>
<td>33.1</td>
<td>26.0</td>
<td>20.0</td>
</tr>
<tr>
<td>&gt;2000 (245)</td>
<td>4.6</td>
<td>68.6</td>
<td>3439</td>
<td>50.5</td>
<td>33.0</td>
<td>26.6</td>
<td>20.2</td>
</tr>
<tr>
<td>p for trend adjusted for sex</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>0.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protein/carbohydrate in 3rd trimester (n)</th>
<th>maternal weight gain (kg)</th>
<th>maternal weight (kg)</th>
<th>birth weight (g)</th>
<th>birth length (cm)</th>
<th>head circumference (cm)</th>
<th>ponderal index (kg/m^2)</th>
<th>placental diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15% (107)</td>
<td>2.0</td>
<td>62.9</td>
<td>3157</td>
<td>49.4</td>
<td>32.3</td>
<td>26.0</td>
<td>19.0</td>
</tr>
<tr>
<td>15%-16% (167)</td>
<td>2.8</td>
<td>65.9</td>
<td>3344</td>
<td>50.4</td>
<td>32.8</td>
<td>26.0</td>
<td>20.8</td>
</tr>
<tr>
<td>16%-17% (176)</td>
<td>2.2</td>
<td>66.0</td>
<td>3364</td>
<td>50.3</td>
<td>32.9</td>
<td>26.3</td>
<td>20.4</td>
</tr>
<tr>
<td>17%-18% (75)</td>
<td>4.8</td>
<td>68.3</td>
<td>3427</td>
<td>50.4</td>
<td>33.1</td>
<td>26.6</td>
<td>20.2</td>
</tr>
<tr>
<td>18%-19% (52)</td>
<td>5.4</td>
<td>69.8</td>
<td>3350</td>
<td>50.5</td>
<td>32.5</td>
<td>26.0</td>
<td>20.1</td>
</tr>
<tr>
<td>19%-20% (61)</td>
<td>5.2</td>
<td>64.3</td>
<td>3354</td>
<td>50.4</td>
<td>32.9</td>
<td>26.2</td>
<td>19.6</td>
</tr>
<tr>
<td>&gt;20% (101)</td>
<td>6.1</td>
<td>68.0</td>
<td>3470</td>
<td>50.7</td>
<td>32.9</td>
<td>26.5</td>
<td>20.2</td>
</tr>
<tr>
<td>p for trend adjusted for sex</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>0.09</td>
<td>0.62</td>
</tr>
</tbody>
</table>
evaluate this problem of collinearity, we not only adjusted for age by adding age into the regression model but also by standardising blood pressure using the age-related increase in blood pressure found in another population of healthy men and women of similar age. The association between protein/carbohydrate ratio in the third trimester and blood pressure was slightly less attenuated when we used the external standard than when adding age into the regression model. The effect size, however, was similar in both approaches and the results suggest that the association between the maternal intake and blood pressure is largely independent of the participants’ age.

Remarkably, blood pressure of the offspring was found to be more strongly linked to relatively small variations in the balance of macro-nutrients than to large changes in absolute amounts of nutrients in the maternal diet during pregnancy. This is consistent with results from a study in Aberdeen that showed that the combination of low intake of animal protein and high intake of carbohydrate was associated with raised blood pressure in the 40-year old offspring. Similarly, animal experiments have shown that the effects of giving low protein diets with unrestricted caloric intake, where protein is substituted by carbohydrate, affected the offspring’s blood pressure more strongly than a reduction of caloric intake, where the balance of macro-nutrients is unaffected. It was found furthermore that the effects of protein restriction during gestation depend on the source of macro-nutrients in the diet. Giving a low protein diet to pregnant rats raised blood pressure in experiments if the diets contained fats rich in linoleic acid, whereas no effects on blood pressure were found in similar experiments using a diet containing fats rich in linolenic acid.

We found indications that adult blood pressure was linked to the balance between protein and carbohydrate intake during the third, but not the second or first trimester of gestation. This suggests that late gestation is a critical period for the nutritional programming of blood pressure. We can only speculate on the biological mechanisms that could range from resetting of hormonal thermostats to structural changes of the kidneys. Some animal studies provide evidence suggesting that maternal glucocorticoids might play an important role in the programming of blood pressure by protein restriction during gestation. It has been shown that protein restriction during gestation down-regulates the expression of placental 11β-hydroxysteroid-dehydrogenase, which protects the fetus from exposure to glucocorticoids.
from the maternal circulation. The ensuing over-exposure of the fetus to glucocorticoids permanently increases the number of glucocorticoid receptors in vascular tissue and the brain \textsuperscript{13}, reduces the number of renal nephrons, impairs renal function \textsuperscript{14}, and raises blood pressure in later life. \textsuperscript{15}
References


