Maternal Macronutrient Intake and Offspring Blood Pressure 20 Years Later

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Background—Results from 2 cohort studies in Scotland established in the 1940s and 1950s (Aberdeen and Motherwell) suggested that a high protein diet during pregnancy might adversely influence offspring blood pressure at adult age. Our objective was to examine this association in the Danish Fetal Origins Cohort (DaFO88).

Methods and Results—This was a prospective birth cohort of 965 women who gave birth in 1988–1989 in Aarhus, Denmark, and whose offspring (n=434) participated in a clinical examination ≈20 years later. Macronutrient intake was assessed in gestational week 30. Multivariable adjusted linear regression was used to examine the relation between higher maternal protein intake, at the expense of carbohydrates, and offspring blood pressure (isocaloric substitution). Main analyses were adjusted for mother's age during pregnancy, prepregnancy body mass index, parity, smoking during pregnancy, educational level, and offspring's sex. The mean total energy intake was 8.7 MJ/day (SD 2.3 MJ/day). The mean energy from carbohydrate, fat, and protein intake was 51, 31, and 16 of total energy, respectively. The results showed that after adjustment, higher maternal protein intake was associated with slightly higher offspring diastolic blood pressure (highest compared with the lowest quintile of protein intake: Δ=2.4 mm Hg; 95% CI 0.4–4.4; *P*=0.03 for trend). Similar differences, although not significant, were found for systolic blood pressure (Δ=2.6 mm Hg; 95% CI −0.0 to 5.3; *P*=0.08 for trend).

Conclusions—Higher maternal dietary protein intake at the expense of carbohydrates was associated with a modest increase in offspring blood pressure in young adulthood. (*J Am Heart Assoc*. 2017;6:e005808. DOI: 10.1161/JAHA.117.005808.)

Key Words: blood pressure • macronutrient • nutrition • pregnancy • protein • young adults

Maternal diet may alter offspring metabolic programming,[1] with macronutrient composition identified as a potentially important etiological factor.[2,3] Extensive evidence from animal studies shows a relation between maternal malnutrition or low-protein diet (≈6–12 total energy [E%]) and an adverse metabolic profile in the offspring,[4] including higher blood pressure (BP).[5,6] Less focus, however, has been directed at high-protein diets, which have gained considerable popularity in recent years, especially as a nutritional intervention to aid weight loss.[7,8] Although human data are limited, evidence from at least 2 studies suggests that the association between maternal protein intake and offspring BP may be U-shaped. A cohort study from Aberdeen, Scotland (established in 1948–1954, n=253) reported different associations between carbohydrate intake and offspring BP, depending on the protein–carbohydrate intake. In that study, low carbohydrate intake combined with high animal protein intake (>50 g/day) was associated with reduced placental size and increased offspring BP 40 years later.[9] Similar results were observed in the Motherwell study (n=626), in which pregnant women attending the same maternity hospital between 1952 and 1976 were advised to eat 450 g of red meat per day and to avoid carbohydrate-rich foods, like bread and potatoes. In that study, offspring of women who reported greater consumption of meat and fish in late pregnancy had higher BP when measured 3 decades later.[10] In line with these findings, adverse effects of a high-protein diet during

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pregnancy on offspring BP, kidney morphology, and anthropometry have also been reported in experimental animals.[11]

Understanding the role of macronutrient composition during pregnancy with regard to offspring chronic disease susceptibility in early life is important to inform preventive measures early in life. Previous studies established in the 1940s and 1950s have found indications that a high-protein diet during pregnancy might influence offspring BP at adult age. Since then, awareness of and focus on the importance of diet during pregnancy has changed considerably, and factors other than protein may have accounted for previous findings. Consequently, it is relevant to examine whether these findings can be replicated in a more contemporary setting. The aim of this study was to examine the relation between dietary carbohydrate substitution with protein and offspring BP at 20 years of age.

Methods

The Study Population

We recruited 965 women with singleton pregnancies in Aarhus, Denmark, from April 1988 to January 1989 (DAFO88 cohort). This number was 80% of a consecutive sample of 1212 eligible women who were attending prenatal care during that time. Details about the cohort and its dietary component have been described previously.[12] These women were scheduled to attend a routine midwife visit in gestational week 30 at which dietary intake was assessed and information on maternal anthropometry, lifestyle, and socioeconomic factors was recorded. Obstetric outcomes were extracted from hospital records.

In the follow-up in 2008–2009, a total of 915 (95% of the original cohort) mother-and-child dyads could be identified in the central registration registry and were alive and living in Denmark. Of the 688 offspring who agreed to participate in the follow-up, 443 offspring attended clinical examination. Offspring of mothers with missing dietary intake or total energy intake <4000 kJ/day were excluded for incomplete registration (n=9). The final data set consisted of 434 mothers and their offspring.

Mothers of offspring who did not attend the clinical examination had lower energy intake (8.4 versus 8.7 MJ/day, P=0.04) compared with mothers of offspring attending the examination. There were no significant differences in maternal protein intake (77 versus 79 g/day, P=0.08), carbohydrate intake (268 versus 269 g/day, P=0.69), or fat intake (70 versus 70 g/day, P=0.33) between these groups. Moreover, age, anthropometry, smoking status during pregnancy, parity status, and gestational age did not differ between mothers whose offspring later did or did not participate in the follow-up study (data not shown).

The study was approved by the Danish Data Protection Agency and the Central Denmark Region Committees on Biomedical Research Ethics (reference no. 20070157). Participants provided written informed consent at recruitment.

Exposure Assessment and Outcomes

Details about the dietary assessment have been described previously.[12] In short, during the prenatal visit in gestational week 30, food frequency questionnaires were handed in. The response was corroborated by trained personnel. In addition, we also conducted a 15-minute face-to-face interview to more accurately assess macronutrient and energy intake. We asked the women about their diet over the previous 3 months, corresponding to the second trimester of pregnancy. The food frequency questionnaire has been validated against biomarkers of n-3 fatty acids only.[12] Nutrient intake was quantified using the Danish food composition table from 1996 (fourth version). At the follow-up in 2008–2009, the offspring were asked to fill out a Web-based lifestyle questionnaire and to attend a clinical examination. The clinical examination included 3 readings of systolic BP (SBP) and diastolic BP (DBP) after 7 minutes of rest with an automatic BP measurement device (Omron M6 Comfort [HEM-7000-E]; Omron Healthcare Co, Ltd), and the means of the SBP and DBP readings were used in our analyses.

Statistics

We used multivariable regression models to examine the association between maternal protein intake at the expense of carbohydrates and offspring BP at ≈20 years of age. The model, therefore, was a substitution model reflecting isocaloric substitution of carbohydrates with protein by allowing all energy-contributing nutrients into the model apart from carbohydrates.[13] All macronutrient variables were energy adjusted using the residual model.[14] We modeled total protein intake in this substitution model both as a continuous variable and in quintiles to account for potential nonlinearity. A test for trend across quintiles was evaluated by entering the categorical variable as a continuous measure.

Covariates included in our models were selected a priori on the basis of former studies.[3,10,11] The following confounders were included in the main model (model A): mother's age from hospital records (in quartiles), prepregnancy body mass index (BMI; in quartiles), parity (nulliparous versus multiparous), smoking status during pregnancy (nonsmoker, <10 or ≥10 cigarettes/day), educational level during pregnancy (elementary schooling, high school or technical schooling, university education) and offspring's sex. We additionally adjusted for offspring BMI (clinical measurements of height and weight at 20 years of age) at follow-up (model B) because

a previous study in this cohort observed an association between higher intake of protein and offspring risk of being overweight.[3] In sensitivity analyses, adjustments were also made for possible intermediary factors such as birth weight, gestational age, gestational weight gain, and pregnancy complications. Missing data ranged from 0% to 6% for individual covariates. Multiple imputations, as implemented in SPSS 24.0 (IBM Corp), were used to impute missing covariates.

In additional analyses, protein intake was divided into animal (from milk, cheese, ice cream, meat, fish, eggs and related products) and plant sources (from cereals, vegetables, fruits, and related products). Analyses were also done separately for men and women to evaluate potential sex-specific associations. Statistical significance was accepted at 2-sided $P<0.05$. All analyses were done in SPSS 24.0.

Results

Anthropometric, demographic, and dietary characteristics of mothers and offspring are presented in Table 1. The mean total energy intake was 8.7 MJ/day (SD 2.3 MJ/day). The mean energy percentage of carbohydrate, fat, and protein intake was 51, 31, and 16 E%, respectively. Among women with high protein intake (quintile 5, mean 20 E%), 15 E% came from animal protein and 5 E% from plant protein, whereas among women with low intake (quintile 1, mean 13 E%), 7 E% came from animal protein and 6 E% from plant protein. Women in the highest quintile of protein intake were more often nulliparous (64% versus 51%), had higher mean gestational weight gain (15 versus 11 kg), lower mean intake of added sugars (5.1 versus 8.7 E%), lower mean fiber intake (23 versus 25 g/day), and lower mean intake of saturated fatty acids (13.3 versus 14.6 E%) and polyunsaturated fatty acids (3.6 versus 4.1 E%) compared with women in the lowest quintile of protein intake. At ≈20 years of age, the mean BMI (kg/m^2) of offspring attending clinical examination was 22±3, and ≈18% had BMI ≥25 (Table 1). The mean offspring SBP and DBP at 20 years was 111±11 and 66±7 mm Hg, respectively.

Table 2 shows the association between maternal carbohydrate substitution with protein (isocaloric model) and offspring BP at 20 years of age. In the fully adjusted model (model A), each 10-g substitution of carbohydrates with protein intake was associated with 0.6 mm Hg (95% CI 0.0–1.1) higher DBP. When comparing the highest and lowest quintiles of protein intake, mean Δ for DBP was 2.4 (95% CI 0.4–4.4) mm Hg. Similar differences were found for SBP (mean 2.6 mm Hg, 95% CI −0.0 to 5.3). The difference was dose-dependent and significant for DBP ($P=0.03$ for trend) but not for SBP ($P=0.08$ for trend). Additional adjustment for

offspring BMI (model B) at age 20 years did not appreciably alter effect estimates; mean Δ for DBP went from 2.4 mm Hg (95% CI 0.4–4.4; model A) to 2.1 mm Hg (95% CI 0.1–4.1; model B) when comparing highest and lowest quintiles (Table 2).

Additional Analyses

Although our primary analyses explored the association with offspring BP as a result of higher maternal protein intake at the expense of carbohydrates (isocaloric model), we observed similar results when we relaxed this substitution condition (ie, protein could be replaced by either carbohydrates or fat). Mean Δ for DBP was 2.0 mm Hg (95% CI 0.0–4.0) when comparing highest and lowest quintiles in this model (data not shown) compared with 2.4 mm Hg (95% CI 0.4–4.4) in the fully adjusted substitution model (Table 2).

When examining the protein source, comparable results were found for animal versus plant protein intake, although the associations were slightly stronger for the former (Table 3). Analyses of protein intake from food groups showed that a higher maternal protein intake from milk and milk products was associated with higher offspring DBP. Each 10-g higher milk protein intake was associated with a 0.5-mm Hg mean increase in DBP (95% CI 0.01–1.00) and 0.7-mm Hg mean increase in SBP (95% CI 0.02–1.33).

The increase in offspring BP was similar for both sexes. When comparing quintile 5 with quintile 1, the increase in offspring mean DBP were 2.4 mm Hg for male offspring (95% CI −1.1 to 5.9) and 2.6 mm Hg for female offspring (95% CI 0.1–5.1). A similar, although nonsignificant, difference was observed for SBP.

Sensitivity analyses also showed that adjustment for potential mediators (ie, birth weight, gestational weight gain in week 30, gestational age, and pregnancy complications) did not substantially alter the results (data not shown).

Discussion

In this prospective study with 20 years of follow-up, we found that higher intake of dietary protein during pregnancy was associated with slightly higher offspring BP when substituted for carbohydrates. We observed a 2.4-mm Hg difference in DBP in offspring of mothers with the highest compared with the lowest quintile of protein intake; a similar, although insignificant, difference was also observed for SBP. Notably, this difference was dose-dependent for DBP but not for SBP.

Elevated BP is a major public health concern because of the accompanying increase in risk of cardiovascular disease and the high global prevalence.[15] In young and middle-aged adults, DBP has been found to be the strongest predictor of coronary

Table 1. Anthropometric and Demographic Characteristics of the Study Population (n=434)

	All Participants* (n=434)	Protein Intake[†]		
		Quintile 1 (n=86)	Quintile 5 (n=87)	P Value[‡]
Mothers anthropometric and demographic characteristics				
Age, y	29±4	30±4	29±4	0.16
Prepregnancy BMI, kg/m^2	21±3	21±3	22±3	0.38
Height, cm	168±6	167±7	168±6	0.41
Gestational age, day	282±11	284±12	281±10	0.14
Gestational weight gain, kg	14±5	11±4	15±5	0.05
Nulliparous, %	60	51	64	0.02
Smoking during pregnancy, %	37	39	48	0.35
University education, %	56	51	51	0.99
Mothers dietary characteristics				
Total energy intake, MJ/day	8.7±2.3	8.8±3.1	8.6±2.0	0.54
Protein, g/kg[†]	1.3±0.3	1.1±0.2	1.6±0.3	<0.01
Protein, g/day[†]	79±11	63±6	94±6	<0.01
Dairy protein, g/day[†]	34±12	20±8	48±10	<0.01
Nondairy animal protein, g/day[†,§]	19±8	14±6	23±8	<0.01
Plant protein, g/day[†,‖]	26±5	28±5	24±4	<0.01
Carbohydrate, g/day[†]	269±27	278±31	260±25	<0.01
Sugar, g/day[†]	37±22	45±29	26±12	<0.01
Fiber, g/day[†]	24±5	25±7	23±4	0.01
SFA, g/day[†]	31±7	32±8	29±7	0.03
MUFA, g/day[†]	19±4	20±4	19±3	0.05
PUFA, g/day[†]	9±2	9±3	8±2	<0.01
Offspring characteristics				
Male, %	40	38	38	0.67
Birth weight, g	3.5±5.1	3.4±5.8	3.5±4.7	0.70
Birth length, cm	51.9±2.3	51.7±2.3	51.9±1.8	0.44
Height, cm	174±9	173±9	174±10	0.49
BMI, kg/m^2	22±3	22±3	23±3	0.06
BMI ≥25, %	18	11	28	<0.01
Systolic blood pressure, mm Hg	111±11	109±12	111±11	0.17
Diastolic blood pressure, mm Hg	66±7	65±7	67±7	0.06
Current smoker, %	18	19	17	0.69
Physical activity (≥12 times per month), %	46	42	51	0.11
Alcohol consumption (≥7 times per month), %	16	27	8	<0.01
Fruit intake (≥6 times per week), %	48	48	51	0.70
Vegetable intake (≥6 times per week), %	54	49	53	0.64
Fish intake (≥5 times per month), %	13	12	21	0.13

BMI indicates body mass index; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

*Values are mean±SD for continuous variables and percentages for categorical variables.

[†]Energy-adjusted by the residual model.

[‡]P values were evaluated by using the *F* test (type III) for continuous variables and the chi-square test for categorical variables.

[§]Animal protein included protein from milk or milk products, cheese, ice cream, meat, fish, and eggs and related products.

[‖]Plant protein included protein from cereals, vegetables, fruits, and related products.

Table 2. The Association Between Maternal Protein Intake (Substituted for Carbohydrates) and Offspring BP at 20 Years of Age (n=434)*

	n	Crude Model[†] β (95% CI)	Model A[‡] β (95% CI)	Model B[§] β (95% CI)
Systolic blood pressure				
Total protein intake (per 10-g change/day)[∥]	434	0.7 (−0.2, 1.7)	0.6 (−0.1, 1.4)	0.6 (−0.1, 1.3)
Protein intake, mean±SD (g/day)				
Quintile 1 (63±6)	86	Reference	Reference	Reference
Quintile 2 (73±2)	86	2.5 (−0.7, 5.7)	2.5 (−0.1, 5.1)	2.1 (−0.4, 4.7)
Quintile 3 (78±1)	87	1.7 (−1.6, 4.9)	2.0 (−0.6, 4.6)	1.9 (−0.6, 4.4)
Quintile 4 (84±2)	88	2.8 (−0.5, 6.0)	2.5 (−0.2, 5.2)	2.4 (−0.1, 5.0)
Quintile 5 (94±6)	87	2.8 (−0.5, 6.0)	2.6 (−0.0, 5.3)	2.1 (−0.4, 4.7)
P for trend[¶]		0.12	0.08	0.12
Diastolic blood pressure				
Total protein intake (per 10-g change/day)[∥]	434	0.6 (0.0–1.2)	0.6 (0.0–1.1)	0.5 (−0.0, 1.0)
Protein intake, mean±SD (g/day)				
Quintile 1 (63±6)	86	Reference	Reference	Reference
Quintile 2 (73±2)	86	0.7 (−1.3, 2.7)	1.3 (−0.7, 3.3)	1.2 (−0.8, 3.1)
Quintile 3 (78±1)	87	1.6 (−0.4, 3.6)	1.5 (−0.5, 3.5)	1.4 (−0.6, 3.4)
Quintile 4 (84±2)	88	1.1 (−0.9, 3.1)	1.4 (−0.6, 3.4)	1.4 (−0.6, 3.4)
Quintile 5 (94±6)	87	2.4 (0.4–4.5)	2.4 (0.4–4.4)	2.1 (0.1–4.1)
P for trend[¶]		0.02	0.03	0.05

*In all models, we examine the association between higher protein intake during pregnancy at the expense of carbohydrates (isocaloric substitution) and offspring blood pressure at 20 years of age.
[†]Protein, fat, and total energy intake entered simultaneously into the model.
[‡]Adjusted for maternal prepregnancy body mass index, maternal age, parity, smoking status during pregnancy, maternal educational level, and offspring sex.
[§]Same covariates as in ‡ but also adjusted for offspring body mass index at age 20.
[∥]The effect estimates can be interpreted as the effect of increasing intake of protein (per 10-g change) at the expense of carbohydrates while keeping calories constant.
[¶]The *t* test with maternal protein intake entered as categorical variable.

heart disease risk over 20-year follow-up.[16] Even small decreases in a population's average BP levels may substantially reduce the population burden of BP-related diseases. Cook et al, for example, showed that a 2-mm Hg reduction in DBP in the mean of the population distribution may result in a 17% decrease in the prevalence of hypertension and a 6% reduction in the risk of coronary heart disease.[17]

Two former cohort studies in Scotland found results in line with ours.[9,10] The cohort study from Aberdeen, Scotland (n=253), found different associations between protein intake and offspring BP 40 years later, depending on the protein:-carbohydrate ratio (mean total protein intake 12.2 E%). When the mother's intake of animal protein intake was high (>50 g/day), each 100-g decrease in carbohydrate was related to an 11-mm Hg rise in SBP and an ≈8-mm Hg rise in DBP.[9] In the Motherwell study in Scotland, women (n=626) attending the maternity hospital were advised to eat 450 g of red meat per day and other sources of animal proteins in moderate quantities but to avoid carbohydrate-rich foods during

pregnancy, resulting in a high protein diet ≈24 E%. They reported that greater consumption of meat and fish in late pregnancy was associated with 0.19 mm Hg (per portion of meat or fish per week) higher offspring BP 3 decades later.[10] The results from these previous studies indicated a dose response. In our study, however, we observed a dose-dependent relationship for DBP but not SBP. Our effect estimates were also of lower magnitude than those reported in the 2 Scottish studies, and that may relate to the younger age of the offspring in our study. Another explanation could be differences in study methodology, as we were able to adjust for total energy intake, for which previous studies did not account for. Differences in effect size could also be related to variation in a number of lifestyle factors that have changed over time, such as dietary habits, smoking, and exercise, that may act as modifiers for our observed association.

Results from animal studies also lend support for our findings. Thone-Reineke et al reported that rats eating a high protein diet (40 E%) at the expense of carbohydrates during

Table 3. The Association Between Maternal Animal and Plant Protein Intake (Substituted for Carbohydrates) and Offspring BP at 20 Years of Age (n=434)*

Protein Intake, Mean±SD (g/day)	SBP[†] β (95% CI)	DBP[†] β (95% CI)
Animal protein intake (per 10-g change/day)[‡]	0.8 (0.0–1.6)	0.7 (0.1–1.3)
Quartile 1 (34±6)	Reference	Reference
Quartile 2 (46±3)	3.3 (0.6, 6.0)	2.0 (−0.1, 4.1)
Quartile 3 (53±2)	2.1 (−0.8, 4.9)	1.5 (−0.6, 3.7)
Quartile 4 (59±2)	2.3 (−0.7, 5.3)	1.4 (−0.9, 3.7)
Quartile 5 (72±7)	4.1 (0.9–7.4)	2.8 (0.3–5.2)
P for trend[§]	0.07	0.11
Plant protein intake (per 10-g change/day)[‖]	2.0 (−0.5. 4.5)	1.6 (−0.3, 3.5)
Quartile 1 (16±2)	Reference	Reference
Quartile 2 (20±1)	2.5 (−0.3, 5.3)	1.7 (−0.4, 3.8)
Quartile 3 (22±1)	2.8 (−0.2, 5.7)	1.9 (−0.3, 4.1)
Quartile 4 (25±1)	2.5 (−0.7, 5.7)	1.3 (−1.1, 3.8)
Quartile 5 (30±3)	2.9 (−0.6, 6.4)	2.1 (−0.6, 4.7)
P for trend[§]	0.19	0.25

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

*In all models, we examine the association between higher protein intake during pregnancy at the expense of carbohydrates (isocaloric substitution) and offspring blood pressure at 20 years of age.

[†]Adjusted for maternal prepregnancy body mass index, maternal age, parity, smoking status during pregnancy, maternal educational level, and offspring sex.

[‡]Protein from animal sources (ie, total protein from milk or milk products, cheese, ice cream, meat, fish, and eggs and related products), protein from other sources, fat, and total energy intake entered simultaneously into the model.

[§]The *t* test with maternal protein intake entered as categorical variable.

[‖]Protein from plant sources (ie, cereals, vegetables, fruits, and related products), protein from other sources, fat, and total energy intake entered simultaneously into the model.

pregnancy had pups with higher offspring BP compared with the group eating a normal-protein diet (20 E%; isocaloric diets).[11] In contrast, another study, also using a rat model,[18] found no effect of maternal high-protein diet on BP, although this result may be related to differences in the study design; for example, the number of animals was about half the size of the study groups of Thone-Reineke et al, and the studies examined different developmental periods. The main supplemented protein source in the study by Thone-Reineke et al was the milk protein casein. When examining the protein source in our study, similar results were found for animal and plant protein intake, although the associations were stronger for animal protein (Table 3). Our analyses of individual food groups, however, showed more pronounced association between maternal protein intake from milk and milk products and offspring BP. Nevertheless, it is worth noting that milk consumption was very high in our cohort (mean 829±369 g/ day). Among women in the highest quintile of protein intake,

51% of the total protein intake came from milk and milk products, and this intake corresponded to 1173±350 g of milk and milk products per day in this group (Table 1). Because of this high intake, we are unable to separate whether the association between maternal protein intake and offspring BP may be due to the dairy protein or just to protein per se.

Difference in BP among offspring whose mothers had higher versus lower protein intake might be related to differences in carbohydrate intake.[9] Our additional analyses, however, showed that the results did not substantially change when we relaxed the substitution condition (ie, protein could be replaced by either carbohydrates or fat), indicating that the association is most likely driven mainly by protein intake alone. There was also limited difference in the carbohydrate intake and quality in our cohort when comparing women with relatively high (quintile 5) versus low (quintile 1) protein intake (Table 1). The main difference observed was a slightly higher intake of added sugar among women with lower protein intake, although both groups had an intake within the recommended maximum of 10 E%.[19]

Animal studies,[11,20] as well as former results in this cohort,[3] have reported that high protein exposure during pregnancy may influence offspring adiposity and risk of being overweight. Because BMI is associated with BP regulation[21] an increase in weight might be mediating this association between a maternal high protein diet and offspring BP; however, further adjustment for offspring BMI in our study did not alter effect estimates (Table 2). Other possible mechanisms for the association between high maternal dietary protein intake and offspring BP suggested in former studies include abnormal placental activity (ie, reduced placental growth), metabolic stress, and abnormalities in glucocorticoid secretion.[9,10,22–24]

The main strength of our study was the long follow-up and the 3 BP measurements taken by health professionals at the clinical visits. We also were able to adjust for a number of potential confounding factors collected during pregnancy. Regarding weaknesses, as in any observational setting, we cannot exclude residual confounding. The focus of this study was on macronutrient intake; maternal intake of other nutrients not examined in this study could also be important with regard to offspring BP, although results have been inconsistent.[25–29] We acknowledge that confounding or effect modification by postnatal dietary factors may be important in our study. According to the early protein hypothesis, higher protein intake during early childhood may induce accelerated weight gain, which has been associated with higher adult BP.[30,31] Interestingly, partially replacing dietary carbohydrate with protein in adulthood has been related to reduction in BP; therefore, higher protein intake in adulthood may have a different influence on BP regulation than early life exposure.[32] Finally, we acknowledge that the clinical relevance of 2.4- to 2.6-mm Hg higher DBP or SBP values as a result of high

maternal protein intake remains uncertain. It is important to keep in mind that our study population consisted of young offspring with normal BP levels, but even mildly raised blood pressure levels present already in adulthood have been found to track to later adulthood and increase the risk of developing hypertension and its sequelae later in life.[17,33,34]

In summary, we found higher maternal dietary protein intake at the expense of carbohydrates during the second trimester of pregnancy to be associated with slightly higher offspring BP in young adulthood. In light of the increased popularity of high-protein diets, a better understanding of long-term health consequences of such regimens during pregnancy and a possible underlying mechanism is needed.

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