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ORIGINAL RESEARCH

# High Amino Acid Intake in Early Life Is Associated With Systolic but Not Diastolic Arterial Hypertension at 5 Years of Age in Children Born Very Preterm

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**BACKGROUND:** The life course of individuals born very premature is a topic of increasing concern. The association between high early amino acid intake and later high blood pressure (HBP) in preterm neonates is debated.

**METHODS AND RESULTS:** In a national, prospective, population-based birth cohort, EPIPAGE-2 (Etude Epidémiologique sur Petits Ages Gestationnels), we assessed blood pressure at 5 years. Eligible infants were those born between 24 and 29 weeks of gestation. Infants were distributed in 2 groups of 717 infants matched on propensity score on whether or not they were exposed to high amino acid intake (>3.5 g/kg per day at day 7); 455 control term infants were also enrolled. A value ≥95th percentile of reference values for age and height defined systolic or diastolic HBP. Blood pressure at 5 years of age was assessed for 389 and 385 children in the exposed and nonexposed groups, respectively. Rates (in percent) of systolic and diastolic HBP were 18.0% (95% CI, 14.5%–22.2%), 13.3% (95% CI, 10.3%–17.0%), 8.5% (95% CI, 6.5%–11.1%), and 9.0% (95% CI, 6.6%–12.3%), 10.2% (95% CI, 7.5%–13.6%), and 5.4% (95% CI, 3.8%–7.6%) in exposed, nonexposed, and term-born groups, respectively. Exposure to high early amino acid intake and maximal serum creatinine (by 50 μmol/L) between day 3 and day 7 were 2 independent risk factors for systolic HBP (adjusted odds ratio [aOR], 1.60 [95% CI, 1.05–2.43] and aOR, 1.59 [95% CI, 1.12–2.26], respectively) but not for diastolic HBP (aOR, 0.84 [95% CI, 0.50–1.39] and aOR, 1.09 [95% CI, 0.71–1.67], respectively). After adjustment for 5-year weight *Z* score, the aOR between high early amino acid intake and systolic HBP was 1.50 [95% CI, 0.98–2.30].

**CONCLUSIONS:** These results suggest that mechanisms of childhood systolic HBP involve neonatal renal challenge by high amino acid intake or dysfunction.

**Key Words:** amino acid intake ■ follow-up ■ high blood pressure ■ preterm infants ■ protein intake

The life course of individuals born very premature has become a topic of increasing importance, because their survival beyond the neonatal period has dramatically increased over the past few decades. The risk for developing systemic arterial high blood pressure (HBP) is increased in this population, but the underlying mechanisms are poorly understood.[1–3]

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## CLINICAL PERSPECTIVE

### What Is New?

- In a national propensity-matched cohort, we confirmed the increased rate of high blood pressure at 5 years in a population of children born very preterm.
- Exposure to high early amino acid intake, and maximal serum creatinine between day 3 and day 7 were 2 independent risk factors for systolic but not for diastolic high blood pressure; the mechanism of high systolic and diastolic blood pressure could be different in children born very preterm, and our results suggest that mechanisms of childhood systolic high blood pressure involve neonatal renal challenge by high amino acid intake or dysfunction.
- The relationship between exposure to high early amino acid intake and later systolic high blood pressure is partially mediated by the 5-year weight *Z* score.

### What Are the Clinical Implications?

- Monitoring of cardiovascular health of children born very preterm should be recommended, and attention to limiting overweight during the first years of life could reduce the excess risk of high blood pressure in this population.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **HBP** | high blood pressure |

Epidemiologic evidence suggests early increased amino acid intake could be associated with later HBP in the general population. This association could be mediated by altered kidney function.[4] Literature suggests postnatal nutritional intakes could be determinants of later HBP at 6.5 years of age in infants born very preterm as well.[5] Concerns have been raised that not only low intakes but also high intakes in infancy might contribute to higher blood pressure (BP) and increased cardiovascular risk later in life in this high-risk population.[6]

In a national birth prospective population-based cohort, EPIPAGE-2 (Etude Epidémiologique sur Petits Ages Gestationnels), we observed that amino acid intake >3.5 g/kg per day at day 7 after birth was independently associated with higher intelligence quotient at 5 years in a propensity score-matched cohort.[7] Because the association between high early amino acid intake and later HBP is debated in this population, we assessed BP at 5 years in this matched cohort.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request, after authorization by the cohort Data Access Committee. The new law for modernization of the French Public Health System voted for in 2016 now provides a legal framework for access to and reuse already-collected cohort data by complying with Reference Methodology MR-004. Therefore, only nonnominative data defined as having a low reidentification risk are accessible. General information on research activities in the institution must be provided to the people concerned (eg, posting on the premises, entry in the welcome booklet).

To this general information, individual patient information must be delivered for each project in which the patient is involved or for which the patient data will be treated. As a consequence, each data access request must be submitted to the EPIPAGE-2 Data Access Committee that evaluates the research projects based on the following criteria: (1) methodological strengths and weaknesses (feasibility, choice of methods to achieve the objectives); (2) absence of overlap with other ongoing projects, in which case discussions with the different teams are organized; and (3) relevance of the requested data for the project and respect for confidentiality.

### Study Population

Very preterm infants were enrolled in the EPIPAGE-2 cohort. Recruitment took place at birth in all neonatal intensive care units (NICUs) in France from April 1, 2011 to December 31, 2011. Eligible children were those born between 24+0 and 29+6 weeks+days of gestation, admitted to the NICU, alive at 7 days after birth, and with information available on amino acid intake at 7 days after birth. Baseline characteristics at birth and during the first week, as well as the maximum creatinine value obtained between day 3 and day 7 after birth, were prospectively recorded during neonatal hospitalization. Children were followed from September 1, 2016 to December 31, 2017. EPIPAGE 2 study was approved by the National Data Protection Authority (CNIL no. 911009) and by the 2 ethics committees: Consultative Committee on the Treatment of Data on Personal Health for Research Purposes (reference n°10.626), and Committee for the Protection of People Participating in Biomedical Research-reference (CPP SC-2873).[8]

Term-born children were from the ELFE (Étude Longitudinale Française Depuis l'Enfance) cohort, followed with the EPIPAGE-2 follow-up protocol. The ELFE cohort is a contemporary French cohort of >18 000 children born in 2011, in 344 randomly selected public and private maternity units

in metropolitan France.[9] Recruitment and data collection occurred only after families had received information and provided oral informed consent to participate in the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

## Amino Acid Intake at 7 Days After Birth

Preterm infants were separated into 2 groups, exposed and nonexposed, based on whether they had been prescribed a high amino acid intake (defined as 3.51–4.50 g/kg per day at 7 days after birth), as recommended in 2011 on a physiological basis,[10] and by the American National Institute of Child Health and Human Development,[11] and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition.[12] In the EPIPAGE-2 study, information about nutritional intake was recorded at days 3, 7, and 28 and at hospital discharge. All data were prospectively collected during NICU hospitalization.

## Outcomes

The primary outcomes were systolic and diastolic HBP defined as a value >95th percentile of reference values for age and height.[13] The secondary outcomes were systolic and diastolic BP considered as continuous variables. Standard operating procedures were used for resting BP measurements.[14,15] Blood pressure (mm Hg) was measured noninvasively during an outpatient visit at 5 years of age by automatic oscillometer with a BP monitor or with a manual sphygmomanometer. The same protocol was been used for children born at term. Children were seated in a quiet examination room for at least 5 minutes before BP assessment. All BPs were assessed by trained, certified staff and done in agreement with Fourth Task Force recommendations of technique and cuff sizes.[14] Three consecutive BP measurements were performed 2 minutes apart. The reported value was the mean of the 2 closer values. If only 2 measurements were performed, the reported value was the mean of these 2 values. In case of only 1 measurement, this value was reported. *Z* scores of weight at 5 years were based on World Health Organization curves.

## Statistical Analysis

The main analysis included 1789 children born preterm with complete data. We analyzed the association between the exposure and the primary outcome using a propensity score approach[16] to control for observed confounding factors that might have consequences for both group assignment (exposed versus nonexposed) and outcome. The propensity score of each infant was defined as the probability of having an amino acid intake >3.50 g/kg per day based on the infant's individual observed covariates. The score was estimated using a logistic regression model, with amino acid intake >3.50 g/kg per day at day 7 as the dependent variable with regard to baseline maternal (maternal level of education, leading causes of preterm delivery, antenatal corticosteroids, mode of delivery), infant (gestational age, sex, birthweight *Z* score, Apgar score, need of assisted ventilation at day 7, intestinal transit and acute kidney failure during the first 7 days after birth, surfactant treatment), and NICU characteristics (patient volume). Birth weight *Z* scores were based on Olsen curves. The proportion of participants with missing data ranged from 0% to 8.5%, exceeding 4.0% only for data on Apgar score at 5 minutes and maternal educational level. Missing data were treated as separate categories. The primary analysis was based on propensity score matching. We used a 1:1 matching algorithm without replacement to match exposed and nonexposed newborns based on propensity score within a caliper of 0.2 SD of the logit of the propensity score.[17] Imbalance after matching was checked. After matching, all standardized difference were <10% (ie, 0.01 for all parameters included in the propensity score) (Table S1). First, we compared rate of systolic and diastolic HBP between exposed and nonexposed preterm infant groups, between exposed preterm infant group and control born-term group, and between nonexposed preterm infant group and control term-born group. Second, we calculated adjusted odds ratios (aORs) to quantify the association between high amino acid intake at day 7, maximum serum creatinine between day 3 and day 7, and primary outcomes (systolic and diastolic HBP) using logistic regression analysis fit by generalized estimating equations to account for paired data.[18]

Sensitivity analyses were performed among the matched cohort but restricted to children with at least 2 BP measurements performed with a validated automatic BP monitor[19] to have an analysis among more homogenous measurements. Complementary analyses were performed using systolic and diastolic BPs as continuous variables. First, we measured the Spearman correlation between systolic and diastolic BPs and macronutrient intake as a continuous variable in the matched cohort. In the overall cohort, we used general linear equations and adjustment for gestational age, sex, and birth weight *Z* score, weighted by the inverse of the propensity score. A pathway analysis was performed to find out whether the relationship between high early amino acid intake and later BP was mediated by the 5-year weight *Z* score.

All tests were 2-sided, and $P<0.05$ were considered statistically significant. All analyses were performed using SPSS version 26. Data were analyzed from January 15, 2023 to May 15, 2023.

# RESULTS

## Study Population

Among the 2136 preterm infants born between 24+0 and 29+6 weeks+days gestation admitted to NICUs during the study period, 170 died within the first 7 days, leaving 1966 alive at day 7. Among these, information about amino acid intake at day 7 after birth was available in 1789 infants. Among the 1789 infants, 938 received >3.5 g/kg per day (exposed group), and 851 did not (nonexposed group) (Figure 1). These infants were hospitalized in 63 NICUs, where the percentage of exposure varied from 0% to 100% (Figure S1). Differences between the exposed and nonexposed infants are presented in Table 1.

## Propensity-Matched Analysis

Propensity scores were calculated in 1789 very preterm infants. Distributions of propensity scores are summarized in Figure S2. Propensity scores ranged from 0.095 to 0.922. The area under the receiver operating characteristic curve for the propensity score model was 0.67 (95% CI, 0.64–0.69) (Figure S2). Among the 1789 preterm infants, 1434 could be matched, with 717 in each group, exposed and nonexposed. The matched groups were found to be well balanced for all recorded baseline variables (Table 1). In particular, the number of children born of hypertensive pregnancies was similar between the exposed and nonexposed groups (24.7% versus 22.5%, $P$=0.37). Maximal creatinine observed in plasma between day 3 and day 7 after birth was significantly lower in the exposed group (Table 2). Characteristics of nutrition intake at day 3, 7, and 28 after birth and outcome at 36 weeks of Postconceptional age are indicated in Table 2. At 36 weeks of postconceptional age and at discharge, nutrition intake was similar.

In the matched cohort, at 5 years, rates of children alive were similar in the 2 groups. Characteristics of preterm infants with and without BP measurement at 5 years were not different excepted for maternal level of education (Table S1). The number of measurements of BP was 3 for 354 and 358, 2 for 21 and 19, and only 1 for 10 and 12 children in the nonexposed and exposed groups, respectively. The mode of measurement was automatic oscillometric method in 291 out of 385 (75.6%) and 308 out of 389 (79.2%) of nonexposed and exposed groups, respectively ($P$=0.023). The mean (SD) systolic BP was higher in the exposed group: 100.2 (10.6) versus 98.6 (10.4) mm Hg ($P$=0.036), but not the mean (SD) diastolic BP: 59.1 (8.9) versus 58.7 (8.6) mm Hg ($P$=0.615) (Table 3). Systolic HBP tended to be more frequent in the exposed group, 18.0% (70/388) versus 13.3% (51/384) ($P$=0.069) but not diastolic HBP rate, 9.0% (35/388) versus 10.2% (39/384) ($P$=0.592). In the control group born at term, rates of systolic and diastolic HBP were 8.5% (49/574) and 5.4% (31/574), respectively. Thus, compared with the control group, the rate systolic HBP was greater in the 2 preterm groups, whether exposed (18.0% versus 8.5%, $P$<0.001) or not exposed (13.3% versus 8.5%, $P$=0.019). Similarly, diastolic HBP rate was more common (9.0% and 10.2% in exposed and nonexposed preterm groups, respectively), compared with 5.4% ($P$=0.03 and $P$=0.006) in controls.

Among preterm infants, exposure to a high amino acid intake at day 7 after birth, and maximal creatinine observed in plasma between day 3 and day 7 after birth, were significantly associated with systolic HBP (aOR, 1.60 [95% CI, 1.05–2.43] and aOR, 1.59 [95% CI, 1.12–2.26], respectively), but not with diastolic HBP (aOR, 0.84 [95% CI, 0.50–1.39] and aOR, 1.09 [95% CI, 0.71–1.67], respectively) (Figure 2A).

In addition, we observed that the relationship between amino acid intake at day 7 after birth and systolic BP as a continuous variable was not significant (adjusted β=1.00 mm Hg per 1 g/kg of amino acid intake [95% CI, −0.19 to 2.71]). We observed a significant linear relationship between maximal creatinine observed in plasma between day 3 and day 7, and systolic BP as a continuous variable (adjusted β=2.01 mm Hg per 50 μmol of creatinine [95% CI, 0.42–3.60]) (Figure 2B). However, we did not observe any significant correlation between amino acid intake at day 7 or maximal creatinine observed in plasma between day 3 and day 7 and diastolic BP. The pathway analysis showed that the relationship between high early amino acid intake and later systolic BP was not mediated by the 5-year weight $Z$ score (Figure S3) or the 5-year body mass index $Z$ score (Figure S4). Nevertheless, the relationship between exposure to high early amino acid intake and later systolic HBP is partially mediated by the 5-year weight $Z$ score, because the aOR was 1.50 (95% CI, 0.98–2.30) after adjustment versus 1.60 (95% CI, 1.05–2.43) without adjustment for the 5-year weight $Z$ score. We observed the same relationship when we adjusted for 5-year body mass index $Z$ score.

## Sensitivity Analyses

These associations were consistent across sensitivity analysis performed in the matched cohort but restricted to infants with at least 2 BP measurements performed with an automatic BP monitor. The mean (SD) systolic BP was higher in the exposed group: 101.4 (10.2) versus 99.3 (10.2) mm Hg ($P$=0.013) but not the mean (SD) diastolic BP: 59.1 (8.6) versus 59.0 (8.1) mm Hg ($P$=0.801). Systolic HBP was more frequent in the exposed group, 20.5% (63/307) versus 13.3% (39/290) ($P$=0.022) but not diastolic HBP rate, 9.0% (35/388) versus 10.2% (39/384) ($P$=0.592). Exposure to

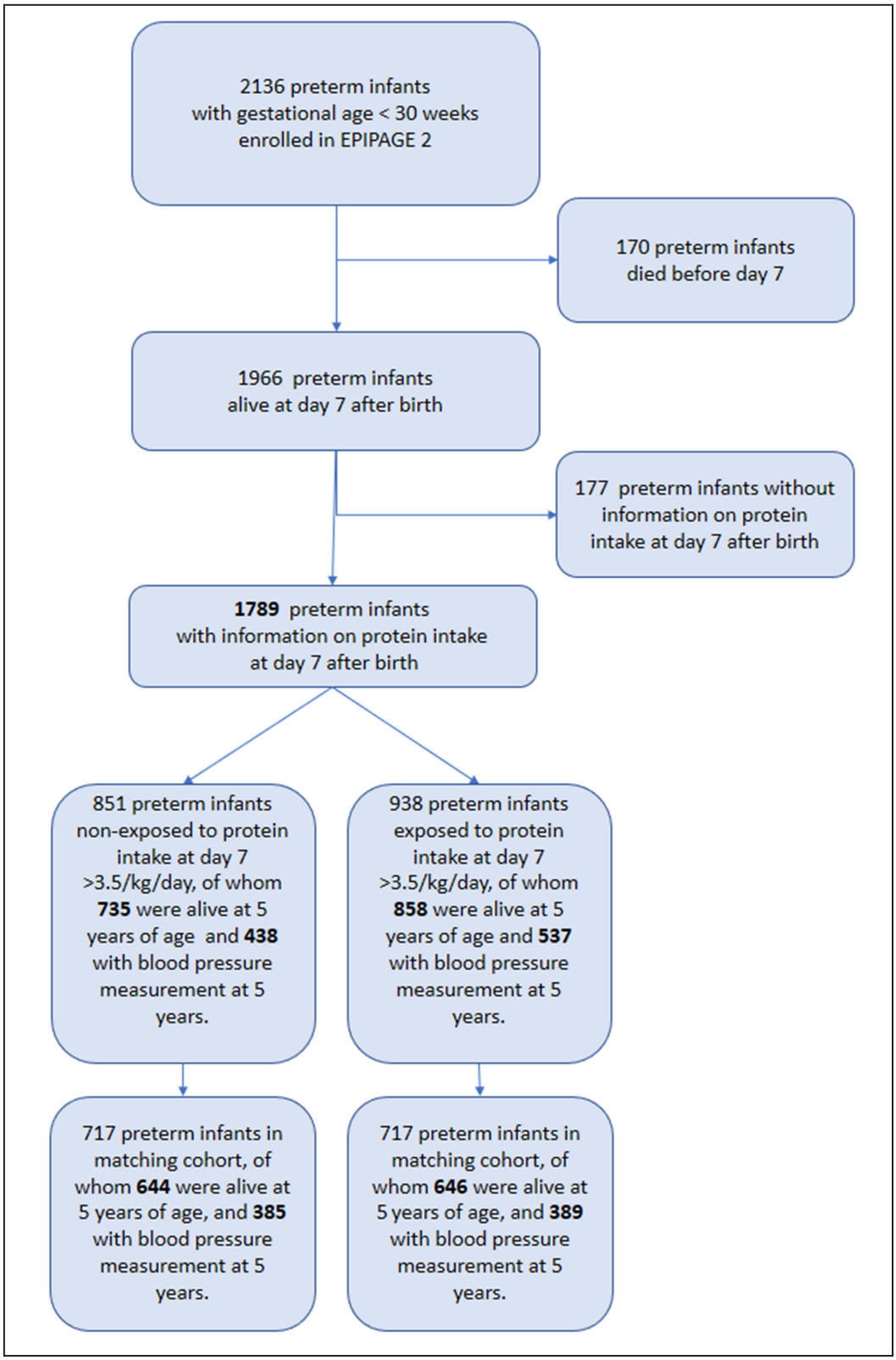


**Figure 1. Study flowchart.**
EPIPAGE-2 indicates Etude Epidémiologique sur Petits Ages Gestationnels.

**Table 1. Baseline Characteristics**

| Characteristic | Overall cohort (N=1789) | | | | Matched cohort (N=1434) | | | |
|---|---|---|---|---|---|---|---|---|
| | Nonexposed, N=851, n (%) | Exposed, N=938, n (%) | Standardized difference (%) | *P* value | Nonexposed, N=717, n (%) | Exposed, N=717, n (%) | Standardized difference (%) | *P* value |
| Maternal level of education | | | | <0.001 | | | | 0.996 |
| Information missing | 137 (16.10) | 103 (10.98) | 15.01 | | 95 (13.25) | 95 (13.25) | 0 | |
| Less than high school diploma | 241 (28.32) | 231 (24.63) | 8.37 | | 194 (27.06) | 193 (26.92) | 0.32 | |
| High school diploma | 157 (18.45) | 175 (18.66) | 0.54 | | 137 (19.11) | 134 (18.69) | 1.07 | |
| Higher than high school diploma | 316 (37.13) | 429 (45.74) | 17.55 | | 291 (40.59) | 295 (41.14) | 1.12 | |
| Gestational age, wk, mean (±SD) | 27.16 (±1.55) | 27.18 (±1.46) | 1.33 | 0.740 | 27.21 (±1.55) | 27.17 (±1.47) | 2.65 | 0.599 |
| Birthweight *Z* score, mean (±SD)* | −0.10 (0.99) | −0.09±1.01 | 1.00 | 0.845 | −0.07 (0.97) | −0.07 (1.01) | 0.00 | 0.992 |
| Sex | | | | 0.100 | | | | 0.597 |
| Boy | 469 (55.11) | 460 (49.04) | 12.11 | | 386 (53.84) | 376 (52.44) | 2.81 | |
| Girl | 382 (44.89) | 478 (50.96) | | | 331 (46.16) | 341 (47.56) | | |
| Leading causes of preterm delivery | | | | 0.364 | | | | 0.993 |
| Information missing | 20 (2.4) | 36 (3.8) | 8.61 | | 17 (2.37) | 19 (2.65) | 1.79 | |
| Twins or triplets | 288 (33.84) | 287 (30.60) | 6.94 | | 242 (33.75) | 225 (31.38) | 5.06 | |
| Singleton with preterm labor | 239 (28.08) | 251 (26.76) | 2.96 | | 195 (27.2) | 207 (28.87) | 3.72 | |
| Singleton with preterm rupture of membranes | 127 (14.92) | 164 (17.48) | 6.95 | | 113 (15.76) | 114 (15.90) | 0.38 | |
| Singleton with vascular disorders and FGR | 66 (7.76) | 71 (7.57) | 0.71 | | 55 (7.67) | 56 (7.81) | 0.52 | |
| Singleton with vascular disorders without FGR | 76 (8.93) | 82 (8.74) | 0.67 | | 63 (9.00) | 63 (9.03) | 0.00 | |
| Singleton with placental abruption | 11 (1.29) | 13 (1.32) | 0.87 | | 10 (1.43) | 10 (1.43) | 0.00 | |
| Singleton with isolated fetal growth retardation | 24 (2.82) | 34 (3.62) | 4.53 | | 22 (3.14) | 23 (3.30) | 0.80 | |
| Antenatal corticosteroids | | | | 0.024 | | | | 0.954 |
| Information missing | 30 (3.53) | 33 (3.52) | 0.05 | | 30 (4.18) | 29 (4.04) | 0.71 | |
| No | 143 (16.80) | 160 (17.06) | 0.69 | | 114 (15.90) | 122 (17.02) | 3.02 | |
| Incomplete cure | 163 (19.15) | 130 (13.86) | 14.27 | | 116 (16.18) | 115 (16.04) | 0.38 | |
| Yes | 515 (60.52) | 615 (65.57) | 10.48 | | 457 (63.73) | 451 (62.90) | 1.72 | |
| Caesarean section | | | | 0.210 | | | | 0.701 |
| Information missing | 13 (1.53) | 8 (0.85) | 6.27 | | 5 (0.70) | 6 (0.84) | 1.60 | |
| Yes | 530 (62.28) | 563 (60.02) | 4.64 | | 450 (62.76) | 435 (60.67) | 4.30 | |
| Apgar ≥7 at 5 minutes after birth | | | | 0.021 | | | | 0.979 |
| Information missing | 77 (9.05) | 54 (5.76) | 12.59 | | 52 (7.25) | 50 (6.97) | 1.09 | |
| Yes | 586 (68.86) | 684 (72.92) | 8.95 | | 505 (70.43) | 507 (70.71) | 0.61 | |
| Regular intestinal transit during the first week after birth | | | | 0.358 | | | | 0.863 |
| Information missing | 34 (4.00) | 43 (4.58) | 2.86 | | 31 (4.32) | 31 (4.32) | 0 | |
| Yes | 430 (50.53) | 499 (53.20) | 5.35 | | 359 (50.07) | 379 (52.86) | 5.58 | |
| Acute kidney failure | | | | <0.001 | | | | 0.943 |
| Information missing | 23 (2.70) | 31 (3.30) | 3.52 | | 20 (3.18) | 19 (2.75) | 2.54 | |
| Yes | 107 (12.57) | 59 (6.29) | 17.31 | | 59 (8.23) | 56 (7.81) | 1.55 | |
| Surfactant | | | | 0.345 | | | | 0.917 |
| Information missing | 4 (0.47) | 2 (0.21) | 4.47 | | 2 (0.28) | 2 (0.28) | 0 | |

(*Continued*)

**Table 1. Continued**

| Characteristic | Overall cohort (N=1789) | | | | Matched cohort (N=1434) | | | |
|---|---|---|---|---|---|---|---|---|
| | Nonexposed, N=851, n (%) | Exposed, N=938, n (%) | Standardized difference (%) | *P* value | Nonexposed, N=717, n (%) | Exposed, N=717, n (%) | Standardized difference (%) | *P* value |
| No | 143 (16.80) | 149 (15.88) | 2.49 | | 127 (17.71) | 117 (16.32) | 3.70 | |
| 1 Dose | 493 (57.93) | 578 (61.62) | 7.53 | | 421 (58.72) | 430 (59.97) | 2.55 | |
| ≥2 Doses | 211 (24.79) | 209 (22.28) | 5.9 | | 167 (23.29) | 168 (23.43) | 0.33 | |
| Assisted ventilation at day 7 | | | | <0.001 | | | | 0.826 |
| Information missing | 3 (0.35) | 11 (1.17) | 9.45 | | 2 (0.28) | 4 (0.56) | 4.33 | |
| Yes | 409 (48.06) | 366 (39.02) | 18.31 | | 314 (43.79) | 282 (39.33) | 9.06 | |
| Patient volume of NICU where the infant was hospitalized at day 7 | | | | <0.001 | | | | 0.705 |
| <20 Infants | 183 (21.50) | 113 (12.05) | 25.50 | | 124 (17.29) | 108 (15.06) | 6.06 | |
| 21–30 Infants | 150 (17.63) | 227 (24.20) | 16.21 | | 137 (19.11) | 145 (20.22) | 2.79 | |
| 31–40 Infants | 132 (15.51) | 111 (11.83) | 10.73 | | 102 (14.23) | 104 (14.50) | 0.77 | |
| >40 Infants | 386 (45.36) | 487 (51.92) | 13.15 | | 354 (49.37) | 360 (50.21) | 1.68 | |

FGR indicates fetal growth retardation; and NICU, neonatal intensive care unit.
*Birth weight *Z* score based on Olsen curve.

a high amino acid intake at day 7 after birth and the maximal creatinine observed in plasma between day 3 and day 7 after birth were significantly associated with systolic HBP (aOR, 1.96 [95% CI, 1.21–3.18 and aOR, 1.78 [95% CI, 1.19–2.66], respectively) (Figure S5A), but not with diastolic HBP (aOR, 1.00 [95% CI, 0.54–1.85] and aOR, 0.87 [95% CI, 0.51–1.48]). Moreover, the linear relationships between amino acid intake at day 7 after birth or maximal plasma creatinine between day 3 and day 7, and systolic BP (adjusted β=1.61 mm Hg per 1 g/kg of amino acid intake [95% CI, 0.28–2.93] and adjusted β=1.94 mm Hg per 50 µmol of creatinine [95% CI, 0.31–3.57], respectively) were significant (Figure S5B). In contrast, we did not observe any significant relationship between amino acid intake at day 7 or maximal plasma creatinine between day 3 and day 7, and diastolic BP. The pathway analysis showed that the relationship between high early amino acid intake and later systolic BP was not mediated by the 5-year weight *Z* score (Figure S6) or by the 5-year body mass index *Z* score (Figure S7). Nevertheless, the relationship between exposure to high early amino acid intake and later systolic HBP is partially mediated by the 5-year weight *Z* score, because the aOR was 1.85 (95% CI, 1.12–3.04) after adjustment versus 1.98 (95% CI, 1.20–3.25) without adjustment for the 5-year weight *Z* score. We observed the same relationship when we adjusted for the 5-year body mass index *Z* score.

## DISCUSSION

The findings of the current study confirm the increased risk of HBP at 5 years in a population of children born very preterm. They further reveal that the risk of systolic HBP is significantly higher in preterm infants that were exposed to higher early amino acid intake in the first week of postnatal life. Finally, they suggest that 2 different mechanisms may be involved for systolic HBP and diastolic HBP, the former likely implicating the kidney, because a higher maximum plasma creatinine between day 3 and day 7 after birth was a risk factor for systolic HBP but not for diastolic HBP.

Systematic reviews and meta-analyses have reported significantly higher BP in very preterm infants, with a difference, depending on studies, ranging from 2 to 7 mm Hg for systolic pressure and 2 to 3 mm Hg for diastolic pressure, compared with control subjects born at full term.[1,5,20–27] We here confirm the risk of higher BP at 5 years for diastolic pressure in our population of very preterm infants, regardless of amino acid intake in the first week of life. Yet the risk for systolic BP was only increased in the exposed infants. Because the heights of children born very preterm are smaller once they reach late childhood, the rate of systolic HBP according to age and height is also significantly higher in nonexposed groups of children born very preterm than those born at term. Such observation is of importance, because preterm-born adults have been found to have a unique left ventricular structure and function that worsens with systolic BP elevation.[28] Thus, additional primary preventive strategies specifically targeting cardiovascular risk reduction in this population may be warranted. To achieve that goal, it seems relevant to briefly discuss our understanding of the underlying pathophysiology of high systemic BP.

In the current study, early exposure to higher amino acid intake was associated with higher systolic BP and increased risk of systolic HBP as a function of age and height. The association could

**Table 2. Neonatal Nutritional Intake in the Nonexposed and Exposed Groups**

| Creatinemia during first week and neonatal nutritional intake | Propensity score-matched cohort | | | | |
|---|---|---|---|---|---|
| | N=717 | Nonexposed | N=717 | Exposed | *P* value |
| Maximal creatinemia between d 3 and d 7 * | 650 | 85.0 (3.2) | 620 | 79.2 (2.4) | <0.001 |
| Neonatal nutritional intake | | | | | |
| D 3 | | | | | |
| Protein†, g/kg per d | 704 | 2.5 (0.8) | 712 | 3.2 (0.7) | <0.001 |
| Carbohydrate, g/kg per d | 706 | 10.9 (3.0) | 714 | 11.2 (2.9) | 0.012 |
| Lipid, g/kg per d | 701 | 1.7 (1.1) | 705 | 2.0 (1.1) | <0.001 |
| D 7 | | | | | |
| Protein†, g/kg per d | 717 | 3.0 (0.5) | 717 | 4.0 (0.2) | <0.001 |
| Carbohydrate, g/kg per d | 716 | 13.8 (3.6) | 716 | 14.9 (3.5) | <0.001 |
| Lipid, g/kg per d | 715 | 3.1 (1.5) | 716 | 3.6 (1.7) | <0.001 |
| D 28 | | | | | |
| Surviving at d 28, n (%) | 717 | 669 (93.3) | 717 | 671 (93.6) | 0.640 |
| Protein†, g/kg per d | 539 | 3.1 (0.7) | 534 | 3.2 (0.7) | 0.037 |
| Carbohydrate, g/kg per d | 546 | 14.6 (3.3) | 537 | 14.3 (3.5) | 0.017 |
| Lipid, g/kg per d | 541 | 5.1 (2.0) | 533 | 5.2 (1.8) | 0.725 |
| Postconceptional age of 36 wk | | | | | |
| Surviving at wk 36, n (%) | 717 | 652 (90.9) | 717 | 657 (91.6) | 0.640 |
| Enteral nutrition, n (%) | 652 | | 657 | | 0.298 |
| Not known | | 64 (9.8) | | 83 (12.6) | |
| Milk of own mother | | 229 (35.1) | | 236 (35.9) | |
| Milk of own mother or maternal milk with fortification | | 73 (11.2) | | 62 (9.4) | |
| Infant formula for preterm infants | | 184 (28.2) | | 190 (28.9) | |
| Specific infant formula | | 102 (15.6) | | 83 (12.6) | |
| At discharge | | | | | |
| Alive at discharge | 717 | 649 (90.5) | 717 | 651 (90.8) | 0.856 |
| Status of breastfeeding | 649 | | 651 | | 0.394 |
| Not known | | 48 (7.4) | | 43 (6.6) | |
| No breastfeeding | | 344 (53.0) | | 331 (50.8) | |
| Partial breastfeeding | | 120 (20.0) | | 118 (18.1) | |
| Exclusive breastfeeding | | 137 (22.8) | | 159 (24.4) | |

Results are presented as mean (SD) or n (%).
*The maximal plasma creatinine value observed between day 3 and 7 after birth.
†Sum of enteral protein and intravenous amino acid supply.

be attributed to amino acid intake per se, because baseline infant characteristics are similar between exposed and unexposed groups in the matched cohort; however, given the observational nature of the study, unidentified confounders could play a role. Only nutritional intake at day 3 and day 7 was different between the 2 groups, and the difference, albeit smaller, remained significant at day 28. Although the intake of all macronutrients was higher in the exposed group among the 3 macronutrients measured (amino acid, carbohydrate, and lipid), only early amino acid intake was significantly correlated to systolic BP. This is consistent with the results of the study reported by Wang et al,[29] where a relationship between random plasma insulin levels at birth and later HBP in early childhood was observed. Though serum insulin was not measured in our study, serum insulin level likely was higher in the exposed group, because a higher intake of amino acid, particularly of branched-chain amino acids, is known to enhance insulin secretion.[30] In our study, higher amino acid intake was associated only with systolic HBP, but not with diastolic HBP. Other studies that have examined the relationship between neonatal nutritional intakes and the later risk of HBP have observed either an association with diastolic HBP[31] or no association,[30–32] but none focused on early amino acid intake in the first week of life.

**Table 3. Growth Characteristics and Blood Pressure at 5 Years in the Nonexposed and Exposed Groups**

| Variable | Propensity score-matched cohort | | | | |
|---|---|---|---|---|---|
| | N=717 | Nonexposed | N=717 | Exposed | *P* value |
| At birth | | | | | |
| Gestational age, wk | 717 | 27.1 (1.5) | 717 | 27.1 (1.5) | 0.599 |
| Birth weight, g | 717 | 1000 (250) | 717 | 990 (250) | 0.501 |
| Birth weight *Z* score | | −0.07 (0.00) | | −0.07 (0.10) | 0.993 |
| Length, cm | 663 | 35.4 (3.0) | 680 | 35.6 (3.0) | 0.566 |
| Birth length *Z* score | | −0.15 (0.97) | | −0.09 (0.97) | 0.274 |
| BMI | 663 | 7.9 (1.2) | 680 | 7.8 (1.1) | 0.123 |
| Birth BMI *Z* score | | 0.07 (1.13) | | −0.01 (1.04) | 0.186 |
| At discharge | | | | | |
| Postconceptional age, wk | 643 | 39.0 (4.5) | 646 | 38.8 (4.0) | 0.340 |
| Weight, g | 634 | 2730 (580) | 638 | 2800 (600) | 0.053 |
| Discharge weight *Z* score | | −1.27 (0.84) | | −1.13 (0.86) | **0.003** |
| Length, cm | 612 | 45.7 (3.2) | 609 | 45.9 (3.2) | 0.165 |
| Discharge length *Z* score | | −1.92 (1.03) | | −1.77 (1.09) | 0.019 |
| BMI | 612 | 13.0 (1.48) | 609 | 13.1 (1.54) | 0.154 |
| Discharge BMI *Z* score | | −0.04 (0.9) | | 0.05 (0.9) | 0.131 |
| Δ Weight *Z* score between birth and discharge | 634 | −1.23 (0.83) | 638 | −1.08 (0.82) | <0.001 |
| Δ Length *Z* score between birth and discharge | 557 | −1.78 (0.99) | 566 | −1.70 (1.02) | 0.176 |
| Δ BMI *Z* score between birth and discharge | 557 | −0.21 (1.25) | 566 | 0.02 (1.20) | 0.003 |
| At 5 y | | | | | |
| Weight, g | 397 | 18.5 (3.1) | 408 | 19.1 (3.6) | 0.008 |
| Weight *Z* score | | −0.30 (1.13) | | −0.07 (1.27) | 0.008 |
| Height, m | 394 | 1.11 (0.05) | 407 | 1.12 (0.06) | 0.140 |
| Height *Z* score | | −0.12 (1.11) | | 0.03 (1.21) | 0.067 |
| BMI | 394 | 14.9 (1.6) | 407 | 15.3 (2.0) | 0.011 |
| Birth BMI *Z* score | | −0.27 (1.12) | | −0.12 (1.25) | 0.072 |
| Children without overweight or underweight, n (%) | | 262 (66.5) | | 270 (66.3) | 0.298 |
| Children with underweight (BMI <−1.04 *Z* score), n (%) | | 91 (23.1) | | 82 (20.1) | |
| Children with overweight (BMI >1.04 *Z* score), n (%) | | 41 (10.4) | | 55 (13.5) | |
| Δ Weight *Z* score between discharge and 5 y | 397 | 1.03 (1.16) | 397 | 1.17 (1.26) | 0.107 |
| Δ Height *Z* score between discharge and 5 y | 394 | 1.90 (1.20) | 394 | 1.89 (1.89) | 0.842 |
| Δ BMI *Z* score between discharge and 5 y | 394 | −0.18 (1.27) | 394 | 0.30 (1.46) | 0.051 |
| All blood pressure measurements | | | | | |
| Systolic arterial pressure, mean (SD) | 385 | 98.6 (10.4) | 389 | 100.2 (10.6) | 0.036 |
| Systolic high blood pressure for sex and height, n (%) | 384 | 51 (13.3) | 388 | 70 (18.0) | 0.069 |
| Diastolic arterial pressure, mean (SD) | 385 | 58.7 (8.6) | 389 | 59.1 (8.9) | 0.615 |
| Diastolic high blood pressure for sex and height, n (%) | 384 | 39 (10.2) | 388 | 35 (9.0) | 0.592 |
| Blood pressure measurements by automated oscillometric methods | 291 | | 308 | | |
| Systolic arterial pressure, mean (SD) | 291 | 99.3 (10.2) | 308 | 101.4 (10.2) | 0.013 |
| Systolic high blood pressure for sex and height, n (%) | 290 | 39 (13.4) | 307 | 63 (20.5) | 0.022 |
| Diastolic arterial pressure, mean (SD) | 291 | 59.0 (8.1) | 308 | 59.1 (8.6) | 0.801 |
| Diastolic high blood pressure for sex and height, n (%) | 290 | 24 (8.3) | 307 | 27 (8.8) | 0.953 |

Results are presented as mean (SD) or n (%). BMI indicates body mass index.

Serum creatinine observed between day 3 and day 7 was significantly lower in the exposed group. At least 3 hypotheses can be raised to account for this observation. First, in theory, this could be due to an indication bias to receive higher amino acid intake (ie, clinicians might have been less prone

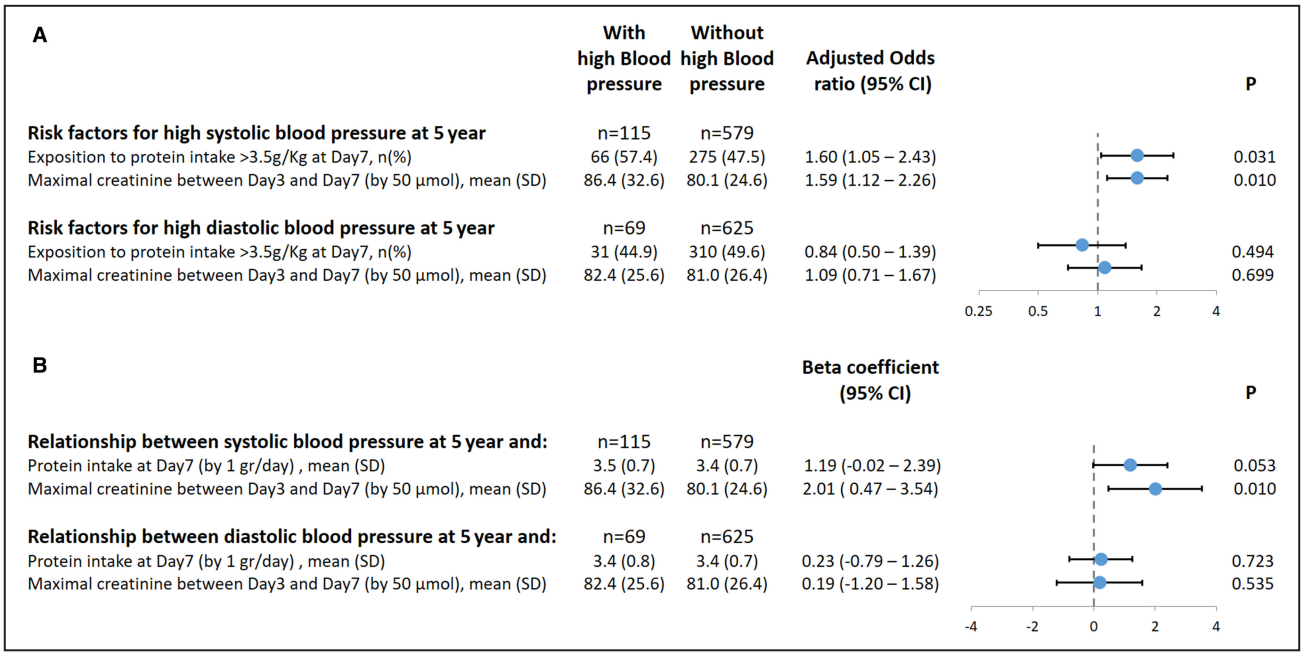


**Figure 2. Relationship between blood pressure at 5 years and 2 risk factors: protein intake at day 7 after birth and maximal creatinine observed between day 3 and day 7 after birth, in matched cohort.**
**A**, Adjusted odds ratio of the 2 risk factors (exposure to high protein intake [yes/no] and maximal creatinine observed between day 3 and day 7) for surviving with high blood pressure at 5 years. The position of each circle represents the point estimate of the exposure effect. Horizontal lines represent 95% CIs. **B**, β coefficient between blood pressure at 5 years as a continuous variable and the 2 risk factors, protein intake at day 7 after birth as continuous variable and maximal creatinine observed between day 3 and day 7 after birth. The position of each circle represents the point estimate of the β coefficient, and the horizontal lines represent 95% CIs.

to prescribe high amino acid intake in infants with a higher serum creatinemia), but this seems unlikely given the high degree of similarity between the 2 matched groups (exposed and nonexposed). Second, a decreased rate of muscle protein breakdown, resulting in a decrease in creatinine release from skeletal muscle, could have occurred in the exposed group, because a higher amino acid intake is known to inhibit proteolysis in infants[33,34] Third, increased glomerular filtration rate (also known as hyperfiltration) could occur in the kidneys in response to exposure to a high early amino acid intake in the exposed group. This latter hypothesis is consistent with animal models.[35] As such, glomerulosclerosis would be the result of glomerular hyperfiltration on immature kidneys, which in turn could lead to secondary increased BP via activation of the renin–angiotensin system as observed in rats. Moreover, because a higher maximum creatinine between day 3 and day 7 after birth was a risk factor for systolic HBP in our cohort, the role of kidneys is likely, as suggested by this study performed in general population where early high protein intake was associated with later systolic hypertension and an increase in kidney volume at 11 years of age.[4] The mechanism underlying this relationship could be the role of senescence pathways as observed in rats.[36]

Overall, in this study we observed 2 risk factors for later systolic BPH at 5 years: maximal creatinine between days 3 and 7, a marker for vulnerable kidney, and exposure to high amino acid intake. The interpretation could be that vulnerable kidneys are not able to respond appropriately to the increase in filtration due to a high intake of amino acids. In this case, high amino acids intake could exacerbate subclinical kidney damage.

Attention to limiting overweight during the first years of life[37] could reduce the excess risk of HBP in this high-risk population, because the relationship between high amino acids intake and further systolic HBP is partially mediated by 5-year weight or body mass index *Z* score.

Our study had several strengths and limitations. Its first strength stems from the fact that a 5-year follow-up in the national population based EPIPAGE-2 cohort allowed us to investigate the association between initial nutritional intake, which had been precisely collected in a prospective fashion, and later BP at the age of 5 years. Second, prospective follow-up with 3 repeated BP measurements reduced potential bias due to inherent BP variability and measurement error. Finally, we used a propensity score approach to control as much as possible for confounding factors. Our study also had a few limitations. First, BP

measurements were performed on only 60% of the children born very preterm alive at 5 years, but the attrition was similar in exposed and nonexposed groups. Second, we used different BP measuring devices, but we trained staff at the consultation centers to follow the Fourth Task Force recommendations, and we performed a sensitivity analysis restricted to children with automated BP measurement. Third, no blood sampling was performed, and thus we have no information on kidney function at 5 years of age. Finally, this study remains an observational study, and as such can only highlight associations rather than elucidate causal relationships.

In conclusion, we confirmed the risk of HBP in mid-childhood in children born very preterm and observed an association between early higher amino acid intake and systolic HBP, whereas we had earlier reported improved cognitive outcomes at age 5 years in the same exposed group in the same matched cohort.[7] Thus, we are still facing a persistent nutritional dilemma in the management of very preterm infants: How can we promote neurocognitive development while preserving long-term cardiovascular health?[38]

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Table S1
Figures S1–S7

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