DOI:10.7499/j.issn.1008-8830.2013.03.001

国外儿科研究

# Influence of nutrition provision during the first two weeks of life in premature infants on adolescent body composition and blood pressure

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**Abstract: Objective** Adequate nutrition is paramount for premature infants. Longitudinal information is scant on the effects of early nutrition and later growth. The purpose of this study was to determine the influence of early energy and protein provision in premature infants on adolescent body composition and blood pressure. **Methods** In 2007-2008 we obtained data from 36 male (12.3±1.7 years) and 25 female (11.5±1.8 years) adolescents born preterm at <34 weeks gestation (range 23-34 weeks) between October 1st 1989 and December 31st 1995 (birth weight <1850 g). The adolescents were divided into groups depending on infant intake mode (enteral vs parenteral), energy provision (<70 kcal/kg/d and ≥70 kcal/kg/d) and protein provision (>2.5 g/kg/d for ≥5 days and >2.5 g/kg/d for <5 days) during the first 14 days of life. **Results** After controlling for birth weight and biological maturity, adolescents who received ≥70 kcal/kg/d during infancy were significantly taller (163±11 cm vs. 156±11 cm) and heavier (58±16 kg vs. 49±16 kg) than adolescents who received <70 kcal/kg/d. There were no significant differences in systolic and diastolic BP and total percent body fat between the two groups. **Conclusions** Our data suggests that higher infant energy provision appears to be related to adolescent size, it does not appear to contribute to adverse risk factors such as higher systolic BP or increased body fat. [**Chin J Contemp Pediatr, 2013, 15(3):161-170**]

**Key words:** Energy provision; Blood pressure; Body fat; Preterm infant; Adolescent

Over the past decade, a growing body of evidence has been accumulated that suggests that nutrition in early life of low birth weight (LBW) and premature infants affects early adulthood health, particularly risk for cardiovascular disease, bone health, and cognitive function[1-11]. Barker[12-13] hypothesized that origins of adult disease can be linked to adaptation and subsequent "programming and/or reprogramming" during fetal and early postnatal development in infants born at LBW and early gestation. Others have also identified a relationship between fetal influences and metabolic changes later in life[14-19]. For example, Singhal et al[20] described the first two weeks of life as a critical programming period with lasting health effects into adulthood, finding that preterm infants who experienced accelerated growth during this time showed increased insulin resistance later in life. This information has led practitioners to evaluate current nutrition practices and goals linked to premature infants[21] as it implies changes to current nutritional guidelines[22-30]. Currently, protein and energy

[Received] September 26, 2012; [Revised] November 23, 2012
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intake are optimized within the first few days of life to prevent a cumulative deficit that typically accrues during hospitalization, which is suggested to have long term negative neurodevelopmental consequences. The study time frame was chosen because the first 14 days of life are considered to be a critical window for metabolic programming[12-13,20]. The purpose of this study was to determine the associations between energy and protein provision as well as between feeding mode [total parenteral nutrition (TPN) vs. enteral (EN)] in premature (≤35 weeks gestation) infants from birth to day 14 of life on stature, body composition and blood pressure (BP) in adolescence. Nutritional intake was provided at the discretion of the attending neonatologists and depended on each infant's clinical status. We hypothesized that: (1) higher energy and protein intake during the first two weeks of life will result in higher adolescent body fat and systolic BP, and, (2) preterm infants who received their nutrition primarily intravenously (TPN-fed) during the first two weeks of life will have higher adolescent body fat and systolic BP.

## 1 Material and methods

### 1.1 Participants

Ethical approval for this study was obtained from the University of Saskatchewan's Biomedical Ethics Board. All relatively healthy infants (i. e., no evidence of chronic illness, metabolic diseases and/or need for prolonged mechanical ventilation) born prematurely (<35 weeks gestation) at Royal University Hospital in Saskatoon, Saskatchewan between October 1, 1989 and December 31, 1995 with birth weight of less than 1850 g ($n = 359$) were invited to participate in this study. Multiple births were included. Excluded were infants who had major congenital malformations, gastrointestinal diseases, or neurodevelopmental abnormalities (e. g. moderate and severe cerebral palsy, seizures), who could not meet energy requirements in the neonatal intensive care unit (NICU) because they were ventilated and fluid restricted as well as infants who received TPN for more than 30 days. In 2007 to 2008, seventy-five eligible participants (21%) consented to participate in the follow-up study by returning previously mailed completed consent (parents and caregivers) and assent (participants).

Complete data were available for 61 subjects (36 male, 25 female), of which 46 had a birth weight that was appropriate for gestational age (AGA), defined as 10 th – 90 th percentile birth weight, 14 were small for gestational age (SGA), defined as < 10 th percentile birth weight, and 1 large for gestational age (LGA), defined as >90 th percentile birth weight[26]. A MANCOVA controlling for birth weight and adolescent biological maturity revealed no significant differences between SGA's, AGA's and LGA's (done separately) in adolescent height, weight, % total body fat and BP measures. As $P$ values were virtually identical, all infants were combined for further analyses. This was done particularly to arrive at a clinically relevant and statistically adequate sample size. Mean gestational age was 30 weeks (range 23 – 34 weeks) and mean birth weight was 1.3 kg (range 0.65-1.82 kg).

The 61 subjects were divided into groups depending on infant intake mode (EN vs. TPN), energy provision (low energy: < 70 kcal/kg/d vs. high energy: ≥ 70 kcal/kg/d) and protein provision (high protein: >2.5 g/kg/d for ≥5 days vs. low protein: > 2.5 g/kg/d for <5 days) during the first 14 days of life.

### 1.2 Hospital health record review

Trained neonatal research nurses reviewed participants' NICU medical charts and extracted information on length of stay, gestational age and birth anthropometry (daily weight, weekly length and head circumference), daily feeding mode (TPN and/or EN), daily total energy intake and weight gain during the first 14 days in NICU and at time of discharge.

### 1.3 Estimated energy and protein requirements

Estimated average energy and protein intake targets during the first two weeks of life were elected to be >70 kcal/kg/d and > 2. 5 g/kg/d, respectively, based on a reference standard of 1995[31].

### 1.4 Anthropometry

Anthropometric measurements in adolescence were obtained. These included standing height, sitting height, weight and waist circumference (WC). Standing heights were recorded to the nearest millimeter using a wall-mounted stadiometer (Holtein Limted, Crymyo, Britain). Body mass was measured to the nearest 0. 5 kg using a calibrated physician's scale

(Toledo Scale Company, Model 2830, Windsor, ON, Canada). All measures were taken twice; if the difference between measures was greater than 0.4, a third measure was recorded. The mean or median was then reported depending on whether two or three measures were recorded, respectively. Participants wore T-shirts and loose-fitting shorts. Shoes and jewelry were removed during all measures.

### 1.5 Adolescent maturation

The range of variability between individuals of the same chronological age in maturity may be large particularly as subjects approach their adolescent growth spurt. Maturity must therefore be considered when examining physiological parameters in adolescence[32]. Age at peak height velocity (APHV) reflects the maximum growth in stature during a 1-year time interval in adolescence and also acts as an indicator of somatic maturation[33]. It provides a benchmark of maximum growth during adolescence within and between individuals[32]. Prediction of APHV does not require invasive procedures, is easy to assess, serves as a maturational marker and occurs in both males and females. As such, it offers the best method of assessing maturity in this cohort. APHV was estimated from anthropometric measures using Mirwald et al's maturity offset equation[32]. The coefficient of determination ($R^2$) for estimation is 0.92 for males and 0.91 for females.

### 1.6 Blood pressure

Resting BP was taken three times using an automated cuff (Philips Sure Signs VM6, Serial Number US81626291). The average of the two closest readings was used.

### 1.7 Dual X-ray absorptiometry

Body composition measurements were obtained using a Hologic dual-energy X-ray absorptiometry (DXA) 2000 or 4500 scanner (Bedford, MA). All measurements assessed using the Hologic 4500 scanner were converted to Hologic 2000 equivalent values using previously developed conversion factors[34]. Data derived from the scans included total body lean mass (LM) and fat mass (FM). A certified radiology technologist administered and analyzed all scans. Quality control phantom scans were performed daily. Our laboratory has determined coefficients of variation for these measures to be 3.0% and 0.5%, respectively. Bone mineral content was also obtained and outcomes were reported in detail elsewhere[35].

### 1.8 Statistical analysis

The Statistical Package for the Social Sciences (version 18.0; SPSS Inc., Chicago, IL) was used to analyze the data. Independent *t*-tests and one-way ANOVA were used to investigate the difference in descriptive statistics between feeding groups. A MANCOVA, controlling for adolescent biological age and birth weight, was used to test whether there was a significant difference in body composition and BP between infants on the two feeding practices. The alpha level was set at 0.05.

## 2 Results

Table 1 presents data on birth anthropometry, adolescent anthropometry and adolescent body composition. As expected, male adolescent LM was higher than that of females , reflecting known gender differences. Figure 1 illustrates the early growth trajectory of participants based on feeding mode in early infancy (TPN vs. EN). Participants who were EN-fed had higher birth weight and improved growth trajectory. In contrast, TPN-fed participants had lower birth weight and showed a slower, less consistent growth trajectory.

**Table 1 General descriptive information for adolescent individuals** ($\bar{x} \pm s$)

| | All subjects ($n$=61) | Male subjects ($n$=36) | Female subjects ($n$=25) |
|---|---|---|---|
| Birth weight (g) | 1326±359 | 1355±342 | 1282±385 |
| Days to regain birth weight (d) | 10±6 | 10±7 | 9±5 |
| Adolescent height (cm) | 161±11 | 162±12 | 158±10 |
| Adolescent weight (kg) | 55±16 | 57±18 | 52±13 |
| Adolescent %FM | 23±8 | 20±8 | 26±6 [a] |
| Adolescent total LM (kg) | 40±11 | 43±12 | 36±8[a] |

Note: FM, fat mass; LM, lean mass; a: $P<0.05$ (females vs. males)

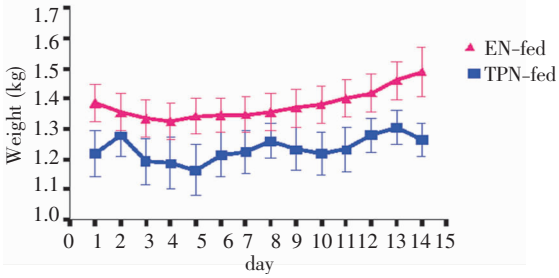


**Figure 1 Infant feeding mode (TPN vs. EN) and weight Day 1-14 of life**

Figure 2 shows the growth trajectory of participants who had high vs. low protein intake in early infancy. Similar to Figure 1, adolescents who received high protein during the first 14 days of infancy had higher birth weight and improved growth trajectory, whereas adolescents who received low protein during the first 14 days of infancy were smaller at birth with slower, less consistent growth.

Table 2 shows adolescent anthropometric data, % body fat and BP of participants who received higher daily calorie intake ( ≥70 kcal/kg/d) compared to those who received lower calorie intake ( <70 kcal/kg/d) during the first 14 days of life. A MANCOVA controlling for birth weight and adolescent biological maturity revealed a significant difference in height and weight between the higher and lower energy intake groups ($P<0.05$).

Adolescent data for participants who were TPN-fed ( >75% total energy intake from TPN for ≥5 days) and those who were EN-fed ( < 75% total energy intake from TPN for ≤ 4 days) is presented in Table 3. A MANCOVA controlling for birth weight and biological maturity showed a significantly higher adolescent diastolic BP (71 ± 13 vs. 65 ± 8 mm Hg) in subjects who were TPN-fed early in infancy.

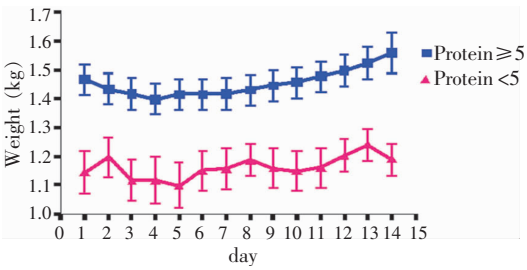


**Figure 2 Infant protein intake (high protein vs. low protein) and daily weight gain**

**Table 2 Adolescent data between participants receiving high and low energy intake during the first 14 days of life** ($\bar{x} \pm s$)

| | High energy intake ($n=41$) | Low energy intake ($n=20$) | $t$ value | $P$ value |
|---|---|---|---|---|
| Standing height (cm) | 163 ± 11 | 156 ± 11 | −2.1 | 0.044 |
| Weight (kg) | 58 ± 16 | 49 ± 16 | −2.1 | 0.042 |
| Systolic BP (mm Hg) | 109 ± 13 | 113 ± 15 | 1.1 | 0.265 |
| Diastolic BP (mm Hg) | 67 ± 11 | 69 ± 11 | 0.9 | 0.387 |
| Total percent body fat (%) | 24 ± 7 | 20 ± 7 | −1.9 | 0.580 |

**Table 3 Adolescent data for TPN and EN-fed participants during the first 14 days of life** ($\bar{x} \pm s$)

| | TPN-fed ($n=28$) | EN-fed ($n=33$) | $t$ value | $P$ value |
|---|---|---|---|---|
| Adolescent age (years) | 14.6 ± 1.9 | 14.3 ± 1.6 | 0.6 | 0.583 |
| Birth weight (g) | 1253 ± 344 | 1387 ± 365 | −1.5 | 0.147 |
| Adolescent height (cm) | 160 ± 13 | 161 ± 10 | −0.3 | 0.788 |
| Adolescent age at PHV (years) | 12 ± 3 | 13 ± 2 | −0.8 | 0.447 |
| Adolescent weight (kg) | 55 ± 18 | 55 ± 15 | 0.02 | 0.983 |
| Adolescent WC (cm) | 73 ± 12 | 72 ± 9 | 0.5 | 0.627 |
| Adolescent percent body fat (%) | 22 ± 9 | 23 ± 7 | −0.3 | 0.770 |
| Adolescent systolic BP (mm Hg) | 112 ± 15 | 109 ± 12 | 0.7 | 0.496 |
| Adolescent diastolic BP (mm Hg) | 71 ± 13 | 65 ± 8 | 2.2 | 0.035 |

Note: PHV, peak height velocity; WC, waist circumference; BP, blood pressure

Table 4 shows adolescent data for participants who received high protein ( > 2.5 g/kg/d for ≥5 days) and those who received low protein ( > 2.5 g/kg/d for < 5 days) during the first 14 days of life. A MANCOVA controlling for birth weight and biological maturity showed that adolescents who received high protein in early infancy had a significantly higher birth weight compared to adolescents who received low protein in early infancy (1475 ± 309 vs 1181 ± 348 g). They were also taller and heavier yet had lower systolic and diastolic BP than those who received low protein during the first 14 days of life, although these differences were not significant.

**Table 4 Adolescent data for participants receiving high and low protein during the first 14 days of life** ($\bar{x} \pm s$)

| | High protein ($n=30$) | Low protein ($n=31$) | $t$ value | $P$ value |
|---|---|---|---|---|
| Adolescent age (years) | 14.5 ± 1.6 | 14.4 ± 1.9 | 0.4 | 0.722 |
| Birth weight (g) | 1475 ± 309 | 1181 ± 348 | 3.5 | 0.001 |
| Adolescent height (cm) | 162 ± 11 | 159 ± 11 | 1.2 | 0.223 |
| Adolescent age at PHV (years) | 12.1 ± 2.3 | 13.0 ± 2.0 | −1.6 | 0.122 |
| Adolescent weight (kg) | 57 ± 15 | 54 ± 18 | 0.6 | 0.527 |
| Adolescent WC (cm) | 73 ± 9 | 73 ± 12 | −0.01 | 0.987 |
| Adolescent percent body fat (%) | 23 ± 7 | 22 ± 8 | 0.7 | 0.503 |
| Adolescent systolic BP (mm Hg) | 107 ± 11 | 113 ± 15 | −1.9 | 0.065 |
| Adolescent diastolic BP (mm Hg) | 65 ± 9 | 70 ± 12 | −1.9 | 0.062 |

PHV: peak height velocity; WC: waist circumference; BP: blood pressure

## 3 Discussion

Nutritional supply is paramount for adequate growth and development of premature infants. It is not surprising then that practitioners who work with this population strive to provide optimal nutrition as early in

life as possible. Fetal and early neonatal growth depends heavily on supply and demand. Adaptation to this on the part of the growing fetus and neonate appears to be multifaceted (genetic, environmental and triggering factors). Recently, several potential mechanisms have been suggested based on epidemiological data[1,3,12-14,17-18,36-42]. Individual thresholds may exist on both the maternal and fetal side, making predictions of long term implications even more difficult. Therefore, the more suitable terminology might be "maternal and fetal origins of adult disease".

Our results showed no significant differences in BP and body fat between the two energy intake groups, even after controlling for birth weight, although infants who received higher energy intake grew taller and heavier in adolescence compared to those who received lower energy. This result is reassuring as it suggests that optimal energy provision early in life has no negative effects on body composition or BP in adolescence. On the other hand, infants who received lower energy also had no adverse health effects in adolescence although they were smaller, suggesting plasticity in programming[43].

Data on participants who were TPN-fed in early life showed significantly higher adolescent diastolic BP compared to those who were primarily EN-fed. A possible biological hypothesis for this could be related to the lack of intestinal and hepatic first pass in TPN-fed individuals. Enteral nutrition exposes nutrients to the intestine and liver prior to release into systemic circulation. In contrast, when using TPN, nutrients are infused directly into systemic circulation, bypassing intestinal and hepatic first pass.

Sun et al [44] found that adult hypertension and the development of metabolic syndrome can be predicted by measuring BP in childhood as early as 5 years of age. Their work showed that when mean systolic BP exceeded age- and gender-specific criteria at any time between 5 – 18 years of age for males or 8 – 18 years of age for females, then the individuals are at increased risk of developing adult metabolic syndrome, independent of whether or not hypertension is present[44]. Although mean systolic and diastolic BP in the subjects of this study were normal[45], it is of interest to note a significant difference in diastolic BP based on feeding mode. It may be possible that TPN plays a role in programming as the body has little ability to regulate substrates. This reconfirms the idea of enteral priming and early institution of enteral feedings in preterm infants as this mechanism is indeed important not only for gut maturation but also for long term growth. Further, we notice an inverse relationship between protein intake and BP, albeit not significant. This result suggests that both feeding mode and protein intake contribute a positive influence to the "metabolic programming/reprogramming" during early growth and that optimal protein intake is beneficial and important for long term health.

Infants who were primarily enterally fed had an improved early growth trajectory, when compared to those who received mainly TPN. A similar pattern was observed in infants who achieved higher protein intake early in life compared to those who consumed less protein. Early enteral feeding and sufficient protein intake may facilitate attainment of the infant's full growth potential while not causing any long term adverse effects. It is noteworthy that a number of neonatal conditions may influence the mode of feeding that is chosen in the early neonatal period, such as intrauterine growth trajectory, gestational age and neonatal intestinal function. It is also important to acknowledge that neonatal nutrition practices have improved since the time of this study. Therefore, long term growth trajectories of infants who receive current nutrition standards of practice may differ.

This study shows that mode of feeding and protein intake in premature infants may contribute positively to long term health in adulthood. Early optimal provision of nutrition (particularly protein) is appropriate and preferable. Our study reiterates the importance of early optimal nutrition for preserving the infant's growth potential. Few published studies have explored the supply of energy and individual macronutrients (carbohydrate, protein and fat) and potential effects on health in adolescence and early adulthood[46-48]; therefore it was not possible to compare them with our study, which confers this report a unique perspective.

Well planned long-term studies examining growth rates in hospital and after discharge are needed to answer questions raised by recent research conclusively. However, such studies are not only difficult and costly

but also extremely rare. In the absence of such studies it becomes important to look at any available long-term studies even though the design may be called into question.

The current study has a number of limitations. The design was retrospective and thus results are based on a small number of participants. Multiple births, SGA and LGA infants were included for combined analysis although several studies suggested that SGA infants who exhibit catch-up growth and LGA infants appear to have long term chronic health consequences[16,49-58]. Enrolment was voluntary; therefore, selection bias might have contributed to the results. Strengths of the study include an objective and precise measurement of adolescent body composition via DXA, estimation and consideration of adolescent growth and maturation and serial growth measurements of weight through the first 14 days of life. Infant illness severity is unlikely to have affected outcomes as severely ill infants were excluded from participation.

Our results, albeit on small numbers, add to the growing body of evidence that suggests that appropriate energy and protein provision in early life of premature infants may contribute to better health parameters in adolescence without adverse cardiovascular health risks.

Acknowledgements: The authors are grateful to the Royal University Hospital Foundation for providing funding for this project and to the neonatal research nurses who assisted with this project. We also thank all participants and families who gave of their time generously. Without their dedication, this study would not have been possible.

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# 附中文参考译文(早产儿生后两周内营养供应对青春期身体组成及血压的影响)

[摘　要] **目的**　充足的营养对早产儿至关重要。关于早期营养及其对后期生长影响的纵向信息十分有限。本研究的目的是确定早产儿的早期能量和蛋白质供应对青春期身体组成和血压的影响。**方法**　本研究于2007～2008 年对 36 例男性青少年(12.3±1.7 岁)和 25 例女性青少年(11.5±1.8 岁)进行了调查,他们系出生于 1989 年 10 月 1 日至 1995 年 12 月 31 日之间胎龄 23～34 周、出生体重 <1850 g 的早产儿。根据其出生后两周内的营养模式(肠内与肠外)、能量供应(每日 <70 千卡/kg 与每日 ≥70 千卡/kg)及蛋白质供应情况(每日超过 2.5 g/kg ≥5 d 与每日超过 2.5 g/kg <5 d),将调查对象分组,比较各组青春期身高、体重、血脂、血压等的差异。**结果**　在控制出生体重和生理成熟度的基础上,婴儿期能量摄入每天≥70 千卡/kg 的青少年身高(163±11 cm)和体重(58±16 kg)大于能量摄入每天 <70 千卡/kg 的青少年(身高 156±11 cm,体重 49±16 kg),差异有统计学意义($P<0.05$);两组间血压与体脂百分含量未见明显差异。**结论**　婴儿期较高的能量摄入与青春期的体格大小相关,但并不会构成不利的风险因素,如血压升高或体脂增加。

过去的十年中,已经有越来越多的证据表明,早产和低出生体重(LBW)儿在生命早期的营养供应会影响成年早期的健康,特别是心血管疾病的风险、骨骼健康和认知功能[1-11]。Barker[12-13]推测,成人疾病的起源都与早产和低出生体重儿在胚胎期和产后早期发育过程中的适应及随后的"编程和/或重新编程"有关。也有研究者发现了胚胎期的影响和生命后期的代谢变化之间的关系[14-19]。例如,Singhal 等[20]称生命头两周是关键的编程时期,对成年后的健康状况有着持久的影响。他们发现在这段时期经历了快速生长的早产儿在后来表现出胰岛素抵抗水平提高。这一发现让医生们开始评估目前对早产儿的营养供应方法及目标[21],因为它意味着目前的营养指南将发生改变[22-30]。目前,对出生后头几天的蛋白质和能量摄入进行了优化,防止出现缺陷累积,其通常会在住院期间出现累积,研究表明这将对神经发育产生长期的负面影响。本研究选择对 61 例早产儿出生后 14 d 内的营养供应情况进行研究,是因为这段时期是代谢编程的一个重要的时间窗[12-13,20]。本研究的目的是确定早产儿(胎龄≤35 周)从出生到 14 d 之间的能量和蛋白质供应及营养模式[肠内(EN)或全胃肠外营养(TPN)]对青春期身高、身体组成和血压的影响。新生儿的营养摄入量由主治医生根据其临床状态而决定。我们提出的假设是:(1)在出生后两周内增加能量和蛋白质摄入会导致青春期体脂含量和收缩压升高;(2)出生后两周内通过静脉注射的 TPN 模式获取营养的早产儿在青春期的体脂含量和收缩压较高。

## 1　资料与方法

### 1.1　研究对象

这项研究通过了萨斯喀彻温大学生物医学伦理委员会的审核。1989 年 10 月 1 日至 1995 年 12 月 31 日在萨斯喀彻温省萨斯卡通皇家大学医院出生的所有体重 <1850 g(359 例)、胎龄 <35 周且相对健康的早产儿(无慢性疾病、代谢性疾病和/或长期呼吸机依赖)都受邀参与这项研究,其中也包括多胞胎,但不包括有严重先天性畸形、胃肠道疾病或神经发育异常(如中、重度脑瘫、癫痫)的婴儿,由于要依靠呼吸机并限制流食而待在重症监护室(NICU)内、不能满足能量需求的早产儿,以及使用 TPN 超过 30 d 的婴儿。2007～2008 年,75 名合格的参与者(21%)返回了参与者及其监护人知情同意书,同意参加随访调查。

最终本研究获得了 61 例(男 36 例,女 25 例)调查对象的完整数据,其中 46 例适于胎龄儿(AGA),即出生体重在相同胎龄儿平均体重的第 10～90 百分位,14 例小于胎龄儿(SGA),即出生体重在相同胎龄儿平均体重的第 10 百分位以下,1 例大于胎龄儿(LGA),即出身体重在相同胎龄儿平均体重的第 90 百分位以上[26]。控制出生体重和青春期生理成熟度的多变量协方差分析显示,SGA、AGA 和 LGA 婴儿在青春期身高、体重、总体脂百分含量和血压指标上差异无统计学意义。由于 $P$ 值几乎相同,合并所有婴儿样本作进一步分析,旨在获得临床相关且足量的统计样本。样本平均胎龄为 30 周(23～34 周),平均出生体重为 1.3 kg(0.65～1.82 kg)。

依据婴儿期营养摄入模式(TPN 或 EN)、能量供给(每天 <70 千卡/kg 的低能量或每天≥70 千卡/kg 的高能量)及蛋白质供给(每天摄入 >2.5 g/kg 蛋白质≥5 d 或 <5 d)情况,对以上 61 例调查对象进行分组。

### 1.2　医院健康记录审核

经过培训的新生儿科护士审核了研究对象的 NICU 病历卡,提取相关信息,包括住院时间、胎龄,以及在 NICU 头 14 d 及出院时的出生人体测量学参数(每日体重、每周身长、头围)、日常营养模式(TPN 和/或 EN)、每日摄入总能量和增加的体重。

### 1.3　能量和蛋白质需求量的估算

参照 1995 年的标准[31],据估算新生儿出生后两周内的能量和蛋白质平均摄入量应分别超过每日 70 千卡/kg 和每日 2.5 g/kg。

### 1.4　人体测量学参数

我们测量了这些青少年的人体测量学参数,其中包括站立身高、坐高、体重和腰围(WC)。站立身高使用英国 Holtein 有限公司的壁挂式测距仪测量,精确到毫米。体重使用加拿大安大略省温莎市托莱多天平公司的 2830 型号校准医用天平测量,精确到 0.5 kg。所有参数都测量了两次;若误差超过 0.4,则会进行第三次测量。测量两次的参数则取平均值,

测量 3 次则取中位数。研究对象穿着 T 恤和宽松的短裤,且测量过程中要脱掉鞋子,摘掉饰品。

### 1.5 青春期发育成熟度评估

相同年龄的不同研究对象之间的发育水平可有较大差异,特别是在接近青春期发育的急速生长期。因此,在检测青春期生理参数时,必须考虑研究对象的发育水平[32]。身高增长峰值(APHV)的出现年龄反映了青少年在 1 年时间内身高的最快增长速度,也可作为体细胞成熟的指标[33],它为个人和不同个体之间提供了一个青春期最大生长速度的基准[32]。APHV 的预测不需要创伤性操作,很容易进行评估,可作为发育成熟的标志,且男性和女性都适用。因此,它为本研究评估成熟度提供了一个最佳方法。可使用 Mirwald 等[32]的成熟度偏移方程,通过人体测量学参数估算得到 APHV,估算的决定系数($R^2$)在男性为 0.92,女性为 0.91。

### 1.6 血压

使用自动血压计(飞利浦 Sure Signs VM6,序列号 US81626291)测量 3 次静息血压,最接近的两个读数取平均值。

### 1.7 双能 X 射线吸收测定法

使用马萨诸塞州贝德福德市 Hologic 公司 2000 型或 4500 型双能 X 线骨密度仪(DXA)测量身体组成。所有 Hologic 4500 型密度仪测量的数据都用之前确定的转换系数转换为 Hologic 2000 型的等效值[34]。测量数据包括全身去脂体重(LM)和脂肪量(FM),一位获得认证的放射技师负责管理和分析所有的扫描数据,同时每天进行质控模体扫描。本实验室已确定这些测量值的变异系数分别为 3.0% 和0.5%,还测定了骨矿物含量并在其他文章中详细报道[35]。

### 1.8 统计学分析

使用 SPSS 公司(伊利诺伊州芝加哥市)的社会科学统计软件包(18.0 版)对数据进行分析。采用独立样本 $t$ 检验法和单因素方差分析对各营养模式之间的差异进行描述性统计分析。采用控制青春期生理年龄和出生体重的多变量协方差分析比较两种营养模式下的早产儿的身体成分和血压是否差异有统计学意义。$P<0.05$ 表示差异有统计学意义。

## 2 结果

表 1 给出的数据包括出生体测指标、青春期体测指标和青春期身体成分。和预期的一样,男性青少年 LM 高于女性,与已知的性别差异吻合。图 1 显示了不同营养模式(TPN 或 EN)下样本的早期成长曲线。采用 EN 营养模式的样本出生体重更重,生长曲线更好。相反,采用 TPN 营养模式的样本出生体重较低,生长较缓慢且生长曲线的一致性较差。

图 2 显示了在婴儿早期阶段蛋白质摄入量较高和较低的样本的生长曲线。与图 1 相似,在其婴儿期的前 14 d 摄入蛋白质量较高的青少年出生体重较高,生长曲线较好,而在其婴儿期的前 14 d 摄入蛋白质量较低的青少年出生体重较低,成长较缓慢且生长曲线的一致性较差。

表 2 显示了在出生后的前 14 d 每日摄取能量较高(每日≥70 千卡/kg)与较低(每日 < 70 千卡/kg)的样本在青春期体测数据、体脂百分含量和血压等数据的对比。控制出生体重和青春期生理成熟度的多变量协方差分析显示,高能量摄入组青少年身高、体重均显著大于低能量摄入组,差异有统计学意义($P<0.05$)。

表 3 列出了采用 TPN 营养模式(5 d 或以上的总能量摄入中超过 75% 来自 TPN 营养模式)的样本和采用 EN 营养模式(4 d 或以下的总能量摄入中低于 75% 来自 TPN 营养模式)的样本的青春期数据。控制出生体重和青春期生理成熟度的多变量协方差分析显示,在婴儿早期采用 TPN 营养模式的样本青春期舒张压明显升高($P<0.05$)。

表 4 显示了在出生后的前 14 d 摄取蛋白质量较高(有 5 d 或以上摄入量大于每日 2.5 g/kg)与较低(5 d 以下摄入量大于每日 2.5 g/kg)的样本在青春期的数据。控制出生体重和青春期生理成熟度的多变量协方差分析显示,在婴儿早期摄取蛋白质量较高的青少年的出生体重(1475 ± 309 g)明显高于摄取蛋白质量较低的青少年(1181 ± 348 g)。相比在出生后的前14 d摄取蛋白质量较低的样本,他们的身高更高、体重更重,收缩压和舒张压也较低,但差异无统计学意义。

## 3 讨论

营养供给对于早产儿的生长发育至关重要,因此相关医生要尽力在早产儿出生后及早为其提供最佳的营养。胎儿和新生儿早期的成长在很大程度上依赖于对营养的供给和需求,成长中的胎儿和新生儿对此的适应显示出多层面性(遗传、环境和触发因素)。最近,有研究者基于流行病学数据提出了几种潜在机制[1,3,12-14,17-18,36-42]。母体和胎儿身上都可能存在个体阈值,这使得对长期影响的预测变得更加困难。因此,讨论此问题更适合的术语可能是“成人疾病在其母体及胎儿期的起源”。

本研究结果显示,两个能量摄入组即使是在控制出生体重后在血压或体脂含量方面也无明显差异,尽管能量摄入较多的婴儿比能量摄入较少的婴儿在青春期时身高更高、体重更重。这一结果也再次表明,在出生后早期的最佳能量供给对青春期的身体组成或血压没有负面影响。另一方面,摄取能量较少的婴儿虽然在青春期体格较小,但也没有出现不良的健康影响,说明了成长中的适应性[43]。

数据显示在出生后早期采用 TPN 营养模式的样本的青春期舒张压比主要采用 EN 营养模式的样本明显要高。对此可以做出生物学假设,这种情况可能与 TPN 营养模式的个体缺乏肠道和肝脏首过有关。EN 营养模式让营养物在进入体循环之前先经过肠道和肝脏;相反,采用 TPN 营养模式时,营养物质会绕过肠道和肝脏,直接进入体循环。

Sun 等[44]发现,早在 5 岁时就可以通过测量儿童血压来预测其成年后发生高血压和代谢综合征的风险。他们的研究表明,如果年龄在 5 ~ 18 岁的男性或 8 ~ 18 岁的女性平均收缩压超过了与其年龄和性别相应的标准值,那么该个体成年后无论是否患有高血压,其出现代谢综合征的风险都会增

加[44]。虽然本次研究对象的收缩压和舒张压平均值均正常[45],但需要注意的是因营养模式的不同其舒张压存在显著的差异。身体本身几乎无法对基质进行调节时,TPN 营养模式可能对“编程”产生影响。这再次证实了对早产儿启动 EN 营养以及尽早实施 EN 营养的想法,因为这种机制不仅有利于肠道发育成熟,对长期生长也尤为重要。此外,我们注意到蛋白质摄入量与血压之间成反比关系,尽管并不显著。这一结果表明,营养模式和蛋白质摄入量都会对生长早期的“代谢编程/重新编程”产生积极的影响,最佳蛋白质摄入量对长期健康有重要的益处。

相比主要采用 TPN 营养模式的婴儿,主要采用 EN 营养模式的婴儿的生长曲线更好,类似的情况也见于出生后早期蛋白质摄入量较高的婴儿与蛋白质摄入量较低的婴儿之间的比较。早期实施 EN 营养和充足的蛋白质摄入量可以帮助婴儿获得充分的生长潜力,同时不会产生任何长期的不良影响。值得注意的是,婴儿的各种情况,如子宫内生长曲线、胎龄和新生儿肠道功能等,可能会影响其出生早期时所选择的营养模式。还有必要注意到,我院新生儿的营养方式自本研究开展之日起已有所改善。因此,按照目前标准获得营养供应的婴儿其长期生长曲线可能会有所不同。

本研究表明,早产儿生后早期的营养模式和蛋白质摄入量可能对其成年长期健康产生积极影响,采取最佳的营养(特别是蛋白质)供应是非常可取的。本研究也再次说明了早期最佳营养供应对保护婴儿生长潜力的重要性。已发表的研究成果中鲜有探究能量和主要营养素(碳水化合物、蛋白质和脂肪)的供应及其对青春期和成年早期身体健康的潜在影响[46-48],因此无法将它们与本研究作比较,这也赋予本研究报告以独特的视角。

要明确回答近期一些研究中发现的有关问题,需要精心设计长期的研究来对住院期间和出院后的生长率进行测定,然而此类研究不仅难于实施且费用昂贵。由于目前尚缺乏这类研究,因此目前可得到的一些有关的长期研究变得十分重要,即便其设计思路可能引起质疑。

本研究有许多局限性。本研究采取的是回顾性的研究设计,因此研究结果是基于数量较少的研究对象而得出。多胞胎、SGA 婴儿和 LGA 婴儿被纳入了合并分析,尽管几项研究表明,表现出追赶性生长的 SGA 婴儿以及 LGA 婴儿似乎会出现长期慢性的健康影响[16,49-58]。另外,研究对象的纳入是自愿的,因此选择偏差有可能影响到研究结果。这项研究的优势包括通过双能 X 线吸收测定法客观精确地测量青春期的身体组成、评估和考量青春期生长和成熟度,以及对胎儿出生后 14 d 内体重的增长进行连续测量。另外,有严重疾病的婴儿被排除在研究对象之外,因此婴儿的疾病严重程度不太可能影响到研究结果。

本研究虽然样本数较少,但也和越来越多的证据一样,再次表明早产儿在出生后早期得到适当的能量和蛋白质供应可促进其获得更好的青春期健康参数,而且不会产生危害心血管健康的风险。

(本文编辑:邓芳明)