The idea that protein intake in the preterm infant may influence, or program, the long-term health of the infant born preterm has been strongly supported by several decades of research starting from the early 1980s. At the time, it was recognized that a high protein intake was required in preterm infants to achieve a postnatal growth rate closer to the intrauterine rate of growth of a normal fetus of the same postconceptional age, a goal regarded optimal for short- and long-term health. Subsequently, long-term follow-up of preterm infants randomized to a high protein formula (for an average of only 4 weeks after birth) demonstrated beneficial effects up to 16 years later on brain structure and function, including 10% greater volume of the caudate nucleus, higher IQ and practical benefits for cognitive function (e.g. mathematical reasoning, numerical operations and reading comprehension) [1]. Since this early research, numerous observational studies have demonstrated an association between suboptimal nutrition in the early postnatal period (as measured by faltering growth, poor growth in head circumference and inadequate protein intake [2]) and impaired long-term neurocognitive development. Consequently, international recommendations for protein intake in infants born prematurely have increased progressively.

Nonetheless, despite the extensive observational evidence, the role of early protein intake in preterm infants for later neurodevelopment remains unclear. For instance, Cochrane reviews of randomized trials have not shown evidence supporting early amino acid administration [3] or higher versus lower protein intake in formula-fed preterm infants for improving later neurodevelopment [4]. Therefore, although there are strong associations between early postnatal protein intake and neonatal growth, and between growth faltering and impaired later neurodevelopment, whether high protein supplementation can improve cognitive function in preterm infants remains controversial.

In contrast to the benefits for neurodevelopment, a longer-term follow-up of the same infants in the preterm nutritional trials mentioned
above have suggested that faster postnatal weight gain increased later risk factors for cardiovascular disease. Infants randomized to a higher protein formula for the first 4 weeks were shown to have increased adiposity, insulin resistance, dyslipidemia, levels of inflammatory markers and vascular endothelial dysfunction up to 16 years later. These programming effects of early growth, termed the growth acceleration hypothesis, have now been demonstrated in randomized and observational studies in several preterm populations, as well as in infants born at term with both low and appropriate weight for gestation [5]. Therefore, as is common in biological systems, faster infant weight gain appears to have both benefits and costs on long-term health outcomes.

Current nutritional policy for preterm infants is based on the widely accepted consensus that supporting optimal neurodevelopment is the neonatologist’s highest priority. Therefore, on balance, this policy favors early administration of a higher protein intake in order to improve later cognitive function, irrespective of any increase in cardiovascular risk. However, this consensus is largely based on research that has focused on infants <31 weeks of gestation and it is uncertain whether the risk-benefit ratio of faster weight gain differs for the larger, more mature, healthy preterm infants than those with extreme prematurity. Furthermore, the critical window for these effects is unknown and whether the same nutritional policy should apply after discharge is controversial. For instance, a randomized trial of formulas fed after discharge showed that a higher protein intake after hospital discharge, although increasing the rate of growth, did not have adverse effects on later body composition or cardiovascular risk factors.

This presentation will consider the role of protein intake on long-term health outcomes in infants born preterm, focusing on the risk-benefit ratio for accelerated growth and emphasizing the need for further research.

References