Article

Timing of Complementary Feeding in Preterm Infants is not associated with Early Adiposity Rebound: Longitudinal Analysis of BMI data from Birth to 7 years.

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Abstract:

Background: Adiposity rebound (AR) refers to the second rise of the BMI curve that usually occurs physiologically between 5 and 7 years of age. AR timing has a great impact on children´s health, being the early adiposity rebound (EAR) associated with the development of metabolic disease later in life.

Aim: We aimed to investigate the prevalence of EAR in a cohort of preterm newborns. Secondary outcomes evaluated if some determinants such as (1) gender (male/female), (2) type of delivery (caesarean/vaginal), (3) birth weight (SGA/NGA/LGA), (4) type of feeding (5) duration of breastfeeding, (6) timing of introduction of solid food, (7) parental education and (8) parental pre-pregnancy BMI can influence EAR in this cohort. Tertiary aim was to evaluate the prevalence of obesity or overweight at 7 years of age in children according to early versus timely AR.

Methods: This is a perspective, population-based longitudinal study, where infants born preterm were evaluated at birth and at 1, 3, 6, 9, 12, 15, 18, 24 months and 3, 4, 5, 6, 7 years of gestational-corrected age. Weight and height data were analyzed, and BMI was calculated. AR was assessed in the growth trajectory in a body mass index (BMI) plot.

Results: Of the 250 preterm newborns included, 100 completed the 7 years follow-up and entered in the final analysis. The prevalence of EAR in our cohort of preterm newborns was 54%. EAR was associated with being LGA at birth. No other factors were associated to EAR. Early adiposity rebounders have a significant higher BMI at 7 years compared to children with timely AR (17.2 ±2.7 vs 15.6 ± 2.05, p=0.021). No significant differences were found in the prevalence of obesity or overweight at 7 years of age in children with early or timely AR (29% vs 14% p=0.202).

Conclusions: Clinical management of preterm infants should focus on reducing excess weight gain to prevent long-term metabolic risk. Others neonatal factors are not associated to an higher risk of EAR.

Keywords: "Adiposity rebound"; "Infant,Premature"[Mesh]; "Pediatric Obesity"[Mesh]; "Complementary Feeding"; "Weaning" "Body Mass Index".

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Introduction

Childhood obesity is one of the worldwide most important public health problems and its prevalence seems to be increasing in the next future.[1] To counteract this increasing epidemic risk and to develop early life interventions during childhood, any effort to better understand early predictors of obesity is fundamental.

Rolland-Cachera et al. identified a typical growth trajectory of the body mass index (BMI) plot. BMI rapidly increases during the first year of life, then it decreases and reaches a "nadir" between 5 and 7 years of life; thereafter it increases again throughout childhood. The exact point of the BMI curve nadir with the immediate subsequent increase represents the 'adiposity rebound' (AR).[2] An early adiposity rebound (EAR) can be predictive of adult obesity and other obesity-related comorbidities.[3-4-5]

Despite EAR has recently been a focus of research, its pathophysiology as well as risk factors are still debate.[6] Growing evidence supports that early life events are pathogenically relate to non-communicable diseases later in life and some authors speculated that even prenatal characteristics are predisposing factors for obesity and cardiovascular diseases.[7] Furthermore, the first few months after birth, in which breastfeeding or formula can be use, and complementary feeding can be started at different time-point, might be considered an important window, influencing rapid weight gain and childhood obesity.[8]

Preterm infants are defined by WHO as "born alive before 37 weeks of pregnancy" and the prevalence of preterm birth ranges from 5% to 18%. According to the "programming theories", preterm infants, during early periods of life, show different postnatal patterns of growth (catch-up growth) than term infants, with greater likelihood to develop adult obesity, cardiovascular disease, and diabetes.

Due to the great improvement of neonatal intensive care and the high survival of preterm infants, their life-long management has become an important field of research with significant impact also for the primary care provider. Primary care pediatricians have to screen all preterm patients for obesity and may offer behavioral interventions and intensive counselling to children at high-risk. So far, there are no clear recommendations for preterm infants on the timing of initiation complementary feeding and few data are available the optimal timing of solid food introduction in preterm infants and the effect on overweight and obesity later in life[9].

The main aim of this population-based longitudinal study is to evaluate the rate of EAR in preterm newborns. Secondary aim is to investigate the role of parental and neonatal factors, and nutritional characteristics, in EAR development. Tertiary aim is to calculate, at 7 years of age, obesity and overweight rates in infants with and without EAR.

Methods

Study design

This study is a perspective, population-based longitudinal study, conducted in the Neonatal Intensive Care Section of Department of Biomedical Science and Human Oncology of "Aldo Moro" University of Bari, Italy. All inborn preterm infants between 2009 and 2011 were eligible for the study. Inclusion criteria were a) Italian speaking-language parents; b) gestational age (GA) at birth between 25 and 36 weeks. Exclusion criteria included genetic syndromes, congenital and/or malformative disorders; any kind of surgery; major neurological, immune, metabolic, cardiac or renal diseases; monozygotic twins; absence of parental consent.

All consecutive newborns were recruited during the first week of life, when still admitted. Clinical visits were scheduled at 3, 6, 9, 12, 15, 18, 24 months of age and at 3, 4, 5, 6, 7 years of age. Infants' growth has been evaluated according to adjusted post-natal age (calculated as postnatal age in weeks minus 40 weeks plus gestational age in weeks), considered until 3 years of age.[10] After three years, during follow-up, chronological age was considered. Auxological data at birth were collected from hospital charts. During the follow-up, weight was measured on an electronic scale, and length was the average of two valid measurement. The measurements were always made in the same place and with the same precision instruments. We have excluded from the final analysis: a) children who developed spasticity problems with difficult anthropometric assessment; b) children with special healthcare needs. The study has been approved by the Ethics Commettee of "Policlinico Hospital" (study n. 4122, 20/2/2013). The parents signed an informed consent before inclusion of their infants in the study.

Outcomes assessment

The primary outcome was the prevalence of EAR in a cohort of Italian preterm newborns.

BMI was calculated based on the anthropometrical data collected during the 7 years follow-up. Timing of AR was the age of the lowest BMI.[11] An AR occurring before the fifth year of life was considered EAR.[2]

The secondary outcomes were to evaluate any associations between EAR and neonatal/infant factors, such as (1) gender (male/female), (2) type of delivery (caesarean/vaginal), (3) birth weight categories (SGA/NGA/LGA), (4) type of feeding (breast milk/formula/mixed) (5) duration of breastfeeding, (6) timing of introduction of solid food, (7) parental education and (8) parental BMI.

All newborns were classified according to birth weight corrected for gestational age for Italian newborns in: normal for gestational age (NGA, weight 10-90th percentile), small for gestational age (SGA, weight <10th percentile) and large for gestational age (LGA, weight >90th percentile).[12]

Timing of introduction of solid foods was considered the corrected age (in months) of the earliest administration of any solid food: before 4 months (corresponding to 16 weeks), between 4 and 6 months (corresponding to 24 weeks) and more than 6 months.

Breastfeeding and its duration were categorized as: a) no breastfeeding, b) less than 6 months, c) from 6 to 12 months and d) more than 12 months.

Parental and social determinants were also investigated. Parental education level was defined as high (any college/associate degree, bachelor, or post-graduate degree) or low.

Parents BMI were, based on self-reported height and pre-pregnancy weight, categorized as: underweight (BMI < 18.5 kg/m2), normal weight (BMI 18.5–24.9 kg/m2), overweight (BMI 25.0–29.9 kg/m2), or obese (BMI ≥ 30.0 kg/m2).

Children BMI at 7 years of age were categorized as: normal (< 85th percentile), overweight (≥ 85th, < 97th percentile), obese (≥ 97th percentile) according to the WHO BMI-for-age- and sex-specific growth charts.[13]

Statistical analysis

A simple description of data was made in terms of mean, standard deviation, and percentage depending on type of data.

The association between EAR and (1) sex, (2) type of delivery, (3) birth weight classification, (4) type of feeding at 6 month of age (breast milk/formula/mixed), (5) duration of breastfeeding, (6) timing of introduction of solid food, (7) parental education and (8) parental BMI was assessed by contingency tables and χ^2 test. Subsequently, a multivariate logistic regression model was created. Gestational age at birth, duration of breastfeeding, time to the first food introduction and BMI were compared between children with or without EAR by t Student for unpaired test. For all the tests, a value of $P< .05$ was considered statistically significant. SPSS vers.23 was employed to analyze the data.

Results:

Out of 411 eligible preterm infants, 161 were excluded because they didn't meet inclusion criteria; 250 children entered the study but 138 were lost to 7 years follow-up and in 12 cases parents withdrew over the course of the study. 100 (40%) completed the 7 years follow-up and entered the final analysis (Figure 1).

Demographical and nutritional characteristics of population are described in table 1 and 2. Parental characteristics are showed in table and 3.

Table 1. Demographic characteristics.

Male, n (%)	43 (43%)

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Vaginal birth, n (%)	14 (14%)
Small for Gestational Age, n (%)	15 (15%)
Adequate for Gestational Age, n (%)	73 (73%)
Large for Gestational Age, n (%)	12 (12%)
ELBW, n (%)	1 (1%)
VLBW, n (%)	2 (2%)
LBW, n (%)	10 (10%)
NBW, n (%)	87 (87%)
Gestational age at birth, weeks mean (SD)	34 (2)

Table 2. Nutritional characteristics

Type of feeding at 6 month of age	
Exclusive breast milk, n (%)	15 (15%)
Exclusive formula, n (%)	35 (35%)
Mixed, n (%)	50 (50%)
Duration of breastfeeding, mean (DS)	6 (7)
No breastfeeding n (%)	35 (35%)
≤ 6 months, n (%)	45 (45%)
6 – 12 months, n (%)	10 (10%)
>12 months, n (%)	10 (10%)
Solid foods Introduction	
<4 months of corrected age	2 (2%)
4-6 months of corrected age	82 (82%)
>6 months of corrected age	16 (16%)

Table 3. Parental characteristics

Mother educational level	
low, n (%)	31 (32%)
high, n (%)	67 (68%)
Father educational level	
low, n (%)	36 (36%)
high, n (%)	64 (64%)
Mother BMI	
BMI < 18.5 kg/m^2, n (%)	0
BMI 18.5–24.9 kg/ m^2, n (%)	74 (74%)
BMI 25.0–29.9 kg/ m^2, n (%)	19 (19%)
BMI ≥ 30.0 kg/ m^2, n (%)	9 (9%)
Father BMI	
BMI < 18.5 kg/ m^2, n (%)	0
BMI 18.5–24.9 kg/ m^2, n (%)	33 (33%)
BMI 25.0–29.9 kg/ m^2 , n (%)	57 (58%)
BMI ≥ 30.0 kg/ m^2, n (%)	9 (9%)

AR age (years) is shown in table 4. Overall, EAR was found in 54 (54%) of preterm infants.

Table 4. Adiposity rebound distribution per years.

AR (year)	Tot. n. (%)
2	15 (15%)
3	25 (25%)
4	14 (14%)
5	17 (17%)
6	21 (21%)
7	8 (8%)

No significant differences between children with or without EAR were observed for gestational age at birth (p=0.85), duration of breastfeeding (p=0.49) and timing of first solid food introduction (p=0.58).

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EAR was not significantly associated to gender (p=0.75), type of delivery (p=0.405), birth weight (p=0.09), type of feeding (p=0.48), duration of breastfeeding (0.99), timing of introduction of solid food (p=0.976), maternal education (p=0.267) and BMI (p=0.979), paternal education (p=0.285) and BMI (p=0.177). Results on multivariate analysis for risk factors associated with EAR are shown in table 5.

Table 5. Multivariate analysis for risk factor associated with early adiposity rebound.

	Early AR	
	OR	p-value
Male (yes/no)	0.82	0.70
Vaginal birth (yes/no)	0.38	0.20
Birth Status		
- SGA vs NGA	0.85	0.80
- LGA vs NGA	6.63	0.04
Formula feeding vs Breastfeeding	5.53	0.11
mix vs Breastfeeding	5.20	0.06
Breastfeeding duration ≤ 6 months vs >6 months	0.54	0.4
Solid Introduction * more than 6 vs 4-6 months	1.40	0.65
Mother educational level none/basic vs higher	1.75	0.44
Father educational level none/basic vs higher	0.96	0.95
Mother BMI		
25-29.9 vs 18.5–24.9 kg/m^2	2.45	0.20
>30 vs 18.5–24.9 kg/m^2	0.89	0.91
Father BMI		
25-29.9 vs 18.5–24.9 kg/m^2	0.56	0.28
>30 vs 18.5–24.9 kg/m^2	0.70	0.70

* Category ≤4 months not was considered in the model due to small number of cases

At 7 years follow-up visit, 6% of children resulted overweight and 23% obese. Ex-preterm infants with EAR have a significant higher BMI at 7 years compared to those with normal AR (17.2±2.7 vs 15.6±2.05, t=2.385 p=0.021). Furthermore, prevalence of obesity in subjects with EAR resulted higher, but not statistically significant (29% vs 14% p=0.202).

4. Discussion:

Our study shows that 54% of ex-preterm children had an early adiposity rebound with BMI rebound at or earlier the fourth year of age. This is a significant very high prevalence in comparison to other European studies on children born at term, in which around 30% of children had EAR.[2-14] This high prevalence of EAR is significantly related to higher BMI at 7 years of age and we believe that it could increase the risk of adult obesity and of non-communicable diseases. Non-communicable diseases (NCDs) constitute a major global health challenge. The four major groups of NCDs are cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes. Metabolic imbalances can induce different expressions of child's genetic potential. Afterwards, in childhood food preferences are formed and are tracked into childhood and beyond, and foundations are laid for a healthy adult life. [15]

In our cohort, none of the investigated neonatal factors were associated to EAR. EAR in our cohort was not associated to gender, despite female obesity susceptibilities is a well-known phenomenon.[16] It is possible that obesity or overweight development later in life are more related to pubertal hormonal changes than EAR.

Some authors have investigated if cesarean section (CS) is associated with overweight and obesity in children, with contrasting results.[17-18-19] Newborns born by cesarean section are not exposed to maternal microbiota so they have lower diversity and richness of gut microbiome compared to newborns vaginally delivered.[20] This might influence both the composition and metabolic functions of gut microbiota and their effects on the storage of dietary nutrients, predisposing infants to overweight or obesity. [21-22-23] We have not found any association between cesarean section and EAR.

SGA newborns are more prone to early adiposity rebound, obesity, and metabolic syndrome, mostly the ones with early catch-up growth phenotype.[24] In our cohort, SGA newborns do not show EAR but this could be due to the small sample size of the cohort.

Conversely, LGA newborns had increased odds of EAR compared to their NGA counterparts, confirming that LGA status is a strong marker for risk of being overweight/obese in early childhood, as previous published. [25-26]

In our sample of preterm infants, parental BMI and educational status have not shown a significant relationship with EAR, despite they have been identified in other studies as strong determinant of AR onset in offspring.[27-28] Up to date, breastfeeding has been demonstrated to have a protective effect against childhood obesity. Regular growth without rapid weight gains of the breastfed infant is recognized as an ideal growth model. Breast milk determs the most correct growth and puts the child in the best conditions to prevent chronic diseases in adulthood.

The switch from an exclusively milk based nutrition to solid foods represents a delicate moment for the infant. This moment was called until some years ago "weaning", but today the term "complementary feeding" better underlines the role of nutritional integration of the breast milk. The age of 4-6 months (never before the fourth month completed) for the introduction of complementary feeding was identified as the most appropriate age, since after six months of life breast milk is not enough for growing child's needs, especially for what concerns proteins, iron, zinc and vitamins.[29]

We couldn't demonstrate in our study any different prevalence of EAR according to type of breastfeeding, formula or mixed.

Furthermore, there are few data regarding the effect of the timing of complementary feeding on the risk of overweight and obesity in ex-preterm. A recent study showed that weaning of these infants is characterized by great heterogeneity.[30-31] In our cohort, both earlier (less than <4 months of corrected age) or late (>6 months of corrected age) weaning time do not relate to EAR. Recently an observational cohort study concluded that a higher BMI at 1 years were found in very preterm infants started complementary feeding at ≤ 26 weeks for corrected age, respect to very preterm infants started complementary feeding at ≥ 26.[32]

However, a recent systematic review regarding who rated the relationship between the timing of complementary feeding in preterm infants and the increasing incidence of overweight didn't show clear conclusions that could be extrapolated and highlighted the needing of well-designed randomized control trial providing more insight on the effect of the timing of complementary feeding on (over)weight in preterm infant.[33]

We are aware of some limitations of our study. First, our inclusion criteria could represent a bias because preterm infants with significant comorbidities have been excluded. Secondly, any association of EAR with obesity or overweight could occur after 7 years of age.[34] Furthermore, timing of the adiposity rebound is influenced by many other confounding factors, such as maternal smoking during pregnancy, socio-economic status of the family, screening time, diet and early protein intake during neonatal admission.[35-36-37]

This paper is the first to show EAR prevalence in a cohort of ex-preterm newborns and to evaluate the role of different neonatal factors on EAR with a follow-up up to 7 years.

We have demonstrated a high prevalence of EAR in ex-preterm newborns that it is not influenced by different neonatal factors, confirming that prematurity *"per se"* represent an high-risk condition. Our data suggest that pediatricians should follow carefully ex-preterm children to screen overweight/obesity very early, because of their confirmed, also by our data, predisposition.[38]

Further studies are needed to confirm our data in ex-preterm babies, focusing on the role of other factors such as feeding type and quality of solid foods during weaning time, to develop further and new prevention strategies. A case-control study on ex-preterm infants matched with at term counterparts would confirm the role of prematurity "per se" on EAR.

5. Conclusion

The timing of adiposity rebound has an impact on adverse health outcomes. More than 50% of preterm newborns in our cohort showed early adiposity rebound. Determinants such as gender, type of delivery, birth weight, feeding type and breastfeeding duration, timing of introduction of solid food, parental education and parental BMI are not associated to EAR. Health follow-up programs for ex-preterm infants

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should focus on the timing of early adiposity rebound and on its role as prognostic factor for obesity development.

Author Contributions: Maria Elisabetta Baldassarre and Margherita Caroli conceptualized and designed the study and reviewed the manuscript; Maria Elisabetta Baldassarre led data acquisition, analysis, and interpretation; had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Antonio Di Mauro made substantial contributions to data interpretation, drafted the initial manuscript and revised the manuscript; Alessia De Giorgi led data acquisition; Valentina Rizzo led data acquisition, drafted the initial manuscript and revised the manuscript; Margherita Fanelli made substantial contributions to the conception and design of the study, as well as carrying out data analysis and interpretation. Nicola Laforgia and Federico Schettini made substantial contributions to conception and design of the study and reviewed the manuscript. All authors approved the final manuscript as submitted.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AR: Adiposity rebound

BMI: Body Mass Index

EAR: Early adiposity rebound

GA: Gestational age

LGA: Large for gestational age

NCDs: Non-communicable diseases

NGA: Normal for gestational age

SGA: Small for gestational age

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