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Original Article

Early metabolic imprinting as a determinant of childhood obesity

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ABSTRACT

Aims: Childhood obesity has seen an alarming increase in recent decades. This study was designed to assess the role of family history and perinatal programming in the aetiology of childhood obesity in a population known to have a high risk of developing metabolic syndrome.
Methodology: The study was carried out among two study populations of children. The first was a population of 206 mixed-gender 5-year-old children; the second of 230 mixed-gender 9-year-old children. The children underwent standard anthropomorphic measurements that were correlated to family history of metabolic syndrome-related illness, the child's birth weight and a history of breastfeeding in early infant life.
Results: No statistically significant correlation was noted with a family history of metabolic syndrome; but a definite ($P = 0.04$) negative correlation was noted with breastfeeding in the 5-year-old children. Children of low birth weight appeared to retain a lower body weight at five years of age than their higher birth weight counterparts ($P = 0.002$). The pattern changed to suggest a U-shaped distribution of obesity among the various birth weight groups of children, though statistical significance was noted only for the macrosomic group ($P = 0.002$).
Conclusions: The study confirms the importance of intrauterine and early infant nutrition towards the development of childhood and later obesity. Children of low or high birth weight should be considered at risk and parents are advised actively regarding health lifestyle and nutrition options.

1. Introduction

A number of population studies have suggested that the developed world is currently seeing an increase in childhood obesity which has reached alarming levels. The reasons for this changing epidemiology are multifactorial. While genetic defects have been linked to syndromatic and monogenetic obesity syndromes, altered nutritional and social habits are strong contributors to the increase in weight gain during childhood [1]. A further contributor to childhood obesity appears to be perinatal metabolic programming or imprinting, whereby intrauterine and early postnatal nutrition modulates the risk for obesity and the metabolic syndrome later on in life [2,3].

The Maltese population is a relatively insular, small central Mediterranean island population that has been identified as having a high prevalence of Type 2 diabetes mellitus and associated metabolic syndrome co-morbidities. An association between this high metabolic syndrome prevalence to "endogenous teratogenesis" in this population has been demonstrated in a number of studies [4]. Childhood obesity in this population, in conformity to what is occurring in the developed world, has also shown an increase over the last decades. The 2001–02 Health Behaviour in Schoolchildren Study (HBSC) has shown that the overweight-obesity prevalence among Maltese children stood at 33.3% (overweight 25.4%; obese 7.9%) [5]. The present study attempts to investigate the role of family history and perinatal feeding in the aetiology of childhood obesity in this high risk population.

2. Methods

The study was conducted among two groups of children aged five and nine years, recruited from six selected schools covering the different regions in Malta. The 5-year-old study group included 206 individuals of different genders; while the 9-year-old study group included 230 individuals. The children were assessed for obesity with standard anthropomorphic measurements including body weight, standing height and waist circumference. BMI definitions for overweight-obesity and waist circumference centiles expected at the two chosen age groups according to gender were adapted from the literature. The BMI cutoff values for overweight 5-year-old boys and girls were considered to be 17.42 and 17.15 kg/m^2, respectively; for 9-year olds, the figures were 19.10

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Table 1
Family history and early infant feeding determinants by BMI.

Body mass index	5-year-old group		9-year-old group	
Males and females	Lean	Overweight – Obese	Lean	Overweight – Obese
Family history of metabolic disease				
No	116 80.6%	46 74.2%	68 70.8%	89 66.4%
Yes	28 19.4%	16 25.8%	28 29.2%	45 33.6%
		$P = 0.40$ ns		$P = 0.57$ ns
Breastfeeding				
No	51 36.7%	33 53.2%	29 30.2%	29 33.0%
Yes	88 63.3%	29 46.8%	67 69.8%	59 67.0%
		$P = 0.04$ sig		$P = 0.81$ ns

*Chi-square statistical 2 × 2 test.

and 19.07 kg/m^2, respectively. The 75th percentile waist circumference measurements for 5-year-old boys and girls were 56.5 cm for both genders; for 9-year-old, the figures were 67.0 and 65.7 cm, respectively [6,7].

The anthropomorphic examination was followed by a parent-administered standard questionnaire that included specific questions related to a family history of metabolic syndrome-related illness (hypertension and/or diabetes mellitus), the child's birth weight and a history of breastfeeding in early infant life. These parameters were statistically correlated to present obesity status, using the chi-square test and student *t*-test as appropriate. Ethical approval for the study was obtained from the University of Malta Medical School Research Ethics Committee.

3. Results

The prevalence of childhood overweight-obesity in Maltese 5-year-old children based on the cut-off points defined in the literature was 28.8% for boys and 32.7% for girls. There was no statistically significant difference in the BMI distribution between the genders ($P = 0.70$). These proportions increased markedly with increasing age, so that 48.9% of Maltese 9-year-old males and 45.1% of girls were found to be overweight-obese. Again, there was no statistically significant difference between the genders ($P = 0.39$).

A family history of metabolic disease, as defined by a history of hypertension or diabetes mellitus in either or both of the parents, did not appear to correlate with an increased risk of childhood obesity at both age groups, though the rate of metabolic abnormalities in the parents did show a non-statistically significant increase in the overweight-obese groups of students. The rate of breastfeeding in the overweight-obese 5-year-old group of children showed a statistically significant low rate when compared to the lean 5-year-old children ($P = 0.04$). While the observation persisted in the 9-year-old children, the differences were not statistically significant in this age group ($P = 0.81$) (Table 1).

It would appear that there is a progressive increase in anthropomorphic mean measures determined by weight at birth when assessed in children now aged 5 years. However the large majority of these differences did not exhibit a statistical significance. The mean body weight of children born with a birth weight under 2500 g, however, was statistically ($P = 0.002$) lower than that registered for infants born with a weight of 2500–3999 g. The proportion of overweight/obese children in those born with a birth weight $\geqslant$4000 g was statistically higher than in those born with a weight of 2500–3999 g ($P < 0.0001$). There were no statistically significant differences between birth weight and anthropomorphic characteristics when BMI and waist circumference for the combined male and female population were classified according to the defined parameters (Table 2).

Table 2
Mean anthropomorphic values at 5-years of age by birth weight.

Birth weight (g) Males and females	<2500	2500–3999	$\geqslant$4000
BMI (kg/m^2)	16.1 ± 2.0 [21] $P = 0.24$ ns	16.7 ± 2.2 [161]	17.5 ± 2.7 [13] $P = 0.22$ ns
BMI (kg/m^2)			
Lean	11 68.7%	104 80.6%	2 8.0%
Overweight/obese	5 31.3% *$P = 0.44$ ns	25 19.4%	23 92.0% *$P < 0.0001$sig
Body weight (kg)	18.1 ± 3.5 [21] $P = 0.002$ sig	20.8 ± 3.7 [162]	22.7 ± 4.8 [13] $P = 0.08$ ns
Waist circumference (cm)	52.7 ± 3.7 [20] $P = 0.21$ ns	54.7 ± 7.0 [161]	55.5 ± 5.4 [13] $P = 0.69$ ns
Waist circumference (cm)			
<75th centile	15 78.9%	116 72.0%	10 76.9%
>75th centile	4 21.1% *$P = 0.72$ ns	45 28.0%	3 23.1% *$P = 0.96$ ns
Height (m)	1.1 ± 0.1 [21] $P = 1.0$ ns	1.1 ± 0.05 [161]	1.1 ± 0.05 [13] $P = 1.0$ ns

*Chi-square statistical 2 × 2 tests comparing to BW 2500–3999 group.
Student statistical tests compared to group with birth weight 2500–3999 g.

At nine years of age, there appeared to be an increase in the anthropomorphic measurements in infants born with a weight of 4000 g or more, when compared to infants born with a weight of 2500–3999 g. Statistical significance in the mean body weight was shown for the higher birth weight group (Fig. 1). The mean measurement of BMI and waist circumference in children born with a birth weight of $\geqslant$4000 g was also statistically higher.

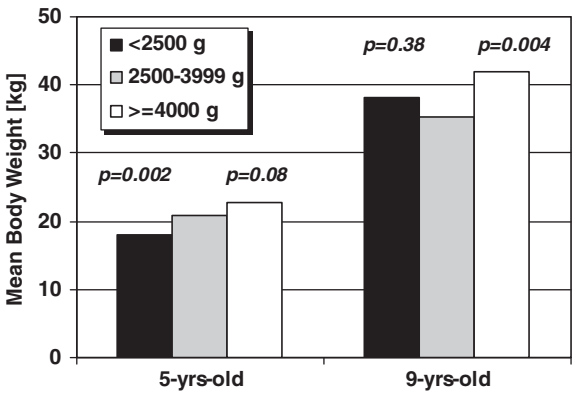

Fig. 1. Mean body weight by birth weight in the two age groups.

Table 3
Mean anthropomorphic values at 9-years of age by birth weight.

Birth weight (g) Males and females	<2500	2500–3999	⩾4000
BMI [kg/m^2]	21.3 ± 5.3 [9] P = 0.14 ns	19.2 ± 4.0 [135]	22.5 ± 4.7 [18] P = 0.002 sig
BMI (kg/m^2)			
Lean	2 25.0%	75 69.4%	4 22.2%
Overweight/obese	6 75.0% *P = 0.03 sig	33 30.6%	14 77.8% *P < 0.0001 sig
Body weight (kg)	38.1 ± 13.3 [9] P = 0.38 ns	35.2 ± 9.2 [135]	42.0 ± 9.0 [18] P = 0.004 sig
Waist circumference (cm)	67.2 ± 11.1 [9] P = 0.49 ns	64.6 ± 10.9 [134]	71.6 ± 8.1 [18] P = 0.01 sig
Waist circumference (cm)			
<75th centile	3 33.3%	86 64.2%	13 41.9%
75th centile	6 66.7% P = 0.15 ns	48 35.8%	18 58.1% *P = 0.04 sig
Height (m)	1.3 ± 0.1 [9] P = 1.0 ns	1.3 ± 0.1 [135]	1.4 ± 0.1 [18] P = 0.0001 sig

*Chi-square statistical 2 × 2 tests comparing to BW 2500–3999 group.
Student statistical tests compared to group with birth weight 2500–3999 g.

Similar statistically significant observations can be made when the data are grouped according to the literature-defined parameters for BMI and waist circumference centiles. Children with high birth weight also appear to be marginally taller. The proportion of overweight/obese children in those born with a birth weight <2500 g was also statistically higher than in those born with a weight of 2500–3999 g (P = 0.03). A higher BMI, body weight and waist circumference are also noted in infants with a low (<2500 g) but the differences did not reach statistical significance (Table 3).

4. Conclusions

Childhood obesity and the consequences of a life-long exposure to the obese state have become a global concern, particularly in the developed world. A steady increase in body weight has been noted in the last decades in many developed countries. This observation has also been made for the Maltese population, and the 2001–02 Health Behaviour in Schoolchildren Study (HBSC) has shown that the overweight-obesity prevalence among Maltese children was 33.3% (overweight 25.4%; obese 7.9%) [5]. The present study suggests that the prevalence of overweight-obesity in 9-year-old Maltese children has now reached a rate of 45.1–48.9% depending on gender. Childhood obesity has been shown to confer long-term effects on mortality and morbitity. Children who have a predisposition to develop obesity have been shown to have pre-existing ‘‘nature” or ‘‘nurture” contributors. The identification of these factors, and their relative importance in a particular population, would serve to identify children at risk, and hence promote targeted lifestyle interventions early in life, to prevent the persistence of the metabolic state into adult life with its attendant morbidities.

In the present study, when a family history defined by a history of hypertension or diabetes mellitus in either or both parents was correlated against childhood obesity in both the age groups studied, an increased tendency for a positive association was found, however without showing statistical significance. This inter-relationship confirms previous studies [8,9]. Glowinska et al. reported that in a series of patients from referral clinics, approximately one third of obese children were found to have a positive family history of cardiovascular disease (CVD) (defined as CVD, myocardial infarction, stroke, or recognized CVD risk factors, including obesity, hypertension, and diabetes). Similarly, Robinson et al reported that a family history of hypertension was associated with higher child body mass index. In this present study, it can be argued that since the parents of the children were still of a relatively young age group, full-blown clinically identified metabolic disease may not yet have set in. It is also possible that not all the parents interviewed in this study were properly aware of their health status and a further percentage of these were actually suffering from elements of insulin resistance, and were still not aware of it. Follow-up interviews 10–15 years later may show a higher prevalence of metabolic disorders in the parents. The study protocol could have been better designed to include formal examination and investigations of the parents to assess for features of metabolic disease, rather than rely on self-filled questionnaires.

Early infant nutrition has also been suggested as playing a role in the development of adult-onset metabolic disease. The extent and duration of breastfeeding have been previously reported to be inversely associated with the risk of obesity in later childhood; the relationship being possibly mediated by physiologic factors in human milk as well as by the feeding and parenting patterns associated with nursing [10,11]. A similar association was found in this current study. In the 5-year-old population studied, a significant negative relationship was found between these children, and a history of breastfeeding. Thus, breastfed children showed a lower prevalence of overweight-obesity, as compared to those who were bottle-fed. This relationship was also evident in the 9-year-old population, but here a statistical significance was not reached. The loss of statistical strength may be possibly attributed by the introduction of other influencing environmental factors, such as diet and lack of physical exercise, with increasing age of the child. These factors by 9 years of age would cancel out and modify the metabolic imprinting of breast feeding. The present study has shown that breastfed children have a reduced risk of becoming overweight-obese. This confirms previous studies [10,11]. Breastfeeding intrinsically allows a baby to set its appetite regulatory pathways in such a way as to limit the propensity to overeat [12].

A number of epidemiological studies have identified that intrauterine nutrition can determine the development of metabolic syndrome in adult life – foetal origins of adult-onset disease theory. These observations have been emulated in the Maltese population [4]. The present study has shown an inter-relationship between birth weight and the risk of developing overweight-obesity in childhood. The macrosomic infant born with a birth weight of 4000 g or more has been shown to have higher mean anthropomorphic measurements both at 5 years and 9 years of age when compared to the corresponding children born with a birth weight of 2500–3999 g. Statistical significance was only shown at 9 years of age; though the proportion of overweight/obese children in the high birth rate group was statistically higher than in those children born with a birth weight of 2500–3999 g.

The low birth weight (<2500 g) individuals showed lower mean anthropomorphic measurements at 5 years of age with statistical significance being shown for mean body weight. At 9 years of age, there was a non-statistical significant rise in mean anthropomorphic measurement. The proportion of overweight/obese individuals in those born with a low birth weight was statistically higher than in those born with a birth weight of 2500–3999 g. It would thus appear that from birth to 5 years, these low birth weight children are still passing through their ‘catch up growth period’, correcting for the effects of their *in utero* period of limited nutritional resources. By 9 years of age, these children have caught up and passed through their ‘catch up growth period’, so that their anthropomorphic parameters now lie in the overweight-obese range. During and following the ‘catch up growth’ the children are exposed to a practically limitless supply of calories. The present findings observed in the 9-year-old population support the

previously reported 'U' odds-risk pattern described in the thrifty phenotype hypothesis of obesity. The thrifty phenotype hypothesis postulates that poor nutrition in foetal life is detrimental to the development and functioning of β-cells and insulin-sensitive tissues, resulting in the emergence of insulin resistance or metabolic syndrome later in life [12]. A similar U-shaped inter-relationship has been described in the Maltese population, in relation to the risk of developing gestational diabetes [13].

The findings engendered by the present study indicate that environmental factors, including intrauterine and postnatal nutrition, strongly influence the risk of eventual obesity development. The family physician must use all the opportunities presented to him during the antenatal period and in the postpartum period to identify those infants particularly at risk of becoming overweight-obese in childhood. Early educational interventions with the parents must be made to encourage breast feeding, and to introduce healthy nutrition and lifestyle practices. Prevention and early identification are the key to decreasing the prevalence of obesity in childhood.

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