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Early causes of child obesity and implications for prevention

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Short title: Early causes of child obesity

Abstract

Child obesity is becoming a serious public health concern, and major research effort is being devoted both to understand its aetiology and to improve the effectiveness of prevention strategies. Early growth patterns, both prenatally and postnatally, are emerging as important markers of later obesity risk, with rapid neonatal weight gain a clear risk factor for later obesity and metabolic syndrome. Thus in two distinct senses child obesity is a growing problem. The paper summarises current evidence on growth pattern and obesity, relating it to infant feeding practice and appetite regulation, and highlights the areas in which public health interventions are feasible. Of the conclusions drawn, one involves a futuristic solution to child obesity where neonates are given an infusion of the hormone leptin to reset their appetite regulation.

Introduction

Child obesity is the leading paediatric public health concern in the developed world.[1] Its prevalence is rising inexorably, and it is linked strongly to both concurrent morbidity and later morbidity and mortality. It is a major research concern both to predict how the obesity epidemic is likely to progress, and to understand its aetiology sufficiently to develop effective interventions to slow its progress.

Diet, physical activity and the familial psychosocial environment are all well-established as risk factors for obesity in childhood, though interventions to alter these behaviours are of limited effectiveness.[2] The aim here is to consider some other less well-known risk factors that operate at an earlier stage of the life course, in infancy, and which have their own implications for policy.

Over the past twenty years there have been major shifts in thinking about the likely early causes of obesity. Barker and his colleagues in the 1980s identified birth weight as an important predictor of adult chronic diseases including obesity, and from this they developed the Fetal Origins of Adult Disease (FOAD) hypothesis.[3] This stated that poor fetal growth, caused by maternal malnutrition, leads to permanent changes in the fetus which make it more susceptible to chronic disease in adulthood. The public health implications of the FOAD hypothesis were clear -- to improve the nutrition of the pregnant woman so as to increase the birth weight of the baby.

Subsequently this same association, between birth weight and later outcome, was shown to imply that the rate of weight gain after birth was itself a risk factor for later disease.[4] Evidence then accrued that early infant weight gain predisposed to obesity in both children and adults.[5] The recently proposed Growth Acceleration hypothesis states that early infant weight gain is a risk factor for later disease, and this includes

FOAD as a special case.[6] In general low birth weight babies show catch-up growth after birth, and this catch-up increases their risk of later disease.

So history shows that the belief in low prenatal growth as a risk factor for later disease was supplanted by a belief in high postnatal growth, and this is the current view. However it raises as many questions as it answers -- what is risky about early rapid weight gain? -- why do infants grow fast? -- are they susceptible to intervention?

Obesity is a growing *problem*

It is clear that in public health terms child obesity is a growing problem. But it is also clearly a *growing* problem in that infants who grow faster are at greater risk of later obesity. There is now evidence for the importance of height gain in this process, from routine measurements on 3-year-old children taken over a 16 year period in the Wirral, England. We know that children of this age became progressively fatter over the period 1988-2003, with mean body mass index (BMI) increasing by 0.7 kg/m^2 overall.[7] However the increase was strongly linked to height, with mean BMI increasing by 1.4 kg/m^2 in the tallest tenth of children as against just 0.1 kg/m^2 in the shortest tenth.[8] Tall stature was a risk factor for obesity.

So we see that children who grow fast, either in terms of infant weight gain or pre-school height, are more likely to be fat later. But why do children grow fast and get fat -- what links growth and obesity? The thermodynamic basis for obesity is an imbalance between dietary energy intake and energy expenditure, so diet and activity are obvious factors to consider. Yet it is difficult to identify environmental aspects of either that are strongly linked to growth rate -- there is no evidence for example that faster-growing children are more likely to over-eat or be more sedentary than slower-

growing children. However faster-growing infants do eat more,[9] and the association between dietary intake and growth is driven by the child's appetite -- a hungry child eats more and tends to grow faster.[10, 11]

It is plausible that increased appetite is the force behind child obesity, and recent work with animal models bears this out.[12] Patterns of fetal and neonatal growth influence appetite regulation, with low birth weight and/or rapid postnatal weight gain up-regulating appetite. This for example is why low birth weight infants grow relatively fast; the appetite hormone ghrelin[13] is up-regulated, being positively correlated with early weight gain[14] and inversely correlated with birth weight[15]. This also may explain why breast feeding is protective against later obesity; the breast-fed infant's first few feeds consist of low-energy colostrum, and in subsequent feeds the infant can regulate their dietary energy intake in a way that the formula-fed infant cannot.[12]

If appetite is the driving force behind the recent rise in obesity, and this looks increasingly likely, there are two distinct ways it might work in early life. Something about appetite must have changed over time -- either appetite itself has increased, in a programming sense through some form of up-regulation, or else the effect of a large appetite on diet has changed, so that the hungriest children are now exposed to the obesogenic environment in a way that they were not one to two generations ago. Children with a large appetite are more likely to be fed the sorts of high-energy-density foods that are now widespread, whereas less hungry children are not exposed in the same way. So the two alternatives to explain recent obesity trends are:

1. programming of appetite has changed, and appetite in some children is up-regulated

2. programming of appetite is unchanged, but hungry children now get fat due to the obesogenic environment.

In practice both alternatives may operate simultaneously.

Parental fatness

By far the strongest risk factor for child obesity is the obesity of the two parents, where the father is as important as the mother.[16, 17] This may reflect to some extent the shared family environment, with its impact on eating and activity patterns, but the link is too strong for the family's lifestyle to be more than a small contributor to the association. The main contributor has to be genetic, in the broadest sense, with the fatness "passed down" from parents to child. But this too cannot be the whole story, as two generations ago children were not fat despite having parents of essentially the same gene pool as now -- it is the interaction of genes and environment that has led to the rise in child obesity.

Child obesity first appeared in the 1980s,[18] whereas adult obesity had been around since the 1960s.[19] So the trends in child obesity over time have lagged behind those for adult obesity by about a generation. It is reasonable to think that once parents started to get fat their offspring were at risk of becoming fat too. This fits with the idea of a transgenerational process, with the fatness of the mother during pregnancy somehow preparing the child to be fat later. The child's fetal growth pattern is clearly influenced by the mother, and the neonatal growth pattern may be influenced by the father, and as stated before growth patterns can program appetite.[12] If fat parents encourage more rapid growth, either fetally or neonatally, this may be enough to explain the increased risk of their children being fat.

Appetite regulation

The amount that people eat is determined by their appetite. If their appetite is up-regulated, or equivalently their satiety mechanism is down-regulated, they will eat more. Appetite is controlled in the hypothalamus, via a complex process involving hormones such as leptin and ghrelin.[20] Leptin appears to measure body mass in some sense, while ghrelin relates more to appetite. A part of the hypothalamus called the arcuate nucleus relays information about leptin to other parts of the hypothalamus, and the pathways involved mature early in postnatal life.[21] Leptin is an intrinsic part of this maturation process, and in mice there is a surge in leptin soon after birth where the timing is critical for the correct development of the pathways.[22] Moreover in rats programmed to be fat *in utero,* neonatal leptin treatment from day 3 to 13 reduces weight gain and avoids later obesity.[23] As Vickers et al say, "This study suggests that developmental metabolic programming is potentially reversible by an intervention late in the phase of developmental plasticity".[23]

Policy implications

Taken together, the evidence summarised here shows that there is much more to child obesity than just the energy balance equation. Individuals vary enormously in their underlying susceptibility to fatness, and the early factors that determine it are the fatness of their parents, their own early growth pattern and their appetite-satiety settings. On top of this the conventional factors of a healthy diet and active lifestyle apply. Infant feeding pattern in particular impacts on growth, and breast feeding reduces early weight gain, possibly via an effect on appetite.

So what are the policy implications of all this -- which of the factors are amenable to intervention? Parental obesity, the strongest predictor, is very common and should be

the starting point in any intervention strategy. However it is also very hard to treat. Perhaps women--and even their partners--should be encouraged lose weight before conceiving, but in practice it is unlikely to make much difference to the fatness of their child.

Rapid early weight gain reflects intra-uterine constraint,[24] so that factors which reduce birth weight, particularly smoking in pregnancy, are likely to increase postnatal weight gain. Premature infants are also at risk as they can grow rapidly after birth. Breast-feeding is an effective counter to rapid weight gain, possibly by reducing energy intake at a time when appetite is being regulated. The weaning diet also needs to be appropriate, so that infants with large appetites, particularly if growing rapidly, are not fed unsuitable energy-dense foods.

In summary the infant's plane of nutrition needs to be kept low, to encourage a modest growth rate now and a healthy lifestyle later. As an aim this is perfectly feasible, and it already fits with existing policies such as discouraging pregnancy smoking, and encouraging breast feeding and a healthy weaning diet. The bigger concern is the issue of the programming of appetite and its possible up-regulation, which occurs early in postnatal life. If this is an important contributor to child obesity there is no simple way to intervene to reduce appetite unless the mechanisms involved can be elucidated, and some form of pharmaceutical intervention developed to down-regulate the appetite setting. One recent study hints at what may be possible in the future: rats programmed *in utero* to be fat were treated with leptin soon after birth to reset their appetite, and they grew up into thin adults.[23] This may not be an attractive vision of the future, and it raises all sorts of ethical issues, but perhaps in years to come we will find ourselves routinely giving newborns their infusion of leptin to set them up for a lean future.

References

1. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. Obesity Reviews 2004;5 (Suppl 1):4-85.

2. Flodmark CE, Lissau I, Moreno LA, Pietrobelli A, Widhalm K. New insights into the field of children and adolescents' obesity: the European perspective. International Journal of Obesity 2004;28:1189-96.

3. Barker DJP. Mothers, babies and health in later life. Edinburgh: Churchill Livingstone; 1998.

4. Lucas A, Fewtrell M, Cole TJ. Fetal origins of adult disease - the hypothesis revisited. BMJ 1999;319:245-9.

5. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 2005;331:929.

6. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? Lancet 2004;363:1642-5.

7. Bundred P, Kitchiner D, Buchan I. Prevalence of overweight and obese children between 1989 and 1998: population based series of cross sectional studies. British Medical Journal 2001;322:326-8.

8. Buchan IE, Bundred PE, Kitchiner DJ, Cole TJ. Body mass index has risen more steeply in tall than in short 3-year olds: serial cross-sectional surveys 1988–2003. Int J Obes 2006;[Epub ahead of print].

9. Whitehead RG, Paul AA, Cole TJ. Diet and the growth of healthy infants. Journal of Human Nutrition and Dietetics 1989;2:73-84.

10. Drewett RF, Amatayakul K. Energy intake, appetite and body mass in infancy. Early Human Development 1999;56:75-82.

11. Oken E, Gillman MW. Fetal origins of obesity. Obes Res 2003;11:496-506.

12. Cripps RL, Martin-Gronert MS, Ozanne SE. Fetal and perinatal programming of appetite. Clin Sci (Lond) 2005;109:1-11.

13. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999;402:656-60.

14. James RJA, Drewett RF, Cheetham TD. Low cord ghrelin levels in term infants are associated with slow weight gain over the first 3 months of life. Journal of Clinical Endocrinology and Metabolism 2004;89:3847-50.

15. Ng PC, Lee CH, Lam CWK, Chan IHS, Wong E, Fok TF. Ghrelin in preterm and term newborns: relation to anthropometry, leptin and insulin. Clinical Endocrinology 2005;63:217-22.

16. Parsons TJ, Power C, Logan S, Summerbell CD. Childhood predictors of adult obesity: a systematic review. Int J Obes Relat Metab Disord 1999;23 Suppl 8:S1-107.

17. Lake JK, Power C, Cole TJ. Child to adult body mass index in the 1958 British birth cohort: associations with parental obesity. Arch Dis Child 1997;77:376-81.

18. Stamatakis E, Primatesta P, Chinn S, Rona R, Falascheti E. Overweight and obesity trends from 1974 to 2003 in English children: what is the role of socioeconomic factors? Archives of Disease in Childhood 2005;90:999-1004.

19. Okosun IS, Chandra KMD, Boev A, Boltri JM, Choi ST, Parish DC, et al. Abdominal adiposity in US adults: prevalence and trends, 1960-2000. Preventive Medicine 2004;39:197-206.

20. Kalra SP, Bagnasco M, Otukonyong EE, Dube MG, Kalra PS. Rhythmic, reciprocal ghrelin and leptin signaling: new insight in the development of obesity. Regulatory Peptides 2003;111:1-11.

21. Bouret SG, Simerly RB. Minireview: Leptin and development of hypothalamic feeding circuits. Endocrinology 2004;145:2621-6.

22. Yura S, Itoh H, Sagawa N, Yamamoto H, Masuzaki H, Nakao K, et al. Role of premature leptin surge in obesity resulting from intrauterine undernutrition. Cell Metabolism 2005;1:371-8.

23. Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A, et al. Neonatal leptin treatment reverses developmental programming. Endocrinology 2005;146:4211-6.

24. Ong KKL, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. British Medical Journal 2000;320:967-71.