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DEVELOPMENTAL ORIGINS OF OBESITY: PROGRAMMING OF FOOD INTAKE OR PHYSICAL ACTIVITY?

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Abstract

Mans ability to capture, harness and store energy most efficiently as fat in adipose tissue has been an evolutionary success story for the majority of human existence. Only over the last 30-40 years has our remarkable metabolic efficiency been revealed as our energy balance increasingly favours storage without regular periods of depletion. Historical records show us that while the composition of our diet has changed markedly over this time, our overall energy intake has significantly reduced. The inevitable conclusion therefore is that habitual physical activity and thus energy expenditure has reduced by a greater extent. Recent studies have illustrated how the finely tuned long-term control of energy intake and of energy expenditure are both developmentally plastic and susceptible to environmentally-induced change that may persist with that individual throughout their adult life, invariably rendering them more susceptible to greater adipose tissue deposition. The central role that lean body mass has upon the 'gating' of energy sensing and the importance of regular physical activity for its potential to reduce the burden of a 'thrifty phenotype' will be briefly discussed in the present review.

Keywords

obesity; physical activity; nutrition; appetite; food intake; programming

1. Introduction – energy handling in humans

Simplistically the Universe is comprised of matter and antimatter. Matter has Mass (a relative weight) and Mass has Energy. Einstein famously described how much energy is contained within any object with mass. Energy in the universe is constant; that is, cannot be created or destroyed only transferred – the First law of Thermodynamics. Plant life first evolved the ability to harness the energy of sunlight to synthesis carbohydrate and produce adenosine triphosphate – the unit of metabolic energy. Animal life then evolved to eat the plants (herbivores), eat the herbivores (carnivores) and/or eat other carnivores and plants (omnivores). At each trophic level some of the transferred energy is lost (mainly as heat) and the absolute demand for energy to fuel metabolic processes is increased i.e. from prokaryotes to eukaryotes (fungi⇒plants⇒animals). Extant animal species have successfully evolved mechanisms to harness, transfer and store metabolic energy, with relative inefficiency an obligatory part of the process. The efficiency of metabolic energy handling is therefore an important evolutionary pressure.

In humans, using adipose tissue to store fat (as triglycerides) represents the most efficient means to 'store' energy, as it is relatively energy dense and dehydrated. In theory, adipose

tissue offers a seemingly unlimited potential for energy storage, but clearly there is an asymptotic plateau in which maintenance of the excess weight becomes a significant demand in itself and reduces an individual's capacity for partitioning energy into reproduction, fertility, and body defences (immune competence) and the necessary accompanying behaviours (physical activity) that ensure continued survival. Consequently, at a species-level, man is relatively fat with a distinct sex-specific bias. Evolutionary pressures act on males to become relatively lean and large (more lean than fat mass) and females to have sufficient energy reserves and other morphometric characteristics that ensure the successful bearing of young. On a population scale therefore, men are generally taller, stronger and leaner than women. The evolutionary pressures that determined the human genotype to subsequently shape our body composition and metabolic competence (i.e. phenotype) to ensure a beneficial evolutionary advantage are, transposed into the current environment, proving too efficient; our paleolithic physiology combined with nutritional abundance without recall to physical activity, is producing an overweight and obese population. This has been described as a nutrition transition; i.e. from a hunter-gatherer society, through the agricultural and industrial revolutions that improved food security, but were often marked by periods of famine, up to a modern society characterized by freely available food and labour saving devices (Popkin, 2006). On the whole and over an extended period of time, intake of energy has exceeded energy expenditure and where previously (Paleolithic era) the excess energy was regularly turned-over through physical activity, this crucial cycle has now been broken (Chakravarthy & Booth, 2004). Such a process reduces metabolic flexibility and increases the rate of degeneration of tissues and organs, which combined with an aging population, is significantly increasing the burden of non-communicable disease in the world-wide population (Popkin, 2006; Smyth & Heron, 2006).

1.1 Obesity and the control of energy balance

The tendency to store excess energy in adipose tissue as fat is multifactorial with potential aetiologies at all biological levels i.e. genetic, physiological and sociological. Although large scale associative genotyping studies have recently revealed potential genetic contributors to an individual's body fat setting or 'adipostat' (Frayling *et al.*, 2007), clearly, obesity reflects a classic environmental*genetic interaction since if it were the case that genes entirely underpinned obesity then obesity would have been as prevalent in the past as it is today, which is not true (Keith *et al.*, 2006). Much debate surrounds sociological aetiologies for obesity, such as societal pressures, portion sizes and marketing strategies; however, ultimately these relate to a desire to eat (appetite) balanced by sufficient activity to effectively utilise that food energy. The relative contribution ascribed to either 'overeating' or 'under-activity' is also much debated. Empirically, overall energy intake as food and drink has declined over the last 20 years (Food Standards Agency & Department of Health, 2004; National Food Survey, 2007) assuming dietary underreporting was as prevalent in 1974 as it is in 2007 (Bedard *et al.*, 2004; Lissner, 2002). Habitual physical activity, on the other hand, has clearly declined by a much greater extent than food intake (Kimm *et al.*, 2005; Sothorn, 2004; Swinburn & Egger, 2004) given the historical trends in obesity (Keith *et al.*, 2006).

Obesity reflects a subtle loss of control of energy balance such that over time, the excess energy is stored as fat. Potential mechanisms underpinning this subtle 'loss of control' are most likely multi-faceted and widely debated, and this brief review shall concentrate on only two main areas; that of a role for the early environment in 'programming' subtle alterations to appetite and/or physical activity and the contributing role each may play in the much touted 'obesity pandemic'. While we may not be eating more energy *per se* the composition of what we now eat is markedly different to the assumed paleolithic, hunter gatherer diet on

which our appetites and metabolic physiology evolved (Popkin, 2006) and upon which we, even as children, were much healthier (Prynne *et al.*, 1999). Globally, the energy density of our diet has increased: traditional African diets are $\sim 450 \text{ kJ} \cdot 100\text{g}^{-1}$ as compared to the average British diet ($\sim 670 \text{ kJ} \cdot 100\text{g}^{-1}$) or average fast-food outlet ($\sim 1100 \text{ kJ} \cdot 100\text{g}^{-1}$) (Prentice & Jebb, 2003) and have become sweeter and more refined, with more simple sugars and reduced fibre (Food Standards Agency & Department of Health, 2004). Total fat intake has decreased, but saturated and artificial (e.g. *trans*) fats have increased (Food Standards Agency & Department of Health, 2004). These changes largely accompany urbanisation, greater wealth, increased processed food and drink intake and decreased consumption of 'raw' foods; whole grains, fruit, vegetables (Popkin, 2006). These subtle compositional changes may 'deceive' ordinary regulatory processes: for example, a 70kg human has $\sim 18.3 \text{ kg}$ stored energy, of which 66.5% (12 kg), 32.8% (6kg) and 0.7% (0.3 kg) is fat, protein and carbohydrate, respectively. This equates to 139, 200 kcal assuming oxidation of fat, protein and carbohydrate yields 9.3, 4.4 and 4.0 kcal, respectively. For total fat, daily intake relative to this 'reserve' is very small (35% of $\sim 2000 \text{ kcal} = 700\text{kcal}$, relative to 'reserve' of 92,568 kcal or $\sim 0.1\%$) and therefore very slight changes in the fat content of food maybe more difficult to effectively sense and regulate. The modern diet is placing more emphasis on pancreatic functional capacity (increased extrinsic sugars, glycaemic index of food) and exceptional dietary regulation of intake within the context of greatly reduced need for overt physical activity. Clearly over long periods of time i.e. years-decades, such an environment facilitates a gradually increasing fat mass. Additionally, there is evidence that both may be susceptible or 'plastic' to early life programming.

2. Developmental programming of energy intake and energy expenditure

The control of food intake through the appetite-regulatory networks in the hypothalamus has been reviewed extensively (Kalra *et al.*, 1999) and its susceptibility through early life programming has also received much recent interest in the scientific community (Langley-Evans *et al.*, 2005; Cripps *et al.*, 2005; Bouret & Simerly, 2006; Horvath & Bruning, 2006). The mouse and rat models from which much of this work has originated has proved particularly useful in this respect due to the neonatal susceptibility of these appetite-regulatory pathways i.e. an early environment stimulus, for example being exposed to under/overnutrition when raised in large/small litters, respectively has long term consequences for food intake and food preference (Oscari & McGarr, 1978; Widdowson & McCance, 1975; Widdowson, 1970). More recently, it has been shown that both the genetically predetermined hyperphagic and obese *ob/ob* mouse phenotype and dietary-induced obese and lethargic rat phenotype (Vickers *et al.*, 2000) may be reversed, very simply, through neonatal exposure to leptin – the humoral 'adipostat' (Bouret & Simerly, 2006; Bouret *et al.*, 2004; Vickers *et al.*, 2005).

The equivalent developmental period for resetting of appetite networks in larger animals such as humans and sheep occurs prenatally, during late gestation. Interestingly, an enhanced nutritional plane at this time in sheep has recently been shown to influence early appetite behaviour (Muhlhauser *et al.*, 2006). Thus diverse and non-specific nutritional inputs can influence an immature hypothalamic appetite network to the detriment of the individual in later life i.e. they become more susceptible to poor nutritional control. A key mediator of this effect is leptin and its effects on hypothalamic reorganisation. This raises interesting questions about the role of maternal body composition, lactational performance and leptin concentration in milk (Lisboa *et al.*, 2006; Miralles *et al.*, 2006; Mostyn *et al.*, 2006; Muhlhauser *et al.*, 2006; Savino *et al.*, 2006) – cumulatively reflected in the infant as the rate of neonatal leptin intake, which may therefore underpin many of the observed developmentally programmed effects on appetite and body composition in later life.

Interestingly, some of the main hypothalamic targets for leptin that have been shown to influence appetite control also influence energy expenditure e.g. central melanocortins (Balthasar *et al.*, 2005). Indeed, when leptin is considered as a systemic mechanism to indicate sufficient energy 'reserves' for maintenance of growth, reproduction and immune competence then it is hardly surprising that excess energy initiates leptin-mediated hypophagia (Bouret *et al.*, 2004) and increased energy expenditure (Mark *et al.*, 2003) as a means to restore somatic energy balance. The central melanocortin pathways involving neurons co-expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) appear to act as the fulcrum balancing energy intake and expenditure (Balthasar *et al.*, 2005). Indeed, alterations to these pathways either through early life experience and/or an interaction with the adult environment may produce a specific hypothalamic leptin resistance that affects both energy intake and expenditure (Enriori *et al.*, 2007). Such a mechanism, coupled with the historical changes in food energy density and composition, may explain why excess energy is gradually stored, over time, in developmentally programmed individuals rather than sensed and regulated.

2.1 Programming of physical activity level

While leptin appears to be the key humoral regulator of somatic 'energy-sensing', overall energy regulation is through variations in physical activity induced energy expenditure. On the whole energy expenditure drives energy intake rather than *vice versa*. Historically, increased physical activity would by necessity accompany periods of reduced energy intake (Chakravarthy & Booth, 2004) and thus energy reserves would become depleted. In this environment any subtle changes to appetite networks were thus masked by continued feed-fast cycles. In modern life this is not happening and the continuous availability of food together with little demand for overt physical activity engenders an environment that encourages weight gain. In this environment, for potentially 'programmed' individuals i.e. those bearing hypothalamic imprints that reflect leptin resistance, excess weight gain will occur at a greater rate, clinical obesity manifests earlier and premature mortality beckons. Few studies have shown direct programming of energy expenditure. One study associated severe maternal undernutrition with both increased food intake and decreased habitual behavioural-related activity prior to maturity onset obesity (Vickers *et al.*, 2003), first suggesting potential programming of reduced energy expenditure through reduced physical activity. Again, neonatal leptin treatment successfully reversed the deleterious effects on energy expenditure (Vickers *et al.*, 2005). We have shown that sheep made obese through restriction of physical activity and increased availability of energy dense food (Williams *et al.*, 2007) exhibit individual variation in physical activity level, but the rank order of activity is maintained from early into later life (Figure 1) suggesting an individual 'activitystat'. Such a proposal is not new and was suggested earlier by Wilkin *et al.* based upon physical activity in school children (Wilkin *et al.*, 2006). Indeed, non-exercise activity thermogenesis (NEAT) i.e. energy expenditure associated with ambulating but not overt physical activity has been proposed to be individually fixed early in life, and to potentially account for up to 15 kg extra fat mass per year between individuals with low or high NEAT (Levine *et al.*, 2005). Clearly, therefore, successful balance of somatic energy transfer relies upon a threshold level of energy expenditure through physical activity. This is exemplified in studies in which overweight individuals engaged in low-moderate physical activity that was not sufficient for them to lose weight, but drastically improved their insulin resistance and presumably long-term morbidity (Nassis *et al.*, 2005; Denton *et al.*, 2004). How does low-moderate physical activity exert such important effects on energy balance?

3. Energy balance and skeletal muscle metabolism

Skeletal muscle gives postural support, enables locomotion and is an important site for turnover of the carbon skeletons of amino acids, fatty acids and carbohydrates. Skeletal

muscle therefore represents a key organ for intermediary metabolism; indeed, it accounts for about 40% of body mass, 20% of energy expenditure but 70-80% of insulin dependent glucose uptake (via glucose transporter 4 [GLUT4]) (Olefsky, 1999). Skeletal muscle is comprised, basically, of primary and secondary fibres which, more importantly, may be subdivided into oxidative (i.e. support resting substrate level oxidation of primarily fatty acids and some glycogen) or glycolytic (i.e. primarily utilise locally stored glycogen for substrate-level oxidation). Primary fibre number appears unresponsive to environmental insults such as a poor prenatal diet i.e. they are largely genetically determined (Maltin *et al.*, 2001; Fahey *et al.*, 2005), but secondary fibres do appear susceptible (Daniel *et al.*, 2007; Zhu *et al.*, 2006; Mallinson *et al.*, 2007). More importantly perhaps is that a prenatal limitation on the amount and activity of oxidative fibres has the potential to impact quite substantially on intermediary metabolism in adult life. For example, oxidative fibres express greater GLUT4 relative to glycolytic fibres (Duehlmeier *et al.*, 2007; Dagaard *et al.*, 2000), contain more mitochondria and subsequently more β oxidative enzymes such as carnitine palmitoyltransferase (CPT-1) (Zhu *et al.*, 2006) and acetyl-CoA carboxylase, (ACC). Although muscle fibre number and type are fixed at birth (Maltin *et al.*, 2001) subtle shifts in muscle oxidative capacity can be induced through activation of peroxisome proliferator activated receptor (PPAR) gamma coactivator alpha (PGC-1 α) and beta (PGC-1 β) (Arany *et al.*, 2007) and adenosine monophosphate (AMP) activated protein kinase (AMPK) (Hardie *et al.*, 2006) in response to physical activity.

Prenatal programming of skeletal muscle metabolism, physical activity and potentially even “intramuscular energy sensing” could have a significant influence on the predisposition to the facets of the metabolic syndrome induced by the *in utero* nutritional milieu. For example, a reduced overall capacity for fatty acid oxidation may pre-empt intramyocellular (ectopic) fatty acid deposition which has been implicated in the pathophysiology of Type 2 Diabetes (T2D; (Roden, 2005) . Furthermore, (Wisloff *et al.*, 2005) demonstrated a clear correlation between prenatally determined skeletal muscle oxidative capacity and cardiovascular health. Prenatal nutrient restriction has been shown to increase intracellular fatty acid deposition in the adult offspring of sheep (Zhu *et al.*, 2006) and alter intracellular insulin signalling (Ozanne *et al.*, 2005). Of course, with sufficient exercise-induced muscle contraction however, then such metabolic dysregulation is avoided by the activation of PGC-1 α , PGC-1 β (Hood *et al.*, 2006; Mortensen *et al.*, 2006) and AMPK (Hardie *et al.*, 2006), leading to improvements in blood glucose clearance, glycogen production and fatty acid oxidation via mitochondrial biogenesis and increased expression of β -oxidative enzymes. Indeed over-expression of skeletal muscle specific PGC-1 confers resistance to T2D (Arany *et al.*, 2007). As Chakravarthy and Booth hypothesised, low-moderate physical activity (or alternatively, the physiological recruitment of oxidative skeletal muscle fibres) appears to act as the gating mechanism for control of resting metabolism (Chakravarthy & Booth, 2004).

4. Conclusion

Any early developmentally-induced compromise in the control of resting metabolism, either through deficits in oxidative fibre number or intramuscular energy sensing and handling could provide the initial trigger for increased susceptibility to the range of adverse symptoms that we associate with the metabolic syndrome; all that appears required to prevent these pathophysiological sequelae is regular low-moderate intensity exercise, irrespective of any reduction in bodyweight (Nassis *et al.*, 2005; Denton *et al.*, 2004)). Perhaps the one easy, effective and economic health promotion initiative or intervention to be considered is prescription of exercise programs to overweight individuals and for those that have been *a priori* identified at particular risk i.e. the ‘developmentally programmed’, low birth weight-early growth acceleration infants.

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Abbreviations

ACC	acetyl-CoA carboxylase
AgRP	agouti-related peptide
GLUT4	glucose transporter 4
NEAT	non-exercise activity thermogenesis
NPY	neuropeptide Y
PPAR	peroxisome proliferator activated receptor
PGC-1α	PPAR gamma coactivator alpha
PGC-1β	PPAR gamma coactivator beta
T2D	Type 2 Diabetes

References

1. Arany Z, Lebrasseur N, Morris C, Smith E, Yang W, Ma Y, Chin S, Spiegelman BM. The transcriptional coactivator PGC-1 β drives the formation of oxidative type IIX fibers in skeletal muscle. *Cell Metab.* 2007; 5:35–46. [PubMed: 17189205]
2. Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, Ferreira M, Tang V, McGovern RA, Kenny CD, Christiansen LM, Edelstein E, Choi B, Boss O, Aschkenasi C, Zhang CY, Mountjoy K, Kishi T, Elmquist JK, Lowell BB. Divergence of melanocortin pathways in the control of food intake and energy expenditure. *Cell.* 2005; 123:493–505. [PubMed: 16269339]
3. Bedard D, Shatenstein B, Nadon S. Underreporting of energy intake from a self-administered food-frequency questionnaire completed by adults in Montreal. *Public Health Nutr.* 2004; 7:675–681. [PubMed: 15251058]
4. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science.* 2004; 304:108–110. [PubMed: 15064420]
5. Bouret SG, Simerly RB. Developmental programming of hypothalamic feeding circuits. *Clin.Genet.* 2006; 70:295–301. [PubMed: 16965320]
6. Chakravarthy MV, Booth FW. Eating, exercise, and “thrifty” genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. *J Appl.Physiol.* 2004; 96:3–10. [PubMed: 14660491]
7. Cripps RL, Martin-Gronert MS, Ozanne SE. Fetal and perinatal programming of appetite. *Clin.Sci. (Lond).* 2005; 109:1–11. [PubMed: 15966867]
8. Daniel ZC, Brameld JM, Craigon J, Scollan ND, Buttery PJ. Effect of maternal dietary restriction during pregnancy on lamb carcass characteristics and muscle fiber composition. *J.Anim Sci.* 2007; 85:1565–1576. [PubMed: 17296773]
9. Dugaard JR, Nielsen JN, Kristiansen S, Andersen JL, Hargreaves M, Richter EA. Fiber type-specific expression of GLUT4 in human skeletal muscle: influence of exercise training. *Diabetes.* 2000; 49:1092–1095. [PubMed: 10909963]
10. Denton JC, Schultz R, Jamurtas AZ, Angelopoulos TJ. Improvements in glucose tolerance in obese males with abnormal glucose tolerance following 10 days of aerobic exercise. *Prev.Med.* 2004; 38:885–888. [PubMed: 15193912]

11. Duehlmeier R, Sammet K, Widdel A, von Engelhardt W, Wernery U, Kinne J, Sallmann HP. Distribution patterns of the glucose transporters GLUT4 and GLUT1 in skeletal muscles of rats (*Rattus norvegicus*), pigs (*Sus scrofa*), cows (*Bos taurus*), adult goats, goat kids (*Capra hircus*), and camels (*Camelus dromedarius*). *Comp Biochem.Physiol A Mol.Integr.Physiol.* 2007; 146:274–282. [PubMed: 17158080]
12. Enriori PJ, Evans AE, Sinnayah P, Jobst EE, Tonelli-Lemos L, Billes SK, Glavas MM, Grayson BE, Perello M, Nillni EA, Grove KL, Cowley MA. Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. *Cell Metab.* 2007; 5:181–194. [PubMed: 17339026]
13. Fahey AJ, Brameld JM, Parr T, Buttery PJ. The effect of maternal undernutrition before muscle differentiation on the muscle fiber development of the newborn lamb. *J.Anim Sci.* 2005; 83:2564–2571. [PubMed: 16230653]
14. Food Standards Agency & Department of Health. Krebs, J.; Johnson, M. National Diet and Nutrition Survey: adults aged 19–64 years. Vol. 5. London: HMSO; 2004. p. 1–142.
15. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Davey-Smith G, Hattersley AT, McCarthy MI. A Common Variant in the FTO Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. *Science.* 2007
16. Hardie DG, Hawley SA, Scott JW. AMP-activated protein kinase--development of the energy sensor concept. *J.Physiol.* 2006; 574:7–15. [PubMed: 16644800]
17. Hood DA, Irrcher I, Ljubicic V, Joseph AM. Coordination of metabolic plasticity in skeletal muscle. *J.Exp.Biol.* 2006; 209:2265–2275. [PubMed: 16731803]
18. Horvath TL, Bruning JC. Developmental programming of the hypothalamus: a matter of fat. *Nat.Med.* 2006; 12:52–53. [PubMed: 16397567]
19. Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, Kalra PS. Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. *Endocr.Rev.* 1999; 20:68–100. [PubMed: 10047974]
20. Keith SW, Redden DT, Katzmarzyk PT, Boggiano MM, Hanlon EC, Benca RM, Ruden D, Pietrobelli A, Barger JL, Fontaine KR, Wang C, Aronne LJ, Wright SM, Baskin M, Dhurandhar NV, Lijoi MC, Grilo CM, Deluca M, Westfall AO, Allison DB. Putative contributors to the secular increase in obesity: exploring the roads less traveled. *Int.J.Obes.(Lond).* 2006; 30:1585–1594. [PubMed: 16801930]
21. Kimm SY, Glynn NW, Obarzanek E, Kriska AM, Daniels SR, Barton BA, Liu K. Relation between the changes in physical activity and body-mass index during adolescence: a multicentre longitudinal study. *Lancet.* 2005; 366:301–307. [PubMed: 16039332]
22. Langley-Evans SC, Bellinger L, McMullen S. Animal models of programming: early life influences on appetite and feeding behaviour. *Matern.Child Nutr.* 2005; 1:142–148. [PubMed: 16881893]
23. Levine JA, Lanningham-Foster LM, McCrady SK, Krizan AC, Olson LR, Kane PH, Jensen MD, Clark MM. Interindividual variation in posture allocation: possible role in human obesity. *Science.* 2005; 307:584–586. [PubMed: 15681386]
24. Lisboa PC, Passos MC, Dutra SC, Bonomo IT, Denolato AT, Reis AM, Moura EG. Leptin and prolactin, but not corticosterone, modulate body weight and thyroid function in protein-malnourished lactating rats. *Horm.Metab Res.* 2006; 38:295–299. [PubMed: 16718624]
25. Lissner L. Measuring food intake in studies of obesity. *Public Health Nutr.* 2002; 5:889–892. [PubMed: 12638596]
26. Mallinson JE, Sculley DV, Craigon J, Plant R, Langley-Evans SC, Brameld JM. Fetal exposure to a maternal low-protein diet during mid-gestation results in muscle-specific effects on fibre type composition in young rats. *Br.J.Nutr.* 2007; 98:292–299. [PubMed: 17391556]

27. Maltin CA, Delday MI, Sinclair KD, Steven J, Sneddon AA. Impact of manipulations of myogenesis in utero on the performance of adult skeletal muscle. *Reproduction*. 2001; 122:359–374. [PubMed: 11597302]
28. Mark AL, Rahmouni K, Correia M, Haynes WG. A leptin-sympathetic-leptin feedback loop: potential implications for regulation of arterial pressure and body fat. *Acta Physiol Scand*. 2003; 177:345–349. [PubMed: 12609005]
29. Miralles O, Sanchez J, Palou A, Pico C. A physiological role of breast milk leptin in body weight control in developing infants. *Obesity*.(Silver.Spring). 2006; 14:1371–1377. [PubMed: 16988079]
30. Mortensen OH, Frandsen L, Schjerling P, Nishimura E, Grunnet N. PGC-1alpha and PGC-1beta have both similar and distinct effects on myofiber switching toward an oxidative phenotype. *Am.J.Physiol Endocrinol.Metab*. 2006; 291:E807–E816. [PubMed: 16720625]
31. Mostyn A, Sebert S, Litten JC, Perkins KS, Laws J, Symonds ME, Clarke L. Influence of porcine genotype on the abundance of thyroid hormones and leptin in sow milk and its impact on growth, metabolism and expression of key adipose tissue genes in offspring. *J.Endocrinol*. 2006; 190:631–639. [PubMed: 17003264]
32. Muhlhauser BS, Adam CL, Findlay PA, Duffield JA, McMillen IC. Increased maternal nutrition alters development of the appetite-regulating network in the brain. *FASEB J*. 2006; 20:1257–1259. [PubMed: 16684802]
33. Nassis GP, Papantakou K, Skenderi K, Triandafillopoulou M, Kavouras SA, Yannakoulia M, Chrousos GP, Sidossis LS. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism*. 2005; 54:1472–1479. [PubMed: 16253636]
34. National Food Survey. Household food expenditure and consumption and nutrient intake 1974-2007. 2007
35. Olefsky JM. Insulin-stimulated glucose transport minireview series. *J.Biol.Chem*. 1999; 274:1863. [PubMed: 9890934]
36. Oscai LB, McGarr JA. Evidence that the amount of food consumed in early life fixes appetite in the rat. *Am.J.Physiol*. 1978; 235:R141–R144. [PubMed: 696852]
37. Ozanne SE, Jenson CB, Tingey KJ, Storgaard H, Madsbad S, Vaag AA. Low birth weight is associated with specific changes in muscle insulin signalling protein expression. *Diabetologia*. 2005 In Press.
38. Popkin BM. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. *Am.J.Clin.Nutr*. 2006; 84:289–298. [PubMed: 16895874]
39. Prentice AM, Jebb SA. Fast foods, energy density and obesity: a possible mechanistic link. *Obes.Rev*. 2003; 4:187–194. [PubMed: 14649369]
40. Prynne CJ, Paul AA, Price GM, Day KC, Hilder WS, Wadsworth ME. Food and nutrient intake of a national sample of 4-year-old children in 1950: comparison with the 1990s. *Public Health Nutr*. 1999; 2:537–547. [PubMed: 10656473]
41. Roden M. Muscle triglycerides and mitochondrial function: possible mechanisms for the development of type 2 diabetes. *Int.J.Obes.(Lond)*. 2005; 29(Suppl 2):S111–S115. [PubMed: 16385762]
42. Savino F, Liguori SA, Oggero R, Silvestro L, Miniero R. Maternal BMI and serum leptin concentration of infants in the first year of life. *Acta Paediatr*. 2006; 95:414–418. [PubMed: 16720487]
43. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. *Nat.Med*. 2006; 12:75–80. [PubMed: 16397575]
44. Sothorn MS. Obesity prevention in children: physical activity and nutrition. *Nutrition*. 2004; 20:704–708. [PubMed: 15212754]
45. Swinburn B, Egger G. The runaway weight gain train: too many accelerators, not enough brakes. *BMJ*. 2004; 329:736–739. [PubMed: 15388619]
46. Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *Am.J.Physiol Endocrinol.Metab*. 2000; 279:E83–E87. [PubMed: 10893326]

47. Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. *Am.J.Physiol Regul.Integr.Comp Physiol.* 2003; 285:R271–R273. [PubMed: 12794001]
48. Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A, Breier BH, Harris M. Neonatal leptin treatment reverses developmental programming. *Endocrinology.* 2005; 146:4211–4216. [PubMed: 16020474]
49. Widdowson EM. Harmony of growth. *Lancet.* 1970; 1:902–905. [PubMed: 4191545]
50. Widdowson EM, McCance RA. A review: new thoughts on growth. *Pediatr.Res.* 1975; 9:154–156. [PubMed: 1091911]
51. Wilkin TJ, Mallam KM, Metcalf BS, Jeffery AN, Voss LD. Variation in physical activity lies with the child, not his environment: evidence for an ‘activitystat’ in young children (EarlyBird 16). *Int.J.Obes.(Lond).* 2006; 30:1050–1055. [PubMed: 16801942]
52. Williams PJ, Kurlak LO, Perkins AC, Budge H, Stephenson T, Keisler D, Symonds ME, Gardner DS. Hypertension and impaired renal function accompany juvenile obesity: The effect of prenatal diet. *Kidney Int.* 2007
53. Wisloff U, Najjar SM, Ellingsen O, Haram PM, Swoap S, Al Share Q, Fernstrom M, Rezaei K, Lee SJ, Koch LG, Britton SL. Cardiovascular risk factors emerge after artificial selection for low aerobic capacity. *Science.* 2005; 307:418–420. [PubMed: 15662013]
54. Zhu MJ, Ford SP, Means WJ, Hess BW, Nathanielsz PW, Du M. Maternal nutrient restriction affects properties of skeletal muscle in offspring. *J.Physiol.* 2006; 575:241–250. [PubMed: 16763001]

Figure 1.

Data for 24h physical activity (a.u.) in all offspring were ranked after recording at 6 months and again at 12 months. The slope of the correlation (with 95% CI) was statistically significant ($r=0.52$; $P=0.002$).