ACTA MEDICA LITUANICA. 2008. Vol. 15. No. 1. P. 9–15

Nutritional protein and body mass index, the neglected correlation

Michael Hermanussen [1],

Wolfgang Sichert-Hellert[2],

Mathilde Kersting[2]

[1] Aschauhof, Altenhof, Germany

[2] Forschungsinstitut für Kinderernährung (Research Institute of Child Nutrition), Dortmund, Germany

Background. The temporal association between modern food habits, the occurrence of fast food, the trend towards convenience products, and the epidemic occurrence of obesity is evident. The causal relation remains less evident.

Material and methods. We re-analyzed body height, body weight, and macronutrient intake of 1028 children (51.3% girls, 48.7% boys) aged 2–18 years who were investigated between 1985 and 2006 as part of the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study. We determined the intake of energy, carbohydrates, fat, and protein.

Results. No correlations were found between the standard deviation scores of the BMI (BMI-SDS) and daily energy intake ($r = 0.060$, $p > 0.1$), between BMI-SDS and fat intake ($r = 0.031$, $p > 0.1$), and BMI-SDS and carbohydrate intake ($r = 0.050$, $p > 0.1$). Yet, we detected a significant positive correlation between BMI-SDS and average daily nutritional protein (all protein: $r = 0.143$, $p < 0.0001$, animal protein: $r = 0.151$, $p < 0.0001$). The correlation further increased when protein uptake was calculated as a percent of energy uptake (all protein: $r = 0.203$, $p < 0.0001$, animal protein: $r = 0.163$, $p < 0.0001$). The correlations depended on the age with maxima just before and during the early puberty (boys: $r = 0.31$, $p < 0.0001$, girls: $r = 0.36$, $p < 0.0001$). It appears that in these age groups up to 13% of the BMI variance can be explained by protein uptake.

Conclusion. The present investigation confirms the hitherto existing evidence of a significant positive correlation between nutritional protein and body mass index.

Key words: body mass index, appetite control, protein, obesity, glutamate

INTRODUCTION

Obesity has reached epidemic levels in the developed countries. The age-adjusted prevalence of obesity in the US was 30.5% in 1999–2000 compared with 22.9% in NHANES III (1988–1994). The prevalence of overweight plus obesity also increased during this period from 55.9 to 64.5%. Extreme obesity (BMI > or = 40) increased from 2.9 to 4.7% (1). Very similar prevalence and trends have been observed in many other developed countries. The most recent German Health Interview and Examination Survey for Children and Adolescents (2) has shown that 6.4% of the 7–10 year old children and 8.5% of the 14–17 year old adolescents are obese. In most developing economies, the prevalence of overweight in young women residing in both urban and rural areas is higher than the prevalence of underweight, especially in the countries at higher levels of socioeconomic development. In urban areas of Egypt, prevalence of overweight among women has risen to 69.9%, in Mexico to 65.4%, and even in the very poorest countries, overweight has become a major health concern particularly in the lower social strata (3). The prevalence of obesity in children has recently been discussed by Dehghan and co-workers (4). Twenty five percent of children in the US are overweight and 11% are obese. The data for children collected in the Health Survey for England in 1998 showed that between 1994 and 1998, the prevalence of overweight children grew from about 13 to 20%. The prevalence of excess body weight among children in England also appeared to be rising at an accelerating rate (5). Preventing and treating obesity has therefore become a major public health concern in this century and certainly needs other than just medical approaches. Yet, current ideas about lifestyle and strategies to maintain health and weight are still dominated by very popular beliefs that clearly contrast scientific evidence.

Traditionally, the displacement of physical activity by sedentary behaviour has been regarded important for the development of excessive weight gain.

Already in 1985, Dietz and Gortmaker (6) first described a significant association between the time spent watching television and the prevalence of obesity. Since then, many authors confirmed the correlations between sedentary lifestyle, eating practices and overweight. Pendola and Gen (7) even described an inverse relationship between population density and auto use as well as higher BMI scores for respondents reporting high levels of auto use for the work/school commute and trips to the grocery store. Yet, recent meta-analyses question the clinical importance of this association. Marshall and co-workers (8) meta-analysed the relationship between media use, body fatness and physical activity in children and youth, and found that almost

Correspondence to: Prof. Michael Hermanussen, Aschauhof 3, 24340 Altenhof, Germany. E-mail: hermanussen.aschauhof@t-online.de

99% of the variance in body fatness was explained by factors other than physical inactivity.

There is no doubt that across all age groups, energy intake has increased (9, 10). The US Department of Agriculture Factbook 2001–2002 (11) provides evidence that the "average American" consumes about 530 Kcal per day more – an almost 25% increase in energy intake – compared with 30 years ago. Almost the same has been reported from British (12) and Dutch cohorts (13). Particularly, increased availability of food supplies, increasing portion size, eating away from home, and consuming a variety of high-energy dense foods has been considered responsible for the increase in energy intake (14–16). The more food is served, the more people overeat (17). Also the presence of other people at meal increases food intake by extending the time spent for it (18). Especially eating late at night lacks satiating value and can result in greater overall daily intake (19). However, similar to physical exercise, the statistical association between energy intake and BMI variance at the population level is amazingly low. Many authors either found no (20, 21) or low correlations that predicted no more than 4% (22) of the BMI variance. In other words, when adding the effects of physical exercise and energy intake (both are indispensable when treating an individual obese patient), the impact of the two parameters on BMI at the level of the population, is more than discouraging, and certainly does not support the emphasis that is currently laid on sports and low-calorie dishes for combating world-wide overweight.

Nutritional fat is energy-dense. Thus, reduction of fat appears to be an appropriate tool for diminishing total energy intake; consequently since many years, fat-reduced and even fat-free dishes dominate diet-food advertisements. Also scientific publications used to support this popular view. In 1993, Astrup (23) summarized ecological, cross-sectional and prospective longitudinal studies showing that obesity was positively associated with dietary fat energy percentage and negatively with carbohydrate energy percentage. For the following decade, fat intake continued to be considered positively related to adiposity (24, 25). However, the low-fat concept has also been questioned. Sanders (26) summarized that the scientific basis for a reduction in the proportion of energy from fat below 30% energy was not supported by experimental evidence. Taking into consideration the fact that during the last two decades within the United States, a substantial decline in the percentage of energy from nutritional fat has corresponded with a massive increase in the prevalence of obesity ("fat paradox"), Willett and Leibel concluded in 2002 (27) that diets high in fat do not appear to be the primary cause of the high prevalence of excess body fat in our society, and that reductions in the percentage of energy from fat will have no important benefits and could even further exacerbate the problem of obesity. This was recently confirmed by a Cochrane database review (28) concluding that weight loss achieved through dietary fat restriction is so small that it should be regarded clinically insignificant.

Similarly discouraging observations have been published in respect to the effect of carbohydrates on body weight. The relation between carbohydrate ingestion and BMI appears to be insignificant or even negative (20). In 1997, the same group (25) showed that also in children, the percentage of energy derived from carbohydrate was inversely related to adiposity, before and after controlling for potential confounding. Similar observations were published by Rolland-Cachera and co-workers (21, 29), and by Astrup (23). Again, the popular vision that sweets and carbohydrates increase the propensity of overweight clearly contrasts the scientific evidence at the population level.

But why is the scientific evidence concerning the relation between physical inactivity, food availability and overweight, though statistically significant, so extremely weak, and fails to explain a major portion of body weight variation at the population level? Although amazing at first glance, the answer is a purely statistical one: most of the physiological weight variation within a population, is independent of environment and nutrition. Numerous large studies indicate that hereditary factors contribute to most of a population's weight variation. Based on 30,000 people from Virginia including twins and their parents, siblings, spouses, and children, Maes and co-workers (30) estimated genetic factors to explain 67% of the variance in BMI. Pietilainen and co-workers (31) estimated that at the age of 16–17, genetic effects accounted for over 80% of the inter-individual variation of BMI. Sorenson and co-workers (32) calculated BMI correlations between the adoptees and biological fathers, mothers and siblings, and concluded that the genetic influence on BMI is already expressed by the age of 7, and that the rearing environment shared by the family has a weak influence on BMI during childhood. Magnusson and Rasmussen (33) showed highly significant BMI correlations among all the biological family relations: 0.28 (95% CI 0.27–0.29) for father-son pairs; 0.36 (0.35–0.37) for full-brothers, 0.21 (0.18–0.24) for maternal half-brothers and 0.11 (0.08–0.14) for paternal half-brothers. Coady and co-workers (34) used longitudinal data from the Framingham heart study and created pedigrees of age-matched individuals. They found moderate heritability estimates for the mean BMI ($h(2) = 0.37$), maximum BMI ($h(2) = 0.40$), and the mean residual of body weight ($h(2) = 0.36$), and concluded that a significant genetic component existed for the magnitude of BMI throughout an individual's middle-adult years.

The magnitude of the genetic contribution therefore does not only explain why the correlation between BMI and the non-genetic contributors to excessive weight gain is statistically so weak, it also underscores the difficulties that impair the studies of environmental and nutritional effects on BMI variation. Possibly for this reason, the scientific literature on the interaction between body weight and the third macronutrient protein still remains surprisingly sparse. Protein intake also correlates with BMI (even though – for the same statistical reasons mentioned above – this correlation is as low as that between exercise, and between energy intake and weight). We present weighing and nutritional data obtained from the DONALD (Dortmund Nutritional and Anthropometrical Longitudinally Designed) Study.

MATERIALS AND METHODS

DONALD is an open cohort study investigating the complex relations between feeding behaviour, food consumption, growth, development, nutritional status, metabolism and health from birth to adulthood since 1985 (35–37). 7182 three-day weighing and nutritional protocols and anthropometric data were

re-analyzed. The protocols were obtained from 1028 healthy children and adolescents aged from 2 to 18 years (51.3% girls, 48.7% boys), measured between 1985 and March 2006. Daily nutritional intake was calculated as mean value of an individual's three-day nutritional protocol.

Mean daily intake of energy, carbohydrates, fat, protein and the amino acid glutamate were evaluated for each subject using the FKE (Forschungsinstitut für Kinderernährung Dortmund) nutritional data base as well as national and international food tables (38–40). Mean daily intakes were correlated with BMI standard deviation (BMI-SDS).

RESULTS

In all the age groups, total energy uptake varies considerably between individuals and differs by more than twofold between those who consume most and those who consume the least. Yet, no correlation was found between energy uptake and the standard deviation score of the body mass index (BMI-SDS) ($r = 0.060$, $p > 0.1$). There was also no correlation detected between absolute fat intake ($r = 0.031$, $p > 0.1$) or carbohydrate intake, and BMI-SDS ($r = 0.050$, $p > 0.1$); but we found a significant correlation between BMI-SDS and the absolute intake of all protein ($r = 0.143$, $p < 0.0001$), and animal protein ($r = 0.151$, $p < 0.0001$). BMI-SDS also correlated with the absolute intake of the amino acid glutamate (protein-bound, and free glutamate, $r = 0.150$, $p < 0.0001$). When expressing macronutrient intake as a percent of energy intake, the fat and carbohydrate correlations remained insignificant with $r = -0.040$, and $r = -0.037$, respectively, whereas the correlation between BMI-SDS and all protein ($r = 0.203$, $p < 0.0001$), and animal protein ($r = 0.163$, $p < 0.0001$) further increased. The correlation between BMI-SDS and percent intake of glutamate even rose to $r = 0.211$ ($p < 0.0001$). The percent variation of the BMI-SDS that is explained by protein intake depends on age (Figure), and reaches maxima in the group of 10–12 year old boys ($r = 0.31$, $p < 0.0001$), and girls ($r = 0.36$, $p < 0.0001$), i. e. protein intake explains almost 10%, respectively, almost 13% of the BMI variance in young adolescents.

These effects are not explained by age-dependent change of food composition. The composition of macronutrients in respect to the percentage of energy supplied by fat, carbohydrate and protein remained almost unchanged across all age groups. None of the correlations between BMI-SDS and total energy uptake nor dietary fat, nor carbohydrate intake showed an age relationship similar to that seen in protein. Only in young women (15–18 years), a significant though negative association was found between BMI-SDS and energy uptake possibly reflecting reporting errors in this age group.

DISCUSSION

In most Western diets, the percentage of nutritional energy that is provided by protein (protein energy percentage) tends to increase, and currently varies around some 15 percent. Protein is an essential compound of everyday food, and popular notion associates nutritional protein with health improvement. Since recent literature suggests high-protein diets to be beneficial for individual weight loss therapies (41, 42 (we will discuss this phenomenon below) protein-rich food has increasingly been recommended, and its consumption has substantially risen. In Germany, the annual per capita meat production has doubled since 1950 and has reached almost 100 kg/a by now. The annual per capita production of milk has been stable since 1970 at some 70 litre/a, but the per capita production of cheese has also doubled since 1970, and reached 20 kg/a. Since 1970, the per capita poultry production has increased from 8 to 14 kg/a (43, 44). Similar data were reported from the Netherlands (13) and from the UK (12).

Yet, the association between protein consumption and the prevalence of obesity has largely been neglected. In spite of some early reports mentioning that protein intake was consistently high in obese children at all ages (45), protein seems to play a minor role even in the recent scientific literature. For example,

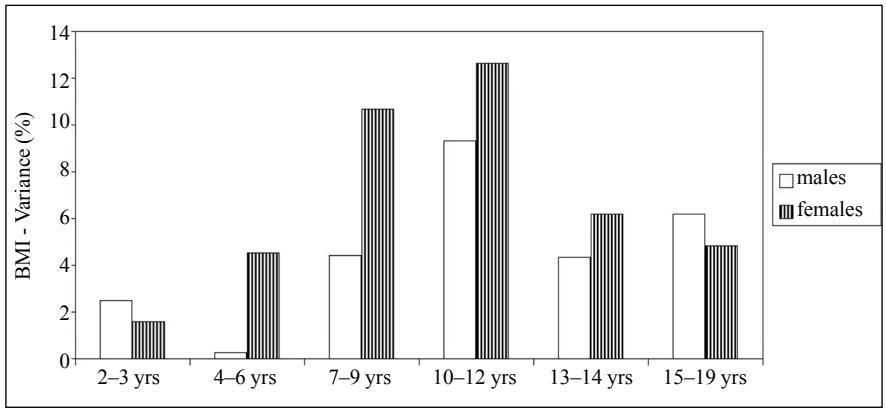

Figure. Nutritional protein significantly contributes to body mass index (BMI) variance in an age dependent manner. Bars indicate the percent of BMI variance that is explained by protein intake (percent of total energy intake). The interaction is strongest in pre- and early pubertal females (age groups 7–9, and 10–12 years) and males (age group 10–12 years)

Davis and co-workers (46) studied the consumption of total fat, carbohydrates, and fibre in obese and non-obese subjects, but never mentioned protein; Erlanson and Mei (47) studied the effect of low-carbohydrate diets on energy metabolism, and attributed the suppressed appetite and the rapid initial weight loss to carbohydrate intake, instead of discussing that the clinical effects of low-carbohydrate could also be caused by high-protein intake, as they admitted later (personal communication 2006).

Protein intake correlates with BMI. In 1992, Taylor et al. (48) surveyed total energy and macronutrient intakes in Melanesians and Indians in Fiji, in Micronesians in Kiribati and in Melanesians in Vanuatu. Urban subjects ate proportionally more protein and fat and were more obese than the rural ones. Galanis and co-workers (49) described the dietary intake of 946 Samoans, and found substantial differences between residents of American Samoa who were more obese, and those of less modernized Western Samoa. American Samoans consumed significantly more energy as carbohydrate and protein and less as fat and saturated fat compared to Samoans in the lowest category of material lifestyle. Recently Ulijaszek (50) studied food availability in the market places and summarized trends in body size and diet in the Cook Islands during the second half of the 20th century. The rate of increase of average weight in females aged 20–29 years was 0.6 kg per decade across the period 1952–1966, and 7.3 kg per decade across the period 1966–1996. In the age group 30–39 years, the rates were 3.2 kg per decade and 5.1 kg per decade, respectively. He found reduced availability of traditional staples, a likely reduction in consumption of fish, a decline in the availability of dietary fats and oils, but an increased consumption of meat. Between 1961 and 2000, the daily per capita availability of meat increased more than fifteen times, from 8 g/d to 122 g/d (Ulijaszek, personal communication 2005).

The relation between nutritional protein and body weight has also been recognized in France (21). Protein (expressed as percent of energy) intake at the age of 2 years was positively correlated with BMI at 8 years ($r = 0.17$, and when adjusted for BMI at 2 years and for parental BMI, the correlation increased to $r = 0.22$). Similar results were published by Gunnarsdottir and Thorsdottir (51) who found that weight gain at 0–12 months and protein intake at 9–12 months explained 50% of the variance in BMI among 6-year old boys. Scaglioni and co-workers (52) found that 5-year old overweight children had a higher percentage intake of proteins at the age of 1 year than non-overweight children and lower intake of carbohydrates, and confirmed by multiple logistic analysis that protein intake at 1 year of age was associated with overweight at 5 years. The same group (53) stated that protein intake above the limit of 14% energy in 6–24 months old infants will lead towards an early adiposity rebound and overweight in young children. Kemper and co-workers (54) investigated fat mass in males and females, aged between 12–28 years of the Amsterdam Growth and Health Longitudinal Study and found an Odds Ratio of 1.5 (1.2–1.8) with the daily intake of proteins. In the context of the European Prospective Investigation into cancer and nutrition, Trichopoulou and co-workers (55) studied 27 862 apparently healthy adult volunteers and found that protein intake was positively associated with BMI. The effects of other macronutrients were less substantial or consistent. The authors concluded that protein intake was conducive to obesity.

These data are in line with our findings in Dortmund children and adolescents. But why does protein intake stimulate weight gain? Increasing evidence suggests that high-protein dishes stimulate the central nervous appetite regulation. Food processing partially hydrolyzes nutritional protein. After the meal, intraluminal pancreatic proteases further digest nutritional protein partially into oligopeptides (some 70%) and partially into free amino acids (some 30% (56)). In 1990, Bergström and co-workers (57) showed that the serum levels of most amino acids increase following a protein-rich meal. Also dietary glutamate penetrates into the human circulation (58). Some regions of the brain grouped as the circumventricular organs, are particularly sensitive to small circulating molecules, including glutamate, as these regions are not protected by the blood brain barrier. Using tracer molecules, it has long been established that some of the centres of appetite regulation, for example the arcuate nucleus, accumulate glutamate and other small molecules (59). Further evidence for the involvement of the circumventricular organs into the regulation of appetite has recently been provided by Cheunsuang and Morris (60). They showed that cells within these regions that accumulate small tracer molecules, also express the leptin receptor.

Stanley and co-workers (61, 62) showed that endogenous lateral hypothalamic glutamate acts to regulate natural eating and body weight and that N-methyl-D-aspartate (NMDA) receptors participate in these functions, and they underscored the functional as well as anatomical heterogeneity of the hypothalamus, and implicate glutamate and NMDA receptors in different portions of the hypothalamus in the control of eating, grooming and arousal. Also other amino acids appear to play an important role in this regulation. Trytophan acts as a precursor of serotonin, another co-regulator of appetite. Leucin (we will discuss this amino acid later) suppresses food intake via hypothalamic mTOR signalling (63), and methionine can increase mitochondrial oxygen radical generation, and oxidative damage to mitochondrial DNA (64). It is increasingly evident that free amino acids regulate metabolism (65), modulate satiety and exhibit complex effects on appetite and body weight maintenance.

Elevated levels of free glutamate are toxic for some of the essential neuronal structures of appetite regulation. Already in 1969, Olney and co-workers (66) reported the formation of brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate (MSG). Administering MSG to newborn rodents destroys arcuate nucleus neurones, and it damages various other hypothalamic areas. Bloch et al. (67) showed that MSG treatment results in the complete loss of growth hormone releasing factor (GRF)-immunoreactive cell bodies within the arcuate nucleus and provokes a selective disappearance of GRF-immunoreactive fibres in the median eminence of rats. Neurotoxic (excitotoxic) effects of glutamate are mediated by the NMDA receptor.

MSG maintains its toxicity when administered orally. MSG feeding results in voracity; MSG feeding (5 g/day) to pregnant rats also results in severe birth weight reduction of the offspring. Weight increments of the offspring remain subnormal when MSG feeding to the mothers is maintained during weaning (68). Also growth hormone (GH) serum levels are affected

in animals that receive MSG during prenatal life via maternal feeding. Animals receiving 2.5 g/d MSG showed low GH serum levels up to day 30 of life, but seem to partially recover in later life. Animals receiving 5 g/d MSG show continuous suppression of GH serum levels similar to those animals that had been MSG injected at neonatal age. Very recent investigations indicate that in young animals the impairment of GH regulation occurs already at oral doses of 1 g/d MSG (approximately 5% MSG in the dry rat food). MSG feeding also suppresses hypothalamic NPYmRNA expression, and reduces hypothalamic leptin receptor mRNA expression in older animals (Garcia et al. unpublished). These studies demonstrate for the first time that a widely used nutritional mono-substance – the flavouring agent monosodium glutamate – at concentrations that only slightly surpass those found in everyday human food exhibit significant potential for damaging the hypothalamic regulation of appetite. Particularly the studies in pregnant rats underline the significance of these findings for pregnant women and during early human life.

Recent literature suggests very high-protein diets to be beneficial for weight loss. This observation needs to be addressed as it contradicts the notion that protein consumption is positively associated with the prevalence of obesity. Indeed, very high-protein weight-loss diets stimulate postprandial thermogenesis and cause the sensation of fullness, suppress appetite and lead to negative energy balance (41, 69–73). Yet, the appetite suppression of very high-protein diets appears to be mediated by mechanisms different from the classic pathways of appetite regulation. Weigle and co-workers (74) were able to demonstrate that the protein mediated inhibition of appetite was not mediated by leptin or ghrelin. It has been shown that the branched-chain amino acid leucin directly suppresses food intake via hypothalamic mTOR signalling (63). At present, it remains to be elucidated whether high-protein mediated direct inhibition of appetite that bypasses the classic leptin regulation has to be considered a toxic event, or whether it just denotes another, less well studied natural mechanism of appetite regulation. Consequently, the protein content of many popular weight loss diets, such as Atkins Diet, Protein Power, South Beach, and the Zone Diet, reaching some 40% of energy, and even more (75), must for these reasons be regarded with caution, and should be particularly avoided during pregnancy and childhood.

CONCLUSION

The present investigation confirms the hitherto existing evidence of a significant positive correlation between nutritional protein and body mass index.

ACKNOWLEDGEMENTS

This work was supported by the Deutsche Gesellschaft für Auxologie and Norddeutsches Zentrum für Wachstumsforschung.

Received 24 October 2007
Accepted 6 February 2008

References

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002; 288: 1723–7.
2. Kurth BM, Schaffrath Rosario A. Die Verbreitung von Übergewicht und Adipositas bei Kinder und Jugendlichen in Deutschland. Ergebnisse des bundesweiten Kinder- und Jugendgesundheitssurveys (KiGGS). Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2007; 50: 736–43.
3. Mendez MA, Monteiro CA, Popkin BM. Overweight exceeds underweight among women in most developing countries. Am J Clin Nutr 2005; 81: 714–21.
4. Dehghan M, Akhtar-Danesh N, Merchant AT. Childhood obesity, prevalence and prevention. Nutr J 2005; 4: 24.
5. Lobstein TJ, James WP, Cole TJ. Increasing levels of excess weight among children in England. Int J Obes Relat Metab Disord 2003; 27: 1136–8.
6. Dietz WH Jr, Gortmaker SL. Do we fatten our children at the television set? Obesity and television viewing in children and adolescents. Pediatrics 1985; 75: 807–12.
7. Pendola R, Gen S. BMI, auto use, and the urban environment in San Francisco. Health Place. 2007; 13: 551–6.
8. Marshall SJ, Biddle SJ, Gorely T, Cameron N, Murdey I. Relationships between media use, body fatness and physical activity in children and youth: a meta-analysis. Int J Obes Relat Metab Disord 2004; 28: 1238–46.
9. Nielsen SJ, Siega-Riz AM, Popkin BM. Trends in energy intake in U.S. between 1977 and 1996: similar shifts seen across age groups. Obes Res 2002; 10: 370–8.
10. Centers for Disease Control and Prevention (CDC). Trends in intake of energy and macronutrients – United States, 1971–2000. Morb Mortal Wkly Rep 2004; 6: 53, 80–2.
11. Rigby N. Commentary: International journal of epidemiology – counterpoint to Campos et al. Int J Epidemiol 2006; 35: 79–80.
12. Prynne CJ, Paul AA, Mishra GD, Greenberg DC, Wadsworth ME. Changes in intake of key nutrients over 17 years during adult life of a British birth cohort. Br J Nutr 2005; 94: 368–76.
13. Bertheke Post G, de Vente W, Kemper HC, Twisk JW. Longitudinal trends in and tracking of energy and nutrient intake over 20 years in a Dutch cohort of men and women between 13 and 33 years of age: The Amsterdam growth and health longitudinal study. Br J Nutr 2001; 85: 375–85.
14. Hensrud DD. Diet and obesity. Curr Opin Gastroenterol 2004; 20: 119–24.
15. Grundy SM. Multifactorial causation of obesity: implications for prevention. Am J Clin Nutr 1998; 67 (Suppl 3): 563S–72S.
16. Hill JO, Peters JC. Environmental contributions to the obesity epidemic. Science 1998; 280: 1371–4.
17. Levitsky DA, Youn T. The more food young adults are served, the more they overeat. J Nutr 2004; 134: 2546–9.
18. de Castro JM. Family and friends produce greater social facilitation of food intake than other companions. Physiol Behav 1994; 56: 445–5.

19. de Castro JM. The time of day of food intake influences overall intake in humans. J Nutr 2004; 134: 104–11.
20. Nelson LH, Tucker LA. Diet composition related to body fat in a multivariate study of 203 men. J Am Diet Assoc 1996; 96: 771–7.
21. Rolland-Cachera MF, Deheeger M, Akrout M, Bellisle F. Influence of macronutrients on adiposity development: a follow-up study of nutrition and growth from 10 months to 8 years of age. Int J Obes Relat Metab Disord 1995; 19: 573–8.
22. McConahy KL, Smiciklas-Wright H, Mitchell DC, Picciano MF. Portion size of common foods predicts energy intake among preschool-aged children. J Am Diet Assoc 2004; 104: 975–9.
23. Astrup A. Dietary composition, substrate balances and body fat in subjects with a predisposition to obesity. Int J Obes Relat Metab Disord 1993; 17(Suppl 3): S32–6; S41–2.
24. Maffeis C, Pinelli L, Schutz Y. Fat intake and adiposity in 8 to 11-year-old obese children. Int J Obes Relat Metab Disord 1996; 20: 170–4.
25. Tucker LA, Seljaas GT, Hager RL. Body fat percentage of children varies according to their diet composition. J Am Diet Assoc 1997; 97: 981–6.
26. Sanders TA. High- versus low-fat diets in human diseases. Curr Opin Clin Nutr Metab Care 2003; 6: 151–5.
27. Willett WC, Leibel RL. Dietary fat is not a major determinant of body fat. Am J Med 2002; 113(Suppl 9B): 47S–59S.
28. Pirozzo S, Summerbell C, Cameron C, Glasziou P. Advice on low-fat diets for obesity. Cochrane Database Syst Rev 2002: CD003640.
29. Rolland-Cachera MF, Bellisle F, Tichet J, Chantrel AM, Guilloud-Bataille M, Vol S, Pequignot G. Relationship between adiposity and food intake: an example of pseudo-contradictory results obtained in case-control versus between-populations studies. Int J Epidemiol 1990; 19: 571–7.
30. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet 1997; 27: 325–51.
31. Pietilainen KH, Kaprio J, Rissanen A, Winter T, Rimpela A, Viken RJ, Rose RJ. Distribution and heritability of BMI in Finnish adolescents aged 16y and 17y: a study of 4884 twins and 2509 singletons. Int J Obes Relat Metab Disord 1999; 23: 107–15.
32. Sorensen TI, Holst C, Stunkard AJ. Adoption study of environmental modifications of the genetic influences on obesity. Int J Obes Relat Metab Disord 1998; 22: 73–81.
33. Magnusson PK, Rasmussen F. Familial resemblance of body mass index and familial risk of high and low body mass index. A study of young men in Sweden. Int J Obes Relat Metab Disord 2002; 26: 1225–31.
34. Coady SA, Jaquish CE, Fabsitz RR, Larson MG, Cupples LA, Myers RH. Genetic variability of adult body mass index: a longitudinal assessment in Framingham families. Obes Res 2002; 10: 675–81.
35. Kersting M, Alexy U, Sichert-Hellert W, Manz F, Schoch G. Measured consumption of commercial infant food products in German infants: results from the DONALD study. J Pediatr Gastroenterol Nutr 1998; 27: 547–52.
36. Alexy U, Kersting M, Sichert-Hellert W, Manz F, Schoch G. Macronutrient intake of 3- to 36-month-old German infants and children: results of the DONALD Study. Ann Nutr Metab 1999; 43: 14–22.
37. Kroke A, Manz F, Kersting M, Remer T, Sichert-Hellert W, Alexy U, Lentze MJ. The DONALD Study. History, current status and future perspectives. Eur J Nutr 2004; 43: 45–54.
38. Souci SW, Fachmann W, Kraut H. Die Zusammensetzung der Lebensmittel. Nährwert-Tabellen. 2000. 6th edition: CRC Press.
39. Danish Food composition Databank. Available from: www.foodcomp.dk/fcdb_namesearch.asp
40. USDA National Nutrient Database. Available from: www.nal.usda.gov/fnic/foodcomp/search/
41. Layman DK, Boileau RA, Erickson DJ, Painter JE, Shiue H, Sather C, Christou DD. A reduced ratio of dietary carbohydrate to protein improves body composition and blood lipid profiles during weight loss in adult women. J Nutr 2003; 133: 411–7.
42. Layman DK, Baum JI. Dietary protein impact on glycemic control during weight loss. J Nutr 2004; 134: 968S–73S.
43. Ernährungsbericht (nutrition report) 1969. Deutsche Gesellschaft für Ernährung. Frankfurt: 37.
44. Ernährungsbericht (nutrition report) 2000. Deutsche Gesellschaft für Ernährung. Frankfurt: 24.
45. Crawford PB, Hankin JH, Huenemann RL. Environmental factors associated with preschool obesity. III. Dietary intakes, eating patterns, and anthropometric measurements. J Am Diet Assoc 1978; 72: 589–96.
46. Davis JN, Hodges VA, Gillham MB. Normal-weight adults consume more fiber and fruit than their age- and height-matched overweight/obese counterparts. J Am Diet Assoc 2006; 106: 833–40.
47. Erlanson-Albertsson C, Mei J. The effect of low carbohydrate on energy metabolism. Int J Obes (Lond) 2005; 29(Suppl 2): S26–30.
48. Taylor R, Badcock J, King H, Pargeter K, Zimmet P, Fred T, Lund M, Ringrose H, Bach F, Wang RL et al. Dietary intake, exercise, obesity and noncommunicable disease in rural and urban populations of three Pacific Island countries. J Am Coll Nutr 1992; 11: 283–93.
49. Galanis DJ, McGarvey ST, Quested C, Sio B, Afele-Fa'amuli SA. Dietary intake of modernizing Samoans: implications for risk of cardiovascular disease. J Am Diet Assoc 1999; 99: 184–90.
50. Ulijaszek SJ. Trends in body size, diet and food availability in the Cook Islands in the second half of the 20th century. Econ Hum Biol 2003; 1: 123–37.
51. Gunnarsdottir I, Thorsdottir I. Relationship between growth and feeding in infancy and body mass index at the age of 6 years. Int J Obes Relat Metab Disord 2003; 27: 1523–7.
52. Scaglioni S, Agostoni C, Notaris RD, Radaelli G, Radice N, Valenti M, Giovannini M, Riva E. Early macronutrient intake and overweight at five years of age. Int J Obes Relat Metab Disord 2000; 24: 777–81.

53. Agostoni C, Scaglioni S, Ghisleni D, Verduci E, Giovannini M, Riva E. How much protein is safe? Int J Obes 2005; 29(Suppl 2): S8–13.
54. Kemper HC, Post GB, Twisk JW, van Mechelen W. Lifestyle and obesity in adolescence and young adulthood: results from the Amsterdam Growth and Health Longitudinal Study (AGAHLS). Int J Obes Relat Metab Disord 1999; 23(Suppl 3): S34–40.
55. Trichopoulou A, Gnardellis C, Benetou V, Lagiou P, Bamia C, Trichopoulos D. Lipid, protein and carbohydrate intake in relation to body mass index. Eur J Clin Nutr 2002; 56: 37–43.
56. Klinke R, Pape HC, Silbernagel S. Physiologie. Stuttgart, New York: Thieme; 2005.
57. Bergström J, Fürst P, Vinnars E. Effect of a test meal, without and with protein, on muscle and plasma free amino acids. Clin Sci 1990; 79: 331–7.
58. Stegink LD, Filer LJ Jr, Baker GL. Plasma amino acid concentrations in normal adults fed meals with added monosodium L-glutamate and aspartame. J Nutr 1983; 113: 1851–60.
59. Vina JR, DeJoseph MR, Hawkins PA, Hawkins RA. Penetration of glutamate into brain of 7-day-old rats. Metab Brain Dis 1997; 12: 219–27.
60. Cheunsuang O, Morris R. Astrocytes in the arcuate nucleus and median eminence that take up a fluorescent dye from the circulation express leptin receptors and neuropeptide Y Y1 receptors. Glia 2005; 52: 228–33.
61. Stanley BG, Willett VL, Donias HW, Dee MG, Duva MA. Lateral hypothalamic NMDA receptors and glutamate as physiological mediators of eating and weight control. Am J Physiol Regul Integr Comp Physiol 1996; 270: 443–9.
62. Duva MA, Tomkins EM, Moranda LM, Kaplan R, Sukhaseum A, Bernardo JP, Stanley BG. Regional differences in feeding and other behaviors elicited by N-methyl-D-aspartic acid in the rodent hypothalamus: a reverse microdialysis mapping study. Brain Res 2002; 925: 141–7.
63. Cota D, Proulx K, Smith KA, Kozma SC, Thomas G, Woods SC, Seeley RJ. Hypothalamic mTOR signaling regulates food intake. Science 2006; 312: 927–30.
64. Sanz A, Caro P, Ayala V, Portero-Otin M, Pamplona R, Barja G. Methionine restriction decreases mitochondrial oxygen radical generation and leak as well as oxidative damage to mitochondrial DNA and proteins. FASEB J 2006; 20: 1064–73.
65. Meijer AJ, Dubbelhuis PF. Amino acid signalling and the integration of metabolism. Biochem Biophys Res Commun 2004; 313: 397–403.
66. Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science 1969; 164: 719–21.
67. Bloch B, Ling N, Benoit R, Wehrenberg WB, Guillemin R. Specific depletion of immunoreactive growth hormone-releasing factor by monosodium glutamate in rat median eminence. Nature 1984; 307: 272–3.
68. Hermanussen M, García AP, Sunder M, Voigt M, Salazar V, Tresguerres JAF. Obesity, voracity and short stature: the impact of glutamate on the regulation of appetite. Eur J Clin Nutr 2006; 60: 25–31.
69. Crovetti R, Porrini M, Santangelo A, Testolin G. The influence of thermic effect of food on satiety. Eur J Clin Nutr 1998; 52: 482–8.
70. Westerterp-Plantenga MS, Rolland V, Wilson SA, Westerterp KR. Satiety related to 24 h diet-induced thermogenesis during high protein/carbohydrate vs high fat diets measured in a respiration chamber. Eur J Clin Nutr 1999; 53: 495–502.
71. Westerterp-Plantenga MS, Lejeune MP, Nijs I, van Ooijen M, Kovacs EM. High protein intake sustains weight maintenance after body weight loss in humans. Int J Obes Relat Metab Disord 2004; 28: 57–64.
72. Johnston CS, Day CS, Swan PD. Postprandial thermogenesis is increased 100% on a high-protein, low-fat diet versus a high-carbohydrate, low-fat diet in healthy, young women. J Am Coll Nutr 2002; 21: 55–61.
73. Luscombe ND, Clifton PM, Noakes M, Parker B, Wittert G. Effects of energy-restricted diets containing increased protein on weight loss, resting energy expenditure, and the thermic effect of feeding in type 2 diabetes. Diabetes Care 2002; 25: 652–7.
74. Weigle DS, Breen PA, Matthys CC, Callahan HS, Meeuws KE, Burden VR, Purnell JQ. A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. Am J Clin Nutr 2005; 82: 41–8.
75. Volpe SL. Popular weight reduction diets. J Cardiovasc Nurs 2006; 21: 34–9.