British Journal of Nutrition (2009), **102**, 1047–1051
doi:10.1017/S0007114509338829

Short-term effects of replacing milk with cola beverages on insulin-like growth factor-I and insulin–glucose metabolism: a 10 d interventional study in young men

Camilla Hoppe[1,2]*, Mette Kristensen[1], Marlene Boiesen[1], Jane Kudsk[1], Kim Fleischer Michaelsen[1] and Christian Mølgaard[1]

[1]*Department of Human Nutrition, University of Copenhagen, Rolighedsvej 30, DK-1958 Fredericksberg, Denmark*
[2]*Department of Nutrition, National Food Institute, Technical University of Denmark, Mørkhøj Bygade 19, DK-2860 Søborg, Denmark*

(Received 26 June 2008 – Revised 19 March 2009 – Accepted 20 March 2009 – First published online 22 September 2009)

In the Western world, a trend towards increased consumption of carbonated soft drinks combined with a decreasing intake of milk is observed. This may affect circulating insulin-like growth factor I (IGF-I) and fasting insulin, as seen in pre-pubertal children. The present study was designed to reflect the trend of replacing milk with carbonated beverages in young men and to study the effects of this replacement on IGF-I, IGF-binding protein 3 (IGFBP-3), IGF-I:IGFBP-3 and glucose–insulin metabolism. A randomised, controlled crossover intervention study, in which eleven men aged 22–29 years were given a low-Ca diet in two 10 d periods with 10 d washout in between. In one period, they drank 2·5 litres of Coca Cola® per day and the other period 2·5 litres of semi-skimmed milk. Serum IGF-I, IGFBP-3 (RIA), insulin (fluoro immunoassay) and glucose (Cobas) were determined at baseline and end point of each intervention period. Insulin resistance and β-cell function were calculated with the homeostasis model assessment. A decrease in serum IGF-I was observed in the cola period compared with the milk period ($P<0·05$). No effects of treatment were observed on IGFBP-3, IGF-I:IGFBP-3, insulin, glucose, insulin resistance or β-cell function. The present study demonstrates that high intake of cola over a 10 d period decreases total IGF-I compared with a high intake of milk, with no effect on glucose–insulin metabolism in adult men. It is unknown whether this is a transient phenomenon or whether it has long-term consequences.

Milk: Cola: Insulin-like growth factor I: Insulin-like growth factor-binding protein 3: Insulin: Insulin resistance: Homeostasis model assessment

The family of insulin-like growth factors (IGF; insulin, IGF-I and II) is an important regulator of linear growth[1,2]. In addition, both IGF-I and insulin might be related to certain cancer forms[3–7] and other non-communicable diseases[8] with high levels of circulating IGF-I associated to higher risk of some cancers, and low levels of circulating IGF-I associated with higher risk of CVD, type 2 diabetes, osteoporosis and cognitive decline.

Circulating IGF-I is, to some degree, regulated by nutritional intakes[9]. Milk seems to contain some growth factors that stimulate IGF. We have seen increased concentrations of both IGF-I and IGF-binding protein 3 (IGFBP-3), the molar ratio of IGF-I:IGFBP-3 in pre-pubertal boys after a 1-week intervention with milk and not meat[10]. Also fasting insulin and insulin resistance as calculated using the homeostasis model assessment from fasting levels of glucose and insulin were significantly increased in the intervention group with milk, but not with meat[11]. However, the dietary effect on the fasting concentrations of these growth factors may differ between boys with a rapid growth velocity and adult men, in whom linear growth has ceased. Whether milk also influences the fasting concentrations of these growth factors in adults, in whom linear growth has ceased, is unknown, since no intervention studies exploring this in adults has been reported to our knowledge. However, several observational studies have reported positive association between milk intake and circulating IGF-I in adults[12–15].

In the Western world, the trend in food consumption is presently moving towards a reduced milk intake coinciding with an increased consumption of soft drinks[16–18], of which the most popular are cola beverages.

The objective of this intervention study was primarily to examine the effect of replacing milk with carbonated beverages on markers of bone turnover in a group of young men[19]. The effects on IGF-I, IGFBP-3 and the molar ratio of IGF-I:IGFBP-3, and on the glucose–insulin metabolism were also investigated and are presented here.

Abbreviations: IGF, insulin-like growth factor; IGFBP-3, IGF-binding protein 3.

* **Corresponding author:** Camilla Hoppe, fax +45 3588 7119, email cahop@food.dtu.dk

Experimental methods

Design

As previously described[19], eleven healthy men participated in a 30 d randomised controlled intervention study. The experiment was arranged in a crossover design with two 10 d experimental periods with 10 d washout in between, in which the subjects consumed their habitual diet. In the two experimental periods, subjects were randomised to consume a strictly controlled diet and either 2·5 litres of Coca Cola® or semi-skimmed milk per day. The study was approved by the Municipal Ethics Committee for Copenhagen and Frederiksberg (KF 01-238/98).

Subjects

Subjects were healthy, Caucasian males aged 22–29 years, all university students. Smoking subjects or subjects who were physically active more than 10 h per week, had taken dietary supplements or donated blood within the past 3 months were excluded from the study. Physical examination included measurement of height and weight.

Diets

Subjects were given the same diet in the two intervention periods in addition to the 2·5 litres of cola or milk, and all foods and drinks were provided and served by the department. The basic diet consisted of ordinary Danish food items (Table 1). Two different lunch meals and three different dinner meals were served in the same order during the two intervention periods in the study; breakfast and snack meals were the same every day. The subjects were instructed to consume a minimum of 1·5 litres of the provided cola or milk in combination with meals. Mineral water was provided *ad libitum*. Energy content of individual diets was adjusted according to the height, weight and physical activity of each subject to 9–14 MJ/d. If subjects were hungry, the energy level was adjusted by adding bread equivalent to either 0·5 or 1·0 MJ from the second day of the first intervention period. The energy content of cola and semi-skimmed milk is the same and provided 4 MJ/d. Thus, individual energy intake was identical in the two periods, with total energy intake ranging from 13 to 18 MJ/d. To ensure compliance, the lunch meals were served at the institute on all weekdays, and researchers maintained daily contact with each subject when handing out the food and drinks for consumption at home. All subjects completed the two intervention periods. Self-recordings of daily mineral water consumption as well as cases of illness and use of medication were collected after each experimental period.

Analytical procedures

Blood was drawn from a vein puncture in the arm after an overnight fast between 08.00 and 09.30 hours in the morning on the first and after the last days of each experimental period. Serum was stored at −20°C until analysed. Serum IGF-I was determined by RIA[20]. Details regarding determination of IGF-I have been presented previously[1]. IGFBP-3 was determined by a RIA[21]. Reagents for the assay were obtained from Mediagnost GmbH (Tübingen, Germany). Details regarding the determination of IGFBP-3 have been presented previously[22]. We used the following equivalents for conversion: 1 ng/ml IGF-I = 0·130 nM IGF-I and 1 ng/ml IGFBP-3 = 0·036 nM IGFBP-3 in order to express the molar ratio of IGF-1:IGFBP-3. Serum insulin was determined with a solid-phase two-site fluoroimmunometric assay (AutoDELFIA, PerkinElmer, Turku, Finland) and serum glucose was determined spectrophotometrically at 340 nm (COBAS MIRA Plus, Roche Diagnostics System, Basel, Switzerland). Homeostasis model assessment index of insulin resistance and β-cell function[23] was calculated: insulin resistance = glucose × insulin/135, and β-cell function = $3\frac{1}{3} \times$ insulin/(glucose − 3·5), where glucose is in mmol/l and insulin is in pmol/l.

Statistical analysis

Statistical analyses were performed with Statistical Analysis System software package, version 9.1 (SAS Institute Inc., Cary, NC, USA). Data were controlled for homogeneity of variance, verified by residual plot, and the changes from baseline to end point were analysed by paired *t* test. Subject characteristics are presented as medians (range) and results are presented as least-square mean values with their standard errors of estimate.

A mixed model analysis was performed using the MIXED procedure (proc mixed). First, it was investigated whether baseline concentrations of the biochemical markers (IGF-I, IGFBP-3, IGF-I:IGFBP-3, insulin, glucose, insulin resistance and β-cell function) differed between the two periods using a mixed linear model, where the effect of treatment, period and their interaction were modelled as class variables and

Table 1. The basic diet used in both experimental periods consisted of ordinary low-Ca foods providing 9–14 MJ/d depending on the estimated energy requirement of the subjects

Breakfast	Carrot bread with butter and raspberry jam (10 d)
Lunch	Coarse-wheat-grained bread, butter, salami, roast beef and tomatoes (5 d) or Coarse-wheat-grained bread, butter, liver pâté, smoked turkey and cucumber (5 d)
Dinner	Pasta Bolognese (4 d) or Rice with goulash (3 d) or Risotto (3 d)
Snack	Apples, digestive biscuits, wine gum (10 d)

The meals were served in the same order in both intervention periods. The number of times the meal was served during a 10 d intervention period is listed in brackets. The department provided all foods and beverages, including mineral water.

subject as a random variable. Hereafter, the effect of treatment on end point concentrations was investigated using a mixed linear model. Denoting the *i*th observation (1,2,...,*n*), the effect of treatment (milk or cola) and period (1 or 2) and their interaction were modelled as a class variable, baseline level of the respective variable was included in the model as a covariate, resulting in the model:

$$Y_{ijk} = \alpha(\text{treatment}_{ij}) + \beta \times \text{baseline}_{ik} + \gamma(\text{period}_{ik}) + \nu(\text{treatment}_{ij} \times \text{period}_{ik}) + \eta(\text{subject}_i) + \varepsilon_{ijk},$$

where subject $\eta(\text{subject}_i)$ are independently distributed subject-specific random effects (approximately $N(0,\sigma_\eta^2)$) and ε_{ijk} are independently distributed random variables (approximately $N(0,\sigma^2)$). If there were no significant treatment by period interaction, the interaction of the model was omitted. $P<0{\cdot}05$ was considered statistically significant.

Results

No deviations from the study design were reported. Baseline anthropometrical and biochemical subject characteristics are presented in Table 2.

There were no differences between baseline concentrations for any of the biochemical end points, and as no treatment by period interactions were observed for any of the dependent variables, the interaction term of the model was omitted. The responses to 10 d intervention with 2·5 litres milk or cola, respectively, are shown in Table 3. Concentrations of IGF-I, IGFBP-3 and molar ratio of IGF-I:IGFBP-3 increased slightly after the intervention with milk, and decreased after the intervention with cola compared with baseline levels, but non-significantly. The concentrations of fasting insulin and glucose as well as insulin resistance and β-cell function were decreased after both interventions, with only the decreased fasting glucose concentration after cola intervention being significant ($P<0{\cdot}001$) resulting in a tendency towards decreased insulin resistance compared with baseline ($P=0{\cdot}062$).

The effect of treatment (milk *v.* cola) was significant only for IGF-I ($P=0{\cdot}05$; Table 3). No significant differences in changes between the two intervention periods were observed in serum concentrations of IGFBP-3, IGF-I:IGFBP-3, insulin, glucose, insulin resistance or β-cell function.

Table 2. Anthropometrical and biochemical characteristics of the subjects measured at baseline of the first experimental period

(Median values and ranges, *n* 11)

	Median	Range
Anthropometrical		
Age (years)	24	22–29
Height (m)	1·77	1·73–1·91
Weight (kg)	77·1	63·2–100·4
BMI (kg/m^2)	23·9	18·7–27·5
Biochemical		
IGF-I (ng/ml)	268	183–360
IGFBP-3 (ng/ml)	3201	2505–4457
Insulin (pmol/l)	23·2	11·4–51·5
Glucose (mmol/l)	4·67	4·25–5·33

IGF-I, insulin-like growth factor I; IGFBP-3, IGF-binding protein 3.

Discussion

The present short-term intervention study demonstrated that consumption of 2·5 litres cola per day for 10 d caused a decrease in circulating IGF-I and no changes in fasting insulin and insulin resistance in comparison with an equal amount of milk with the same energy content.

The strengths of the present study include the crossover study design that implies that each subject was his own control, since all subjects had both interventions in a randomised order. The diets were identical in the two intervention periods, and thus the only difference was the replacement of milk with cola. Also, the fully controlled diet caused the energy intake to be identical during both intervention periods, which excludes the possible effect of energy intake on circulating IGF-I[24].

However, the present study also has some limitations. We have no knowledge of the habitual intake of neither milk nor cola of the subjects. Therefore, the effect on IGF-I might be from a decrease in milk intake in the cola period rather than an effect of an increased cola intake. The amount of soft drinks varies a great deal among individuals, and the 2·5 litres of cola consumed in the present study is an extreme amount, but may reflect intakes seen in a small percentage of the population, since high intakes of cola have been reported previously[16,18]. Also, 2·5 litres of milk per day is a large quantity of milk, which does not reflect the intake in the general population, although milk consumption is high in Denmark and other Nordic countries, and a daily milk intake of approximately 500 ml is common in Denmark in men of this age group[25]. As only little research has been conducted in this area, we chose to study the extremes as we only intervened for a short period of time.

Cola contains caffeine, which has been observed both to contribute[26] and to improve[27,28] insulin resistance and type 2 diabetes. In the present study, we observed a tendency towards decreased insulin resistance in the cola period ($P=0{\cdot}062$). Also, protein intake differed between the two intervention periods, in that 20 % of energy derived from protein in the milk period, whereas only 9 % of the energy was protein derived in the cola period. This may have contributed to the observed effect on IGF-I, since dietary protein is associated with circulating IGF-I[29].

Also, the intervention periods lasted only for 10 d, and thus no long-term conclusions on cola or milk in relation to glucose–insulin metabolism can be made, since adaptation might occur over a period longer than 10 d. Young men were chosen for this intervention in order to obtain a homogenous study population and to avoid the possibility for the menstrual cycle to affect the results if women were included. Also, bones of males cease to grow at a later stage, thus the bone metabolism of young males would resemble that of children more so than bone metabolism in young women. However, it should be noted that the sexes have different levels of circulating IGF-I, and thus different results may be obtained if a different study population was used.

We have previously shown that in 8-year-old boys, a 1-week intervention with 1·5 litres of skimmed milk increased circulating IGF-I by 19 %, IGF-I:IGFBP-3 by 13 %[10], fasting insulin by 101 % and insulin resistance by 75 % ($P<0{\cdot}01$ for all)[11] with no significant changes after 1 week with a high meat intake with the same amount of animal protein.

Table 3. Responses to 10 d intervention with 2·5 litres milk or cola, respectively, in young men on a basic diet (*n* 11) (Least square mean values and standard errors of estimate)

	Baseline		After 10 d			
Parameter and treatment	Mean	SEE	Mean	SEE	Paired *t* test, *P**	Treatment, *P*†
IGF-I (ng/ml)						
Milk	287·9	19·15	304·8	13·25	0·254	0·049
Cola	295·0	19·15	270·4	13·25	0·074	
IGFBP-3 (ng/ml)						
Milk	3257	131	3348	91·1	0·482	0·191
Cola	3290	131	3168	91·1	0·234	
IGF-I:IFGBP-3‡						
Milk	0·317	0·014	0·335	0·013	0·245	0·159
Cola	0·324	0·014	0·306	0·013	0·256	
Insulin (pmol/l)						
Milk	26·58	4·48	22·71	2·70	0·439	0·535
Cola	30·12	4·48	24·34	2·70	0·145	
Glucose (mmol/l)						
Milk	4·64	0·09	4·56	0·06	0·115	0·199
Cola	4·87	0·09	4·46	0·06	$<$0·0001	
Insulin resistance§						
Milk	0·92	0·17	0·78	0·09	0·338	0·688
Cola	1·10	0·17	0·81	0·09	0·062	
β-Cell function¶						
Milk	81·14	13·4	74·37	9·83	0·784	0·832
Cola	72·28	13·4	71·83	9·83	0·438	

IGF-I, insulin-like growth factor I; IGFBP-3, IGF-binding protein 3.
* Level of significance between baseline and after 10 d of intervention with adjustment for period.
† Level of significance for difference between response in cola and milk periods.
‡ Molar ratio.
§ Homeostasis model assessment: glucose (mmol/l) × insulin (pmol/l)/135[23].
¶ Homeostasis model assessment: $3\frac{1}{3}$ × insulin (pmol/l)/(glucose (mmol/l) − 3·5)[23].

High levels of IGF-I are associated more or less with non-communicable diseases such as various cancer forms[3–8], whereas low levels of IGF-I are associated with CVD and type 2 diabetes[30–32], osteoporosis[32] and cognitive decline[33,34].

In the study with pre-pubertal boys, the intake of total and animal proteins was identical in the two intervention groups, whereas in the present study the protein intake was higher during the milk intervention than during the cola intervention. However, in the study with the boys, the energy intake was higher in the milk group than the meat group, whereas in the present study, the energy intake was identical during the two intervention periods. Also, the milk intake in the boys was equivalent to 51 ml milk per kg body weight, whereas in the adult men it was 32 ml/kg. Although we cannot exclude that these differences might contribute to the different findings in the two studies, it is likely that the growth factors IGF-I and insulin, and therefore also the IGF-system and the glucose–insulin metabolism, are stimulated differently by milk in children during growth than that in adults, whose growth has ceased. Since a high milk intake did not increase fasting insulin and insulin resistance in adult men, it is likely that the potentially worrying finding that increased milk intake elevated fasting insulin in children might be contributed to the fact that insulin acts as a growth factor in infants and children.

In conclusion, in comparison with an equal amount of milk with the same energy content, consumption of 2·5 litres cola per day for 10 d caused a decrease in circulating IGF-I. There was no significant effect of milk on IGF-I, IGFBP-3, insulin, glucose, insulin resistance or β-cell function. This is in contrast to what is observed in children. Therefore, it is likely that the nutritional regulation of the growth factors IGF-I and insulin are regulated differently in children during linear growth and in adults after cessation of linear growth. It is unknown whether the effect on IGF-I is caused by an increased cola intake or a decreased milk intake, and whether this effect is a transient phenomenon or if it has long-term consequences.

Acknowledgements

We are grateful to H. Jensen, H. L. Petersen, K. Ebbesen, B. Hoielt, K. H. B. Larsen and K. G. Rossen for their help with the study. We would like to thank Dr Med Sci A Juul for being responsible for all IGF-I and IGFBP-3 measurements. Also, we thank Arla Foods for sponsoring the milk. The authors (C. M., M. K., M. B. and J. K.) were involved in the design of the study and were responsible for the collection of data (M. K., M. B. and J. K.). C. H. was responsible for the analysis of data and writing of the manuscript. All authors participated in the discussion of the results and revision of the manuscript. None of the authors have any financial or personal interest in Arla Foods.

References

1. Juul A, Bang P, Hertel NT, *et al.* (1994) Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *J Clin Endocrinol Metab* **78**, 744–752.

2. Andrade Olivie MA, Garcia-Mayor RV, Gonzalez LD, *et al.* (1995) Serum insulin-like growth factor (IGF) binding protein-3 and IGF-I levels during childhood and adolescence. A cross-sectional study. *Pediatr Res* **38**, 149–155.
3. Chan JM, Stampfer MJ, Giovannucci E, *et al.* (1998) Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* **279**, 563–566.
4. Ma J, Pollak MN, Giovannucci E, *et al.* (1999) Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst* **91**, 620–625.
5. Hankinson SE, Willett WC, Colditz GA, *et al.* (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* **351**, 1393–1396.
6. Giovannucci E, Pollak MN, Platz E, *et al.* (2000) A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers Prev* **9**, 345–349.
7. Brand-Miller JC, Liu V, Petocz P, *et al.* (2005) The glycemic index of foods influences postprandial insulin-like growth factor-binding protein responses in lean young subjects. *Am J Clin Nutr* **82**, 350–354.
8. Juul A, Scheike T, Davidsen M, *et al.* (2002) Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case-control study. *Circulation* **106**, 939–944.
9. Isley WL, Underwood LE & Clemmons DR (1983) Dietary components that regulate serum somatomedin-C concentrations in humans. *J Clin Invest* **71**, 175–182.
10. Hoppe C, Mølgaard C, Juul A, *et al.* (2004) High intakes of skimmed milk, but not meat, increase serum IGF-I and IGFBP-3 in eight-year-old boys. *Eur J Clin Nutr* **58**, 1211–1216.
11. Hoppe C, Mølgaard C, Vaag A, *et al.* (2005) High intakes of milk, but not meat, increase s-insulin and insulin resistance in 8-year-old boys. *Eur J Clin Nutr* **59**, 393–398.
12. Gunnell D, Oliver SE, Peters TJ, *et al.* (2003) Are diet-prostate cancer associations mediated by the IGF axis? A cross-sectional analysis of diet, IGF-I and IGFBP-3 in healthy middle-aged men. *Br J Cancer* **88**, 1682–1686.
13. Giovannucci E, Pollak M, Liu Y, *et al.* (2003) Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. *Cancer Epidemiol Biomarkers Prev* **12**, 84–89.
14. Ma J, Giovannucci E, Pollak M, *et al.* (2001) Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. *J Natl Cancer Inst* **93**, 1330–1336.
15. Holmes MD, Pollak MN, Willett WC, *et al.* (2002) Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. *Cancer Epidemiol Biomarkers Prev* **11**, 852–861.
16. Whiting SJ, Healey A, Psiuk S, *et al.* (2001) Relationship between carbonated and other low nutrient dense beverages and bone mineral content of adolescents. *Nutr Res* **21**, 1107–1115.
17. Mrdjenovic G & Levitsky DA (2003) Nutritional and energetic consequences of sweetened drink consumption in 6- to 13-year-old children. *J Pediatr* **142**, 604–610.
18. Harnack L, Stang J & Story M (1999) Soft drink consumption among US children and adolescents: nutritional consequences. *J Am Diet Assoc* **99**, 436–441.
19. Kristensen M, Jensen M, Kudsk J, *et al.* (2005) Short-term effects on bone turnover of replacing milk with cola beverages: a 10-day interventional study in young men. *Osteoporos Int* **16**, 1803–1808.
20. Bang P, Eriksson U, Sara V, *et al.* (1991) Comparison of acid ethanol extraction and acid gel filtration prior to IGF-I and IGF-II radioimmunoassays: improvement of determinations in acid ethanol extracts by the use of truncated IGF-I as radioligand. *Acta Endocrinol (Copenh)* **124**, 620–629.
21. Blum WF, Ranke MB, Kietzmann K, *et al.* (1990) A specific radioimmunoassay for the growth hormone (GH)-dependent somatomedin-binding protein: its use for diagnosis of GH deficiency. *J Clin Endocrinol Metab* **70**, 1292–1298.
22. Juul A, Dalgaard P, Blum WF, *et al.* (1995) Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the relation to IGF-I, IGF-II, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. *J Clin Endocrinol Metab* **80**, 2534–2542.
23. Matthews DR, Hosker JP, Rudenski AS, *et al.* (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419.
24. Isley WL, Underwood LE & Clemmons DR (1984) Changes in plasma somatomedin-C in response to ingestion of diets with variable protein and energy content. *J Parenter Enteral Nutr* **8**, 407–411.
25. Andersen NL, Fagt S, Groth MV, *et al.* (1996) Publication no. 235. *Dietary Habits in Denmark Main Results*. Soborg: National Food Agency.
26. Petrie HJ, Chown SE, Belfie LM, *et al.* (2004) Caffeine ingestion increases the insulin response to an oral-glucose-tolerance test in obese men before and after weight loss. *Am J Clin Nutr* **80**, 22–28.
27. Moisey LL, Kacker S, Bickerton AC, *et al.* (2008) Caffeinated coffee consumption impairs blood glucose homeostasis in response to high and low glycemic index meals in healthy men. *Am J Clin Nutr* **87**, 1254–1261.
28. Tunnicliffe JM & Shearer J (2008) Coffee, glucose homeostasis, and insulin resistance: physiological mechanisms and mediators. *Appl Physiol Nutr Metab* **33**, 1290–1300.
29. Hoppe C, Udam TR, Lauritzen L, *et al.* (2004) Animal protein intake, serum insulin-like growth factor I, and growth in healthy 2·5-y-old Danish children. *Am J Clin Nutr* **80**, 447–452.
30. Ezzat VA, Duncan ER, Wheatcroft SB, *et al.* (2008) The role of IGF-I and its binding proteins in the development of type 2 diabetes and cardiovascular disease. *Diabetes Obes Metab* **10**, 198–211.
31. Janssen JA & Lamberts SW (2002) The role of IGF-I in the development of cardiovascular disease in type 2 diabetes mellitus: is prevention possible? *Eur J Endocrinol* **146**, 467–477.
32. Jehle PM, Schulten K, Schulz W, *et al.* (2003) Serum levels of insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-1 to -6 and their relationship to bone metabolism in osteoporosis patients. *Eur J Intern Med* **14**, 32–38.
33. Okereke O, Kang JH, Ma J, *et al.* (2007) Plasma IGF-I levels and cognitive performance in older women. *Neurobiol Aging* **28**, 135–142.
34. Dik MG, Pluijm SM, Jonker C, *et al.* (2003) Insulin-like growth factor I (IGF-I) and cognitive decline in older persons. *Neurobiol Aging* **24**, 573–581.

British Journal of Nutrition