Acta Diabetol (2013) 50:713–719
DOI 10.1007/s00592-012-0385-2

ORIGINAL ARTICLE

High meat consumption is associated with type 1 diabetes mellitus in a Sardinian case–control study

Sandro Muntoni · Roberto Mereu · Luigi Atzori · Alessandra Mereu · Sabrina Galassi · Stefania Corda · Paola Frongia · Efisio Angius · Paolo Pusceddu · Paolo Contu · Francesco Cucca · Mauro Congia · Sergio Muntoni

Received: 17 January 2012 / Accepted: 21 February 2012 / Published online: 4 March 2012

Abstract The large worldwide variation in type 1 diabetes incidence and increasing incidence over time points toward important environmental risk factors. Among them, nutrition plays an important role. The objective was to investigate the relationship between type 1 diabetes and nutritional factors in pregnancy and early in life. We carried out, using semi-quantitative food frequency questionnaires, a retrospective case–control study in 298 children of 0–15 years old, 145 of which were affected by type 1 diabetes. The diet of all children and of their mothers during pregnancy and lactation was assessed. In children, a statistically significant dose–response association between type 1 diabetes and the amount of meat consumption was found while no other nutritional factors were associated with the disease. High meat consumption seems to be an important early in life cofactor for type 1 diabetes development, although these findings need to be confirmed in wider prospective follow-up studies.

Keywords Meat · Insulin-dependent diabetes mellitus · Sardinia · Increasing incidence

Communicated by Antonio Secchi.

S. Muntoni (✉) · R. Mereu · L. Atzori
Unit of Oncology and Molecular Pathology,
Department of Toxicology, University of Cagliari,
Via Porcell 4, 09124 Cagliari, Italy
e-mail: smuntoni@unica.it

S. Muntoni · S. Galassi · S. Corda · S. Muntoni
Centre for Metabolic Diseases and Atherosclerosis,
The ME.DI.CO. Association, Cagliari, Italy

A. Mereu · P. Contu
Department of Public Health, University of Cagliari,
Cagliari, Italy

P. Frongia · E. Angius · P. Pusceddu
Division of Paediatrics, S. Michele Hospital, Cagliari, Italy

F. Cucca
Department of Biomedical Sciences, University of Sassari,
Sassari, Italy

M. Congia
Department of Biomedical Science and Biotechnologies,
University of Cagliari, Cagliari, Italy

Introduction

Type 1 diabetes mellitus (T1D) results from an organ-specific, T-cell-mediated autoimmune destruction of the pancreatic β-cells [1–4], while α- and δ-cells are spared [5], as a consequence of genetic [6–8] and environmental [9, 10] factors.

The worldwide variation in the incidence (per 100,000 per year) of T1D children under 15 years of age is very large: the overall age-adjusted incidence rates in the 90s varied from 0.1 per 100,000 in Zunyi (China) and Caracas (Venezuela) to 36.8 per 100,000 in Sardinia (Italy) and 36.5 per 100,000 in Finland, representing a more than 350-fold variation among 100 populations worldwide [11, 12].

Environmental factors act on the genetic proneness as inducers or triggers [13, 14], so contributing to the frequency of T1D [15, 16]. The polygenic nature of T1D susceptibility [17, 18] and its interaction with environmental factors has been deeply studied [9, 19–23], while the role of childhood vaccinations is still a controversial matter [24]. Each of these factors (viral infections, toxins, nutrition) may not be sufficient to produce diabetes when present alone, but sometimes needs a sequential insult to

β-cells, such as viral infections plus nutrition [25]. Epidemiological studies in about 40 countries in the world have shown that nutrition may influence T1D risk both transversally (differences among countries) [22] and longitudinally (increasing incidence in the same country) [26].

Nutritional factors may affect the risk of T1D both during pregnancy and early in life. Association between maternal nutrition and increased risk of T1D in the offspring has been suggested for maternal nitrite intake [27], while vitamin D supplementation during pregnancy might have a protective effect [28]. Use of cod-liver oil or other vitamin D supplements was not associated with T1D in children of Norwegian pregnant women [29]. However, no associations between maternal intake of antioxidant vitamins or minerals (retinol, β-carotene, vitamin C, vitamin E, selenium, zinc, manganese) during pregnancy and the development of advanced beta-cell autoimmunity in the offspring among the DIPP study subjects were found [30].

Although numerous studies have been performed to investigate the role of childhood diet in T1D, the results have been contradictory. Breastfeeding, nicotinamide (vitamin B3), zinc and vitamins C, D and E have been reported as possibly protecting against T1D, whereas N-nitroso compounds, early exposure to cows' milk and wheat, increased weight gain, and obesity may increase the risk [31]. High serum concentrations of vitamin E did not protect against advanced beta-cell autoimmunity in the DIPP study children [30], while consumption of cod-liver oil [29] and intake of total omega-3 fatty acids [32] have been associated with a reduced risk of islet cell autoimmunity. Moreover, it has been suggested that dietary protein sources other than milk (wheat, soy) may also affect the pathogenesis of T1D in susceptible individuals [33]. Finally, the reduction in an early exposure to complex dietary proteins may reduce the risk of beta-cell autoimmunity and type 1 diabetes in children with genetic susceptibility [34].

The main objective of the present study was to investigate possible relationships between nutrition during pregnancy, infancy and in childhood and T1D risk in the Sardinian population.

Methods

Subjects

A case–control study was carried out during years 2010–2011. The entire sample was collected from the Paediatric Department, Brotzu Hospital, Cagliari, Italy and consisted of 298 Sardinian children of 0–15 years old, of which 145 were new T1D diagnosis following the American Diabetes Association guidelines [35], while 153 were used as controls. These latter were admitted to the hospital mainly for respiratory viral infections, while celiac disease or other conditions capable of interfering with child's diet were excluded. Mothers of all children were also enrolled and gave their informed consent to the study. In 22 T1D and 26 controls, the questionnaires concerning child's diet were not included in the analysis because not fully completed. Thus, for statistical analysis, we considered a sample of 250 children of 3–15 years old, of which 123 were affected by T1D and 127 were controls. Table 1 summarizes the main clinical features of the population analyzed.

Questionnaires

Two different semi-quantitative food frequency questionnaires (FFQ) were administered: the first one was related to anagraphic, anthropometric data of mother's child, pathological history and diet of the mother during pregnancy and lactation; the second one concerned diet starting from the first month of life, including breastfeeding, weaning and vaccinations, until the age when the questionnaire was administered. For the purposes of this study, breastfeeding meant a child that received exclusive breast milk from the mother for at least 3 months. This kind of questionnaires, previously validated in different studies [36], were derived from the National Research Council and the ATS-Sardegna Project [37]. A caveat of FFQ analysis consists in the fact that it provides only a gross estimate of nutrient consumption giving a synthetic picture of dietary intake in which no information on portion size and component nutrients can be precisely established [38]. However, it is the only feasible option for studying very large samples in which resource-consuming and time may limit the study.

Dietary habits were estimated from FFQ information on different food items (Table 2). For each one, the mother had to select one of the following five options: every day; 4–5

Table 1 Main clinical characteristics of the population analyzed

	T1D	Controls
Number	123	127
Mean age	9.4	7.4
Males	60	74
Females	63	53
Mean age of mothers at delivery	29.08	29.78
Pre-pregnancy BMI	22.48	22.51
Mean weight at birth (kg)	3.20	3.18
Mean duration (months) of breastfeeding	9.02	8.82
Mean age at T1D onset	6.26	–
Mean time (years) between weaning and interview	8.63	7.24

Table 2 List of the food items analyzed

Potatoes	Vegetables
Legumes	Vegetables
Greengroceries	Vegetables
Greens	Vegetables
Meat	Meat
Homogenized meat	Meat
Ham	Meat
Salami	Meat
Eggs	Meat
Oil	Lipids
Butter	Lipids
Margarin	Lipids
Fruit	Fruit
Homogenized fruit	Fruit
Juices	Fruit
Orangeade	Fruit
Fish	Fish
Homogenized fish	Fish
Shellfishes	Fish
Crustaceans	Fish
Whole milk	Dairy products
Skim milk	Dairy products
Yogurt	Dairy products
Skim yogurt	Dairy products
Cheese	Dairy products
Ricotta	Dairy products
Chocolate	Chocolate
Bread	Cereals
Pasta	Cereals
Pizza	Cereals
Rice	Cereals
Corn	Cereals
Polenta	Cereals
Cakes	Carbohydrates
Sugar	Carbohydrates
Honey	Carbohydrates
Coffee	Beverages
Tea	Beverages
Coke	Beverages
Beer	Alcohol
Wine	Alcohol
Spirits	Alcohol

times a week; 1–3 times a week; 1–3 times a month; and rarely or never. All questionnaires were administered by the same doctor in postgraduate training and never filled in by mothers. No information on portion size was collected.

The different food items were grouped in food categories, like cereals, meat, fruit, vegetables, seasonings, drinks and other foods (Table 2).

Statistics

In order to investigate the relationship between food categories and T1D, a multivariate logistic regression was performed. T1D was the dependent variable; gender, breastfeeding, child food item consumption during and after the first 2 years of life, consumptions of the mother during pregnancy and lactation were the independent variables. The second order interactions between the independent variables were also included in the model. The logistic regression analysis was performed through a backward procedure based on eliminating at each step the least significant interaction and independent variables.

The results are reported indicating the Odds Ratio, CI 95% and the p value for each variable.

A first logistic regression was calculated using SPSS software. On the basis of the results, a second logistic regression model was used to analyze the association between diabetes and different levels of meat consumption during and after the first 2 years of life: low level (frequency of food consumption never or 1–3 times a week); middle level (frequency of food consumption 4–5 times a week); and high level (frequency of food consumption every day).

Results

No difference was found for newborn weight at delivery, for duration of breastfeeding, for children's mean age and for the time between weaning and interview as well as for gender, pre-pregnancy mother's BMI and for mean age of mothers during pregnancy and at delivery (Table 1).

No differences in completing the mandatory vaccination schedule between the two groups were found. As far as the food item consumption is concerned, the results of the first logistic regression showed that only child meat consumption during and after the first 2 years of life was significant. In fact, a statistically significant association was found between diabetes and meat consumption during and after the first 2 years of life (Table 3), while no other different food categories resulted to be associated with diabetes (data not shown).

The variables such as breastfeeding ($p = 0.232$; OR = 0.537; 95% CI = 0.193–1.489), meat consumption of the mother during pregnancy and lactation ($p = 0.059$; OR = 0.318; 95% CI = 0.097–1.043) and the other different food categories did not show a statistical significance. It is interesting to note that a trend toward significance ($p = 0.059$) was found for the category of meat consumption during pregnancy and lactation.

A statistically significant dose–response relationship ($p < 0.0001$) between the frequency of meat consumption more pronounced during the first 2 years of child's life but

Table 3 Meat consumption during and after the first 2 years of life in children affected by T1D and in controls

Meat consumption	Low 1–3 times a month	Middle 1–3 times a week	High 4–5 times a week	Every day
Meat consumption in the first 2 years of life				
Controls	0	48	40	39
T1D	2	2	34	85
OR	26.15 (L vs. H)[a]		10.2 (L vs. M)[b]	18.07 (L vs. M + H)[c]
(CI)	8.80–77.6		3.33–31.19	6.2–52
p	<0.0001		<0.0001	<0.0001
Meat consumption after the first 2 years of life				
Controls	3	50	48	26
T1D	2	13	51	57
OR	7.74 (L vs. H)[a]		3.75 (L vs. M)[b]	5.15 (L vs. M + H)[c]
(CI)	3.70–16.19		1.87–7.52	2.70–9.82
p	<0.0001		<0.0001	<0.0001

[a] Low versus high

[b] Low versus middle

[c] Low versus middle + high

also present later and the probability of diabetes was also shown by the second logistic regression (Table 3).

Discussion

This case–control study suggests that meat consumption is associated with T1D in children especially during the first 2 years of life and also later in a dose–response manner (Table 3). The dose–response relationship between meat consumption and the risk of diabetes fosters the hypothesis of relationship between the determinant and the disease. In fact, in our analysis, the risk of developing the disease is related to the degree of exposure especially in the first 2 years of life (Table 3).

It is important to note that dietary data collected retrospectively may be one reason for inconsistency with previous studies as well with upcoming studies. In fact, a limitation of the study comes from the reported attenuation of association between diet and disease using FFQ [39] with retrospective approach [40].

Another possible caveat limiting the statistical power of our finding may be related to the small number of T1D patients (4 out of 123) in the low meat consumption category resulting in very wide 95% CI. Although no statistical difference was found for the mean time between weaning and interview in T1D and controls, a further limitation may derive from the food data collection since several mothers gave birth more than 10 years before the epoch of interview, challenging the acquisition of precise information about the mother's diet during pregnancy and the infant's diet during the first years of life. Also for school-aged children, the mother may not exactly remember the food items the children ate during school days.

Nevertheless, these findings are consistent with our previous ecological analyses showing a significant correlation between not only T1D worldwide incidence [22], but also worldwide increasing incidence [26], and meat consumption. The study of Dahlquist et al. [19] concluded that nutrients and food additives such as protein, carbohydrate and nitrosamine compounds may influence the risk of developing insulin-dependent diabetes in childhood. Also, the study of Virtanen et al. [41] pointed out that serum biomarkers of milk and ruminant meat fat consumption are directly associated, and linoleic acid is inversely associated with advanced beta-cell autoimmunity in children with HLA-conferred susceptibility to type I diabetes. Siemiatycki et al. [42] reported that in both univariate and multivariate analyses, there was high risk of T1D among children who had experienced selected stressful life events during the 12 months preceding the onset of T1D or who had exhibited symptoms of social or psychological dysfunction during that time.

On the other hand, previous prospective cohort studies in other populations did not show an association between maternal meat consumption and islet autoimmunity risk in the child [43, 44].

Differences in the study design, in questionnaires and in the statistical analysis may be responsible for slight discrepancies among these studies including our own. For instance, our study did not take into account stressful life events. On the other hand, in analogy with our findings, Dahlquist et al. and Virtanen et al. emphasize the importance of meat or proteins in T1D development.

The diabetogenic mechanism of high meat consumption and T1D is not yet known. One possibility is that some metabolites as amino acids are involved before appearance of autoimmunity [45, 46]. Another possibility rests on the strong insulinogenic response to the increase in plasma amino acids after consumption of meat, even if stripped of fat, with or without carbohydrates [47–49]. This response by pancreatic β-cells increases the risk of T1D because insulin is a β-cell-specific autoantigen [50, 51].

The fact that meat consumption during and after the first 2 years of life may be followed by T1D many years later is consistent with the variability of the rate of β-cell destruction that is rapid in some individuals and slow in others [35]. So, in the latter residual, β-cell function may be retained for many years before insulin dependence develops [35]. Therefore, a relationship between meat consumption and T1D contributing to worldwide variation in the incidence of the disease may be hypothesized. Also, the dramatic increase in T1D incidence in both low- and high-incidence populations over the past decades can be, at least in part, explained by the changes in meat consumption that increased dramatically in the second half of the past century, paralleling the increase in T1D incidence [26]. In the same period, the WHO Regional Office for Europe recorded a steady increase in the production of red meat and milk [26]. In addition, several epidemiological studies have shown that red and processed meat intake is also associated with risk of type 2 diabetes [52, 53]. A possible link between T1D and type 2 diabetes might involve the consumption of processed meats that contain nitrites and nitrates that can be converted to nitrosamines by interaction with amino compounds either in the stomach or within the food product. Nitrosamines have been found to be toxic to pancreatic beta cells and to increase the risk of type 1 and type 2 diabetes in animal studies and of T1D in some, but not all, epidemiological studies [52, 53].

High red and processed meat consumption is associated with several chronic conditions: ischemic heart disease [54, 55], stroke [56], colon cancer [57], breast cancer [58], type 2 diabetes [59, 60] and increases in total mortality [61].

Conclusions

This case–control study suggests that meat consumption is associated with T1D in particular in children during the first 2 years of life in a dose–response manner. However, these findings need to be confirmed in future prospective follow-up studies from pregnancy/birth and with a higher sample-size.

Although a global strategy for the prevention of non-communicable diseases is beyond the aims of the present study, a possible implication of our finding could be a reduction in meat consumption in the very early periods of life, especially in populations with genetic proneness to T1D such as Finns [62] and Sardinians [16, 63].

Acknowledgments This work was supported by grant from Fondazione Banco Di Sardegna Prot. 562/2011.1052.

Conflict of interest All authors declare no conflicts of interest.

References

1. Bettini M, Vignali DA (2011) T cell-driven initiation and propagation of autoimmune diabetes. Curr Opin Immunol 23:754–760
2. Ferraro A, Socci C, Stabilini A, Valle A, Monti P, Piemonti L et al (2011) Expansion of Th17 cells and functional defects in T regulatory cells are key features of the pancreatic lymph nodes in patients with type 1 diabetes. Diabetes 60:2903–2913
3. Matteucci E, Ghimenti M, Di Beo S, Giampietro O (2011) Altered proportions of naive, central memory and terminally differentiated central memory subsets among CD4+ and CD8+ T cells expressing CD26 in patients with type 1 diabetes. J Clin Immunol 31:977–984
4. Roep BO, Peakman M (2011) Diabetogenic T lymphocytes in human type 1 diabetes. Curr Opin Immunol 23:746–753
5. Heward J, Gough SC (1997) Genetic susceptibility to the development of autoimmune disease. Clin Sci (Lond) 93:479–491
6. Pociot F, Akolkar B, Concannon P, Erlich HA, Julier C, Morahan G et al (2010) Genetics of type 1 diabetes: what's next? Diabetes 59:1561–1571
7. Todd JA (1995) Genetic analysis of type 1 diabetes using whole genome approaches. Proc Natl Acad Sci U S A 92:8560–8565
8. Todd JA (2010) Etiology of type 1 diabetes. Immunity 32: 457–467
9. Akerblom HK, Knip M (1998) Putative environmental factors in type 1 diabetes. Diabetes Metab Rev 14:31–67
10. Akerblom HK, Vaarala O, Hyoty H, Ilonen J, Knip M (2002) Environmental factors in the etiology of type 1 diabetes. Am J Med Genet 115:18–29
11. Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J (2000) Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. Diabetes Care 23:1516–1526
12. Soltesz G, Patterson CC, Dahlquist G (2007) Worldwide childhood type 1 diabetes incidence—what can we learn from epidemiology? Pediatr Diabetes 8(Suppl 6):6–14
13. Karvonen M, Jantti V, Muntoni S, Stabilini M, Stabilini L, Tuomilehto J (1998) Comparison of the seasonal pattern in the clinical onset of IDDM in Finland and Sardinia. Diabetes Care 21:1101–1109
14. Muntoni S, Karvonen M, Tuomilehto J (2002) Seasonality of birth in patients with type 1 diabetes. Lancet 359:1246 author reply 1247–1248
15. Muntoni S (1997) Genetic versus environmental factors in insulin-dependent diabetes mellitus. Lancet 349:1626
16. Muntoni S, Fonte MT, Stoduto S, Marietti G, Bizzarri C, Crino A et al (1997) Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy. Lancet 349:160–162
17. Davies JL, Kawaguchi Y, Bennett ST, Copeman JB, Cordell HJ, Pritchard LE et al (1994) A genome-wide search for human type 1 diabetes susceptibility genes. Nature 371:130–136

18. Ronningen KS, Keiding N, Green A (2001) Correlations between the incidence of childhood-onset type I diabetes in Europe and HLA genotypes. Diabetologia 44(Suppl 3):B51–B59
19. Dahlquist GG, Blom LG, Persson LA, Sandstrom AI, Wall SG (1990) Dietary factors and the risk of developing insulin dependent diabetes in childhood. BMJ 300:1302–1306
20. Hyoty H, Taylor KW (2002) The role of viruses in human diabetes. Diabetologia 45:1353–1361
21. Moya-Suri V, Schlosser M, Zimmermann K, Rjasanowski I, Gurtler L, Mentel R (2005) Enterovirus RNA sequences in sera of schoolchildren in the general population and their association with type 1-diabetes-associated autoantibodies. J Med Microbiol 54:879–883
22. Muntoni S, Cocco P, Aru G, Cucca F (2000) Nutritional factors and worldwide incidence of childhood type 1 diabetes. Am J Clin Nutr 71:1525–1529
23. Tracy S, Drescher KM, Chapman NM (2011) Enteroviruses and type 1 diabetes. Diabetes Metab Res Rev 27:820–823
24. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M (2004) Childhood vaccination and type 1 diabetes. N Engl J Med 350:1398–1404
25. Vaarala O, Klemetti P, Juhela S, Simell O, Hyoty H, Ilonen J (2002) Effect of coincident enterovirus infection and cows' milk exposure on immunisation to insulin in early infancy. Diabetologia 45:531–534
26. Muntoni S (2006) Epidemiological association between some dietary habits and the increasing incidence of type 1 diabetes worldwide. Ann Nutr Metab 50:11–19
27. Virtanen SM, Jaakkola L, Rasanen L, Ylonen K, Aro A, Lounamaa R et al (1994) Nitrate and nitrite intake and the risk for type 1 diabetes in Finnish children. Childhood Diabetes in Finland Study Group. Diabet Med 11:656–662
28. Brekke HK, Ludvigsson J (2007) Vitamin D supplementation and diabetes-related autoimmunity in the ABIS study. Pediatr Diabetes 8:11–14
29. Stene LC, Joner G (2003) Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr 78:1128–1134
30. Uusitalo L, Kenward MG, Virtanen SM, Uusitalo U, Nevalainen J, Niinisto S et al (2008) Intake of antioxidant vitamins and trace elements during pregnancy and risk of advanced beta cell autoimmunity in the child. Am J Clin Nutr 88:458–464
31. Virtanen SM, Knip M (2003) Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age. Am J Clin Nutr 78:1053–1067
32. Norris JM, Yin X, Lamb MM, Barriga K, Seifert J, Hoffman M et al (2007) Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA 298:1420–1428
33. Lefebvre DE, Powell KL, Strom A, Scott FW (2006) Dietary proteins as environmental modifiers of type 1 diabetes mellitus. Annu Rev Nutr 26:175–202
34. Knip M, Virtanen SM, Seppa K, Ilonen J, Savilahti E, Vaarala O et al (2010) Dietary intervention in infancy and later signs of beta-cell autoimmunity. N Engl J Med 363:1900–1908
35. (2009) Diagnosis and classification of diabetes mellitus. Diabetes Care 32(Suppl 1):S62–S67
36. Massari M, Freeman KM, Seccareccia F, Menotti A, Farchi G (2004) An index to measure the association between dietary patterns and coronary heart disease risk factors: findings from two Italian studies. Prev Med 39:841–847
37. Muntoni S, Stabilini L, Stabilini M (1999) Results of a five-year community-based programme for cardiovascular disease prevention: the ATS-Sardegna Campaign. Eur J Epidemiol 15:29–34
38. Riley MD, Blizzard L (1995) Comparative validity of a food frequency questionnaire for adults with IDDM. Diabetes Care 18:1249–1254
39. Brown D (2006) Do food frequency questionnaires have too many limitations? J Am Diet Assoc 106:1541–1542
40. Rhoads GG, Kurinij N (1988) Epidemiological studies in nutrition: utility and limitations. J Nutr 118:240–241
41. Virtanen SM, Niinisto S, Nevalainen J, Salminen I, Takkinen HM, Kaaria S et al (2010) Serum fatty acids and risk of advanced beta-cell autoimmunity: a nested case-control study among children with HLA-conferred susceptibility to type I diabetes. Eur J Clin Nutr 64:792–799
42. Siemiatycki J, Colle E, Campbell S, Dewar RA, Belmonte MM (1989) Case-control study of IDDM. Diabetes Care 12:209–216
43. Lamb MM, Myers MA, Barriga K, Zimmet PZ, Rewers M, Norris JM (2008) Maternal diet during pregnancy and islet autoimmunity in offspring. Pediatr Diabetes 9:135–141
44. Virtanen SM, Uusitalo L, Kenward MG, Nevalainen J, Uusitalo U, Kronberg-Kippila C et al (2011) Maternal food consumption during pregnancy and risk of advanced beta-cell autoimmunity in the offspring. Pediatr Diabetes 12:95–99
45. Bougneres P, Valleron AJ (2008) Causes of early-onset type 1 diabetes: toward data-driven environmental approaches. J Exp Med 205:2953–2957
46. Oresic M, Simell S, Sysi-Aho M, Nanto-Salonen K, Seppanen-Laakso T, Parikka V et al (2008) Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes. J Exp Med 205:2975–2984
47. Elliott RB, Martin JM (1984) Dietary protein: a trigger of insulin-dependent diabetes in the BB rat? Diabetologia 26:297–299
48. Floyd JC Jr, Fajans SS, Conn JW, Knopf RF, Rull J (1966) Insulin secretion in response to protein ingestion. J Clin Invest 45:1479–1486
49. van Loon LJ, Saris WH, Verhagen H, Wagenmakers AJ (2000) Plasma insulin responses after ingestion of different amino acid or protein mixtures with carbohydrate. Am J Clin Nutr 72:96–105
50. Nakayama M (2011) Insulin as a key autoantigen in the development of type 1 diabetes. Diabetes Metab Res Rev 27:773–777
51. Vafiadis P, Bennett ST, Todd JA, Nadeau J, Grabs R, Goodyer CG et al (1997) Insulin expression in human thymus is modulated by INS VNTR alleles at the IDDM2 locus. Nat Genet 15:289–292
52. Aune D, Ursin G, Veierod MB (2009) Meat consumption and the risk of type 2 diabetes: a systematic review and meta-analysis of cohort studies. Diabetologia 52:2277–2287
53. Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Willett WC et al (2011) Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. Am J Clin Nutr 94:1088–1096
54. Ascherio A, Willett WC, Rimm EB, Giovannucci EL, Stampfer MJ (1994) Dietary iron intake and risk of coronary disease among men. Circulation 89:969–974
55. Fraser GE (1988) Determinants of ischemic heart disease in Seventh-day Adventists: a review. Am J Clin Nutr 48:833–836
56. Knutsen SF (1994) Lifestyle and the use of health services. Am J Clin Nutr 59:1171S–1175S
57. Armstrong B, Doll R (1975) Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 15:617–631
58. Lubin JH, Burns PE, Blot WJ, Ziegler RG, Lees AW, Fraumeni JF Jr (1981) Dietary factors and breast cancer risk. Int J Cancer 28:685–689
59. Schulze MB, Manson JE, Willett WC, Hu FB (2003) Processed meat intake and incidence of type 2 diabetes in younger and middle-aged women. Diabetologia 46:1465–1473

60. Song Y, Manson JE, Buring JE, Liu S (2004) A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the women's health study. Diabetes Care 27: 2108–2115
61. Sinha R, Cross AJ, Graubard BI, Leitzmann MF, Schatzkin A (2009) Meat intake and mortality: a prospective study of over half a million people. Arch Intern Med 169:562–571
62. Tuomilehto J, Karvonen M, Pitkaniemi J, Virtala E, Kohtamaki K, Toivanen L et al (1999) Record-high incidence of type I (insulin-dependent) diabetes mellitus in Finnish children. The Finnish Childhood Type I Diabetes Registry Group. Diabetologia 42: 655–660
63. Muntoni S, Atzori L, Mereu R, Manca A, Satta G, Gentilini A et al (2009) Prevalence of diagnosed and undiagnosed diabetes mellitus and impaired fasting glucose in Sardinia. Acta Diabetol 46:227–231