Nutritional factors and worldwide incidence of childhood type 1 diabetes[1,2]

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ABSTRACT

Background: Some dietary factors have been associated with the risk of type 1 diabetes in childhood.
Objective: We investigated relations between dietary energy from major food groups and incidence of childhood type 1 diabetes by using an ecologic study design.
Design: We conducted univariate and multivariate regression analysis with incidence rates of type 1 diabetes in the late 1980s and early 1990s among children aged <15 y in 40 countries as the dependent variable and average per capita daily intake of major food items and other socioeconomic, demographic, and geographic risk factors as the independent variables.
Results: In the univariate regression model, per capita total energy intake was nonsignificantly associated with type 1 diabetes incidence ($r = 0.31$, NS), whereas energy from animal sources was associated ($r = 0.61$, $P < 0.01$) and energy from vegetal sources was inversely associated ($r = -0.35$, $P < 0.05$) with diabetes incidence. Among dietary items of animal origin, meat ($r = 0.55$, $P < 0.001$) and dairy products ($r = 0.80$, $P < 0.0001$) were predictors of elevated incidence rates, whereas among dietary items of vegetal origin, cereals ($r = -0.64$, $P < 0.001$) were inverse predictors. In the multivariate analysis, the inverse relation of diabetes incidence with energy from vegetables and the direct correlation with energy from animal sources explained the positive associations of type 1 diabetes incidence with geographic and socioeconomic covariates.
Conclusion: The incidence of type 1 diabetes varied worldwide according to dietary patterns. In-depth exploration of dietary risk factors during pregnancy and early neonatal life is warranted to confirm whether and to what extent diet cooperates with genetic susceptibility in the early onset of type 1 diabetes. *Am J Clin Nutr* 2000;71:1525–9.

KEY WORDS Cereals, energy intake, type 1 diabetes, meat, milk, nutrition, children

INTRODUCTION

There is increasing evidence that type 1 diabetes results from an interaction of a polygenic trait (1) with various environmental risk factors (2). Among the latter, an increase in type 1 diabetes risk has been associated with several nutrients and accompanying food additives or toxic agents (3, 4). A positive association between type 1 diabetes incidence and daily cow milk intake was reported in several countries (5, 6). Moreover, an ecologic analysis showed a positive correlation between nitrate concentrations in drinking water and type 1 diabetes risk (7). However, no clear evidence of a relation between the disease and solid food items has emerged from experimental animal or human studies (3, 8). We conducted an ecologic study of average daily amount and type of energy intake in relation to incidence of childhood type 1 diabetes.

SUBJECTS AND METHODS

Incidence rates of childhood (age of onset <15 y) type 1 diabetes in the late 1980s and early 1990s in 40 countries were derived from a published report of the World Health Organization DIAMOND Project Group (9). The countries for which information was available were the following: Algeria, Sudan, and Tanzania (Africa); Canada and the United States (North America); Cuba, Mexico, and Puerto Rico (Central America); Brazil, Chile, and Peru (South America); Israel, Japan, Kuwait, and Republic of Korea (Asia); Australia and New Zealand (Oceania); and Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Russia, Spain, Sweden, and the United Kingdom (Europe).

Publicly available resources were searched to obtain, for the years 1988–1990, worldwide country-specific information on percentage of urban residents, population density, average annual temperature, per capita gross domestic product (GDP), percentage employed in agriculture, and education expenses as a percentage of the GDP (10). Average per capita daily intake of total dietary energy, percentages of energy from food items of animal origin and of vegetal origin, and percentages of energy from selected dietary items, such as meat, dairy products (mainly

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TABLE 1
Univariate regression parameters of socioeconomic variables predicting incidence of childhood type 1 diabetes[1]

Covariate	n	Intercept	Regression coefficient	SE	r
Percentage of urban residents	39	3.12	0.089	0.062	0.22
Population density	40	9.31	−0.0003	0.002	0.02
Percentage employed in agriculture	40	11.65	−0.149	0.056	−0.40[2]
Expenses for education as a percentage of the GDP	35	−0.067	1.786	0.769	0.38[2]
Per capita GDP	37	3.338	0.552	0.144	0.54[3]
Average temperature	29	28.05	−0.325	0.102	−0.52[3]
Per capita energy intake	34	−7.158	5.247	2.832	0.31
Energy intake from animal food items	34	−1.343	12.002	4.386	0.61[3]
Energy intake from vegetal food items	34	30.802	−9.487	2.104	−0.35[2]

[1] GDP, gross domestic product.
[2] $P < 0.05$.
[3] $P < 0.01$.

milk), cereals, and fruit and vegetables were obtained from food balance sheets published by the Food and Agriculture Organization (FAO) for 1988–1990 (11). Data from food balance sheets for 1979–1981 were also obtained (12).

We conducted univariate linear regression analyses with childhood type 1 diabetes incidence as the dependent variable and each of the country-specific socioeconomic, geographic, and dietary indicators as the independent variables. We then selected variables that were directly or inversely correlated with type 1 diabetes incidence in the univariate analysis to fit multiple regression models with the disease incidence rate as the outcome. Information was available for all covariates contributing to the multiple regression model for 34 countries. The significance of the slope associated with an independent variable was derived from the ratio of the corresponding regression coefficient to its SE, with $n - 2$ degrees of freedom in the univariate regression analysis and with $n - 1 - k$ degrees of freedom (where k is the number of covariates in the model) in the multivariate regression analysis (13).

RESULTS

Among the socioeconomic and geographic variables examined, average annual per capita GDP and annual state expenses for education as a percentage of the GDP were significantly correlated with the incidence rate of type 1 diabetes, whereas the percentage of the population employed in agriculture and average annual temperature were inversely correlated with diabetes incidence (**Table 1**). The percentage of urban residents and population density, which were shown previously to be associated with type 1 diabetes incidence (14), were not correlated with diabetes incidence in the present study.

Among nutritional factors, average daily per capita total energy intake was not a significant predictor of type 1 diabetes incidence. On the contrary, type 1 diabetes incidence was positively correlated with average daily per capita energy intake of food items of animal origin and inversely correlated with intake of food items of vegetal origin (Table 1). Among specific dietary items, expressed as a percentage of total energy intake, meat and dairy products showed a significant direct correlation with type 1 diabetes incidence, whereas cereals showed a significant inverse correlation (**Figure 1**). Intakes of fats, fruit and vegetables, and legumes were not correlated with diabetes incidence. These results were confirmed when the data were plotted as absolute amounts of energy intake from the specific dietary items, instead of as a percentage of total energy intake. The same analysis was repeated by using the FAO's 1979–1981 data (12) because we thought that diet 10 y earlier might better fit current incidence data. The above results were confirmed (data not shown).

To disentangle the effects of individual risk factors, we fitted multiple regression models with type 1 diabetes incidence rate as the outcome and per capita GDP, average annual temperature, and average daily energy intake from animal and vegetal food items as the independent covariates. Energy intake from animal food items, expressed either as an absolute value or as a percentage of total energy intake, explained the positive association of type 1 diabetes incidence with per capita GDP and the negative association with average annual temperature. When the regression model was fitted with both dietary covariates and only 1 of the 2 socioeconomic covariates, the opposite influence of the 2 main sources of dietary energy intake was statistically significant, but the association with the respective socioeconomic covariate was not (animal food, $P < 0.001$; vegetal food, $P < 0.05$; average temperature, NS; per capita GDP, NS). However, when we fitted the regression model with all 4 independent covariates (15), multicollinearity among the covariates reduced the strength of the association between the incidence rate of type 1 diabetes and the individual covariates. Therefore, because the effects of socioeconomic covariates were explained by the confounding effect of diet, we fitted a regression model with the 2 main sources of dietary energy, whose opposite influence was supported by statistical significance (animal food, $P < 0.001$; vegetal food, $P < 0.05$) (**Table 2**).

DISCUSSION

The interpretation of our results requires a preliminary discussion of the reliability of the information provided by the publicly available resources used. Age- and sex-adjusted incidence rates of childhood type 1 diabetes were taken from registries covering one or more areas within a country. This coverage was not always complete. When more than one source was available for the same country, the median incidence rate was taken because the dietary information in the food balance sheets referred to whole countries. This is a source of concern when interpreting our results. However, registries at the national level are rather uncommon, and the incidence rates we used are the only reasonable estimates available. Furthermore, caution is required when interpreting the
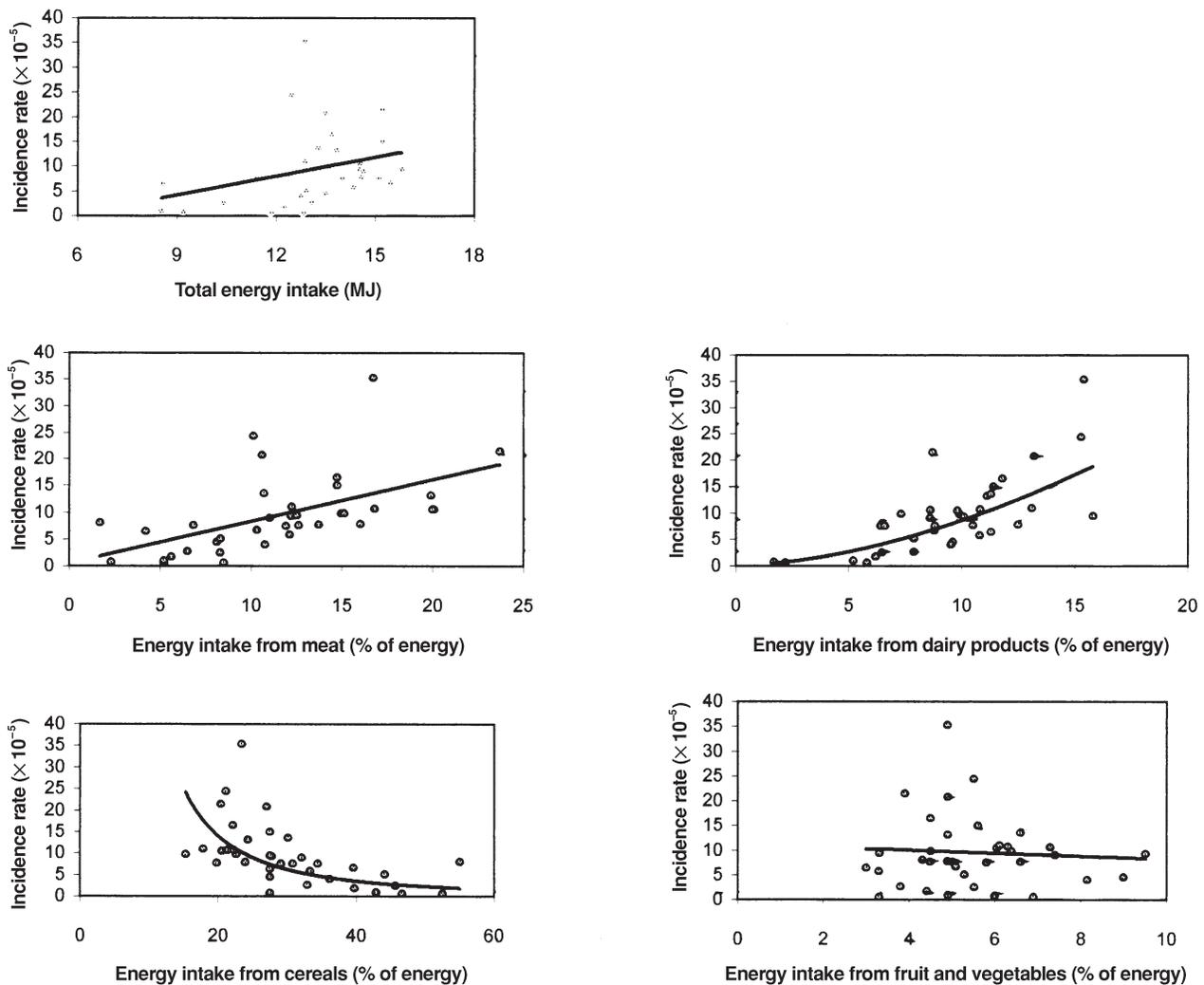
FIGURE 1. Scatter plots and regression lines of energy intake from selected dietary variables (1988–1990) predicting incidence of childhood type 1 diabetes ($n = 34$). For total energy, the incidence rate (IR) $= -7.16 + 1.26x$ ($r = 0.31$, NS). For meat, IR $= 0.45 + 0.78x$ ($r = 0.55$, $P < 0.001$). For dairy products, IR $= 0.16x^{1.73}$ ($r = 0.80$, $P < 0.0001$). For cereals, IR $= 6322.5x^{-2.04}$ ($r = -0.64$, $P < 0.001$). For fruit and vegetables, IR $= 11.17 - 0.32x$ ($r = 0.07$, NS).

results of ecologic studies because of the possible occurrence of the so-called ecological fallacy (16). Also, we cannot exclude a role of other unknown confounders. Nutritional data were derived from the FAO's food balance sheets, the only source of worldwide information on per capita food availability rather than intake. Therefore, food intake was expected to be overestimated in wealthy countries, where substantial amounts of food are presumably wasted. Nonetheless, FAO food balance sheets closely reflect major differences in food availability in different countries and over different time periods (17, 18). Also, food intake values in children do not differ significantly from those in adults (17), which is most relevant to the present study.

Overall, the results of the present ecologic study suggest an association between eating patterns and the incidence of childhood type 1 diabetes at the population level. Incidence of type 1 diabetes was directly correlated with average daily intake of energy of animal origin and inversely correlated with energy from vegetal food items. The lack of correlation with average

daily total energy intake in our study likely reflects the opposite influence of these 2 sources of energy. Among individual dietary items, average daily energy intake from dairy products and meat was directly associated with type 1 diabetes incidence, whereas average daily energy intake from cereals was inversely associated with diabetes incidence. The association of socioeconomic and geographic variables, such as per capita GDP and average annual temperature, with type 1 diabetes incidence rates in previous reports (14, 19) was largely explained by the influence of these variables on dietary habits. In fact, countries with higher per capita GDPs and lower average annual temperatures tended to have higher incidence rates. The dietary patterns in these countries featured a high energy intake from animal food items, both proportionally and as absolute values. Dietary patterns in countries with a lower per capita GDPs and higher average annual temperatures were the opposite.

Evidence is increasing that type 1 diabetes is initiated in early childhood (20) and that it may even be a congenital or perinatal

TABLE 2
Parameters of the multiple linear regression model predicting incidence of type 1 diabetes as a function of energy intake from animal or vegetal food items[1]

Covariate	Regression coefficient	SE	t	P
Intercept	16.483	8.861	-2.089	$0.10 > P > 0.05$
Energy intake from animal food items	11.358	2.620	4.336	< 0.001
Energy intake from vegetal food items	-7.639	3.640	-2.099	< 0.05

[1] $n = 34$ countries.

disease resulting in autoimmunity (21). The results of previous case-control (3) and epidemiologic (8) studies suggest that dietary exposure in early life is associated with risk of type 1 diabetes. It is plausible that amount and quality of energy intake in particular periods of life can influence the processes of β cell injury (22) and defense (23). We previously reported a direct association between cow milk intake and incidence of type 1 diabetes (6). In a Swedish case-control study, meat protein rather than fat was a risk factor for diabetes (3). A link between average per capita milk consumption and type 1 diabetes seems to be based on the induction of β cell autoimmunity through molecular mimicry of bovine serum albumin with ICA69 antigen (8).

In contrast, evidence from experimental animal and human studies suggests that a high protein intake, particularly of animal protein, is involved in type 1 diabetes pathogenesis (24). The underlying mechanism of this association is not clear. However, beef or chicken proteins have been shown to elicit a strong insulinogenic response in humans (25). Because insulin is a β cell–specific autoantigen (26), its augmented expression could increase the risk of developing type 1 diabetes. Consistent with this theory, hyperinsulinism following overnutrition early in life was shown to predispose to type 1 diabetes (27, 28). On the contrary, type 1 diabetes incidence is reportedly low in countries with low average protein intake (24) and among subjects born in periods of food shortage (27), when a greater proportion of daily energy intake is from food items of vegetal origin (29). Our results also lend credibility to the speculation that the increasing dietary supply of animal protein after World War II may have contributed to the reported increasing incidence of type 1 diabetes in wealthy European and non-European countries over the past several decades (27, 30).

The negative correlation between energy from vegetal food items and incidence of childhood type 1 diabetes may fit within the more general context of a lower prevalence of chronic diseases, including diabetes, among vegetarians than among nonvegetarians. This finding is also consistent with the requirement for lower insulin doses to control hyperglycemia in diabetic vegetarians than in diabetic nonvegetarians (31).

In conclusion, eating patterns at the population level appear to influence type 1 diabetes incidence. Further research is warranted to assess the mechanism by which nutrition interacts with genes and to explore the potential of appropriate dietary manipulations for type 1 diabetes prevention in genetically susceptible individuals, families, and populations. This would be of special interest for populations with a strong genetic tendency to the disease, such as Finns (9) and Sardinians (32, 33).

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