

- Trans Assoc Am Phys* 100:C305–15, 1987
6. Chazan JA, Boshell BR: Etiological factors in thiazide-induced or aggravated diabetes mellitus. *Diabetes* 14:132–36, 1965
 7. Chowdhury FR, Bleicher SJ: Chlorothalidone-induced hypokalemia and abnormal carbohydrate metabolism. *Horm Metab Res* 2:13–16, 1970

Cow's Milk Consumption and IDDM Incidence in Sardinia

Marked geographical differences in the incidence of insulin-dependent diabetes mellitus (IDDM), with a south-north gradient, have been reported in past years (1) and confirmed recently by the EURODIAB ACE Study (2). Sound evidence exists that IDDM incidence rates have been rising in several countries over the last decades (3). This phenomenon points to environmental factors capable of converting genetic susceptibility for IDDM into overt disease. Among these factors, cow's milk consumption early in life is associated with increased risk for IDDM in the following years (4). Moreover, positive correlation between cow's milk mean consumption per person and IDDM incidence in various countries has been described (5,6).

Sardinia, a large Mediterranean island with a geographically well-defined and ethnically homogeneous population (7), has been shown to have a very high (8) and rising (9,10) IDDM incidence rate, which is now 30.2 per 100,000/year. This is the second highest rate in Europe after Finland (2). Sardinia also has a very high (3.08%) prevalence of positive islet cell antibodies (ICA⁺) in schoolchildren, again the second highest after Finland (11). Here we report data on cow's milk consumption and IDDM incidence in Sardinia compared with a number of geo-

graphical areas to detect a possible correlation between the two variables. Data on IDDM incidence (per 100,000/year) in children 0–14 years of age in various European countries or regions and Israel in the 2-year period from 1989 to 1990 were derived from the EURODIAB ACE Study (2). Data on fluid cow's milk consumption per person/year between 1975 and 1990 in the same countries were obtained from the Italian National Institute of Statistics in Rome (12). Available data on both variables concerned 17 regions. For each region, the mean annual variation rate (%) over the 15-year period was calculated. In no region did this rate exceed $\pm 4.5\%$; in Sardinia the rate was 1.22%. Therefore, mean annual consumption over the 15-year period was used for statistical analysis.

IDDM incidence rates and cow's milk consumption in individual countries

fit a linear regression model with an r_2 of 0.44 (Table 1). In this model, Sardinia lies considerably far from the regression line, its actual IDDM incidence (30.2) being three times higher than the incidence predicted by milk consumption (10.35). Hence, this makes a good 19.85 residual, which is by far the highest one among the 17 regions considered. Therefore, in this study, Sardinia represents the most considerable exception to the association between the two variables, much the same as it does to the one between IDDM incidence and latitude (2,8).

Among the variables that can account for latitude-related, cross-country differences in IDDM risk, diet, temperature, cultural practices, viral infections, and genetic factors must be considered (1). In this regard, cow's milk consumption early in life has been implicated as a possible primer of the autoimmune re-

Table 1—Observed and predicted values of IDDM incidence according to cow's milk consumption in 17 populations

Region	Cow's milk consumption	IDDM incidence	Predicted IDDM incidence	Residuals
Portugal	62.0	7.5	7.56	-0.06
Greece	66.7	9.3	8.18	1.12
Sicily	69.1	10.1	8.5	1.6
Lazio	77.8	6.5	9.64	-3.14
Luxembourg	78.6	12.4	9.75	2.65
Lombardy	80.6	6.8	10.01	-3.21
Belgium	81.1	9.8	10.08	-0.28
Sardinia	83.2	30.2	10.35	19.85
France	86.3	7.8	10.76	-2.96
Israel	90.0	5.5	11.25	-5.75
Spain	104.9	10.6	13.21	-2.61
Netherlands	120.9	11	15.31	-4.31
U.K.	135.0	16.5	17.17	-0.67
Denmark	145.5	21.5	18.55	2.95
Austria	148.7	7.7	18.97	-11.27
Norway	222.1	20.8	28.63	-7.83
Finland	224.9	42.9	29	13.9

Variable	Parameter estimate	SE	T for H0: parameter = 0
Intercept	-0.596817	4.60097216	-0.13
Milk consumption	0.131589	0.03810263	3.454

Cow's milk consumption measured in liters per person/year. IDDM incidence per 100,000/year in those 0–14 years of age. $r^2 = 0.44$.

sponse that destroys pancreatic β -cells in concurrence with infectious events in genetically susceptible hosts, thus causing IDDM (4,13-18).

In the case of Sardinians, who are genetically different from other European populations including Italians (7), a genetic basis for IDDM susceptibility has been described (19,20). However, the rising IDDM incidence over the last decades (9,10) points also to environmental factors implicated in the etiology of the disease. Whereas cow's milk consumption appears to be an important candidate among such factors in most countries, this does not seem to be the case for Sardinia, where no more than one-third of actual IDDM incidence is accounted for by cow's milk consumption (Table 1).

In conclusion, although a possible triggering role for cow's milk in the pathogenesis of IDDM is not entirely ruled out, a strong role for some other still unidentified environmental factor(s), to which Sardinians with their peculiar genetic susceptibility are uniquely exposed, is definitely suggested by this study.

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References

1. LaPorte RE, Tajima N, Akerblom HK, Berlin N, Brosseau J, Christy M, Drash AL, Fishbein H, Green A, Hamman R, Harris M, King H, Laron Z, Neil A: Geographic differences in the risk of insulin-dependent diabetes mellitus: the importance of registries. *Diabetes Care* 8:101-107, 1985
2. Green A, Gale EAM, Patterson CC, the EURODIAB ACE Study Group: Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. *Lancet* 339:905-909, 1992
3. Bingley PJ, Gale EAM: Rising incidence of IDDM in Europe. *Diabetes Care* 12:289-95, 1989
4. Kostraba JN, Cruickshanks KJ, Lawler-Heavner J, Jobim LF, Rewers MJ, Gay EC, Chase HP, Klingensmith G, Hamman RF: Early exposure to cow's milk and solid foods in infancy, genetic predisposition, and risk of IDDM. *Diabetes* 42:288-95, 1993
5. Scott FW: Cow milk and insulin-dependent diabetes mellitus: is there a relationship? *Am J Clin Nutr* 51:489-91, 1990
6. Dahl-Jorgensen K, Joner G, Hanssen KF: Relationship between cow's milk consumption and incidence of IDDM in childhood. *Diabetes Care* 14:1081-83, 1991
7. Cavalli-Sforza LL, Piazza A: Human genomic diversity in Europe: a summary of recent research and prospects for the future. *Eur J Hum Genet* 1:3-18, 1993
8. Muntoni S, Songini M, Sardinian Collaborative Group for Epidemiology of IDDM: High incidence rate of IDDM in Sardinia. *Diabetes Care* 15:1317-22, 1992
9. Silveti M, Angius E, Pusceddu P, Chessa M, Dentoni F, Frongia P, Masile P, Borghero G, Dessi M, Mura C, Marinaro AM, Delitala G, Zuirrida G: Epidemiology of juvenile diabetes in Sardinia. *J Endocrinol Invest* 13 (Suppl. 3):83, 1990
10. Songini M, Loche M, Muntoni Sa, Stabile M, Coppola A, Dessi G, Green A, Bottazzo GF, Muntoni Se: Increasing prevalence of juvenile onset type I (insulin-dependent) diabetes mellitus in Sardinia: the military service approach. *Diabetologia* 36:547-52, 1993
11. Muntoni Sa, Loviselli A, Martino E, Veluzzi F, Shattock M, Balestrieri A, Songini M, Muntoni S, Bottazzo GF: High prevalence of islet cell antibodies (ICA) in healthy schoolchildren in Sardinia. *Diabetologia* 35 (Suppl. 1):32A, 1992
12. Istituto Nazionale di Statistica: Le regioni in cifre. In *Istat*. Rome, 1977-1992
13. Robinson BH, Dosh HM, Martin JM, Akerblom HK, Savilahti E, Knip M, Ilonen J: A model for the involvement of MHC class II proteins in the development of type I (insulin-dependent) diabetes mellitus in response to bovine serum albumin peptides. *Diabetologia* 36:364-68, 1993
14. Nepom GT: A unified hypothesis for the complex genetics of HLA associations with IDDM. *Diabetes* 35:1153-57, 1990
15. Sheehy MG: HLA and insulin-dependent diabetes: a protective perspective. *Diabetes* 41:123-29, 1992
16. Virtanen SM, Rasanen L, Aro A, Lindstrom J, Sippola H, Lounamaa R, Toivanen L, Tuomilehto J, Akerblom HK, Childhood Diabetes in Finland Study Group: Infant feeding in Finnish children 7 years of age with newly diagnosed IDDM. *Diabetes Care* 14:415-17, 1991
17. Karjalainen J, Martin JM, Knip M, Ilonen J, Robinson BH, Savilahti E, Akerblom HK, Dosh HM: A bovine albumin peptide as a possible trigger of insulin-dependent diabetes mellitus. *N Engl J Med* 327:302-307, 1992
18. Savilahti E, Saukkonen TT, Virtala ET, Tuomilehto J, Akerblom HK, The Childhood Diabetes in Finland Study Group: Increased levels of cow's milk and B-lactoglobulin antibodies in young children with newly diagnosed IDDM. *Diabetes Care* 16:984-89, 1993
19. Muntoni F, Congia M, Cucca F, Cossu P, Porcu S, Frau F, Arnone M, Songini M, Muntoni S, Cao A, Pirastu M: The HLA DQB1*0502 allele is neutrally associated with insulin-dependent diabetes mellitus in the Sardinian population. *Tissue Antigens* 39:262-65, 1992
20. Cucca F, Muntoni F, Lampis R, Frau F, Argiolas L, Silveti M, Angius E, Cao A, De Virgili S, Congia M: Combination of specific DRB1, DQA1, DQB1 haplotypes are associated with insulin-dependent diabetes mellitus in Sardinia. *Hum Immunol* 37:85-94, 1993

Adherence Consistency Across Treatment Regimens

Adherence to one or more aspects of prescribed treatment for one diagnosis does not predict adherence to treatment for a second diagnosis or even the same diagnosis. Research suggests