Rapid westernization of children's blood cholesterol in 3 countries: evidence for nutrient-gene interactions?[1–4]

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ABSTRACT The aim of this study was to examine potential factors that modify blood cholesterol among children in countries in which dietary and lifestyle habits are becoming westernized. Population data on serum total and lipoprotein cholesterol, anthropometric indexes, and dietary intake were reviewed and compared for children aged 1–18 y from Japan, Spain, and the United States. The data show that total serum cholesterol in Japanese and Spanish children recently exceeded the 75th percentile for US children, primarily reflecting LDL cholesterol, although both LDL and HDL cholesterol contributed. Adiposity indexes do not explain the trends observed. Total and saturated fat intakes increased substantially in both Japan and Spain but in Japan are still lower than intakes in the United States. The Hegsted equation was used to relate differences in serum cholesterol to dietary fat intake. Changes in total serum cholesterol followed established dietary correlations among children in Spain, but not in Japan. Serum cholesterol in Japanese children was predicted to be 0.20–0.32 mmol/L lower than in US children; actual concentrations were considerably higher. These results suggest that a rapid westernization of children's blood cholesterol concentrations has occurred in Japan and Spain. Changes in fat intake predict changes in blood cholesterol in Spain, but not in Japan. Differences in genetic response to diet in certain populations, such as the Japanese, may explain higher blood cholesterol concentrations with lower fat intakes compared with the United States. *Am J Clin Nutr* 2000;72(suppl):1266S–74S.

KEY WORDS Cholesterol, dietary fat, children, heart disease, Japan, Spain, Hegsted equation

INTRODUCTION

Organizations in the United States and Europe have established population guidelines aimed at reducing the risk of coronary artery disease (CAD) by initiating intervention during childhood and adolescence (1, 2). The rationale for this preventive approach is based on extensive evidence collected in both the United States and elsewhere that early lesions of coronary atherosclerosis begin in childhood (3–6) and are associated with serum cholesterol concentrations (5). Furthermore, higher serum cholesterol concentrations in children from different countries are associated with higher cholesterol concentrations in adults in the same country and with higher CAD mortality rates (1). Although blood cholesterol concentrations in US children have remained relatively stable over the past 2–3 decades (7, 8) and are accompanied by a decline in mortality from CAD in the United States (9), recent data, as will be summarized here, show that in Spain and Japan, children's blood cholesterol concentrations have increased rapidly to levels that now exceed those in US children. Given this increase in childhood blood cholesterol in populations who are rapidly undergoing westernization in lifestyles (10, 11), identification of potential factors modifying blood cholesterol concentrations among children would be important in designing effective intervention and prevention programs aimed at reducing CAD risk in populations and individuals.

In Japan today, cardiovascular disease is now the second leading cause of death (10). Autopsy studies in children showed that fatty arterial lesions begin in early life; in one study, all youths aged >11 y had lipid deposits of various degrees in the aorta (6, 12). Similarly, in Spain, the increased incidence of cardiovascular disease risk factors (13–15) has raised concern about the need to take preventive steps to reduce morbidity and mortality (16–18). Despite the increasing prevalence of risk factors, cardiovascular disease mortality in Spain has declined slowly at a rate of 1%/y from 1968 to 1987 (19), perhaps due in part to better health care. In Japan, CAD prevalence has increased over the past decades, as have correlated risk factors such as blood cholesterol concentrations and obesity (10).

In this review, we present current trends in serum cholesterol concentrations among children between the ages of 1 and 18 y in Japan and Spain compared with the United States. Dietary intake and anthropometric data were evaluated to determine whether changes in these factors contributed to rising serum cholesterol concentrations. Additionally, a prediction equation derived in the

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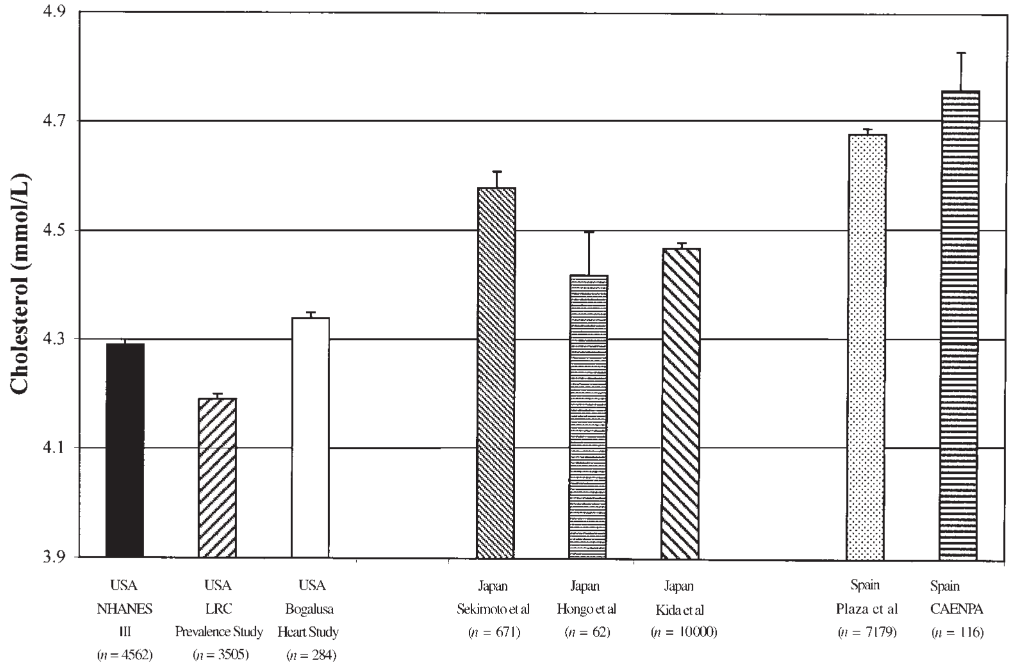

FIGURE 1. Mean (±SE) serum cholesterol concentrations of children < 10 y of age as reported in population studies conducted between 1974 and 1992 in the United States (7, 22, 23), Japan (24, 25, 26), and Spain (27, 28). Mean cholesterol concentrations of children from Japan and Spain were notably higher than those of American children of the same age. NHANES, National Health and Nutrition Examination Study; LRC, Lipid Research Clinics; CAENPE, Consumo de alimentos y nutrientes por edades y sexo en escolares de la Communidad de Madrid (Nutrient and food consumption by age and gender in school children from the community of Madrid).

United States was used to relate differences in serum cholesterol to differences in dietary intake.

ANALYTIC APPROACH

Data for children aged 1–18 y from the United States, Japan, and Spain were reviewed to describe longitudinal trends in serum lipid concentrations and anthropometric indexes and to correlate these trends with changes in dietary intakes. Data on heights and weights, serum lipid concentrations, and dietary intake by age from population studies conducted in Japan, Spain, and the United States were first examined. Data separated by sex were weighted to determine group means by age. US data, which were separated by ethnic groups, were compiled to determine population means.

To account for differences in height between children of the same age in different countries, body mass index (BMI; in kg/m^2) was used as a measure of obesity. Recent data suggest that BMI may be used as a reasonable marker of fatness in children, providing that BMIs are not compared across groups that differ in age (20). For our comparison, mean BMI values were compared for children aged 10 y from different countries. Data comparisons focused mainly on children aged 9–10 y because children at this age are almost always prepubertal and the serum cholesterol data are less likely to be confounded by factors such as smoking and alcohol consumption.

Finally, the Hegsted equation (21) was used to relate differences in cholesterol concentrations to differences in dietary fat intake among the 3 populations. Although this equation was not originally developed for and applied to children, changes in the same directions as for adults would be expected.

RESULTS

Changes in cholesterol concentrations in the United States, Japan, and Spain

Total serum cholesterol concentrations reported for 10-y-olds in several studies were consistently lowest in US children, higher in Japanese children, and highest in Spanish children (**Figure 1**). According to national reports from the Ministry of Health and Welfare of Japan (29) and the Japan Association of Health Services (30), the rise in mean serum cholesterol concentrations in Japanese children occurred over 3 decades. These agencies reported mean cholesterol concentrations in 9–10-y-olds of 4.01 mmol/L in 1960 (below the mean for US children of 4.14 mmol/L), 4.27 mmol/L in 1980, and 4.42 mmol/L in 1990 (which exceeded the 75th percentile for US children of 4.40 mmol/L).

In Spain, the rise in serum cholesterol was faster, occurring over a single decade. Plaza et al (27) summarized mean serum cholesterol concentrations from data compiled from all epidemiologic studies in Spanish children between 1980 to 1990 (**Figure 2**). Initially below US concentrations, the mean cholesterol concentration of Spanish children rose above the mean concentration for US children in 1982 (4.19 mmol/L) and by 1985 was above the US 75th percentile (4.45 mmol/L).

In contrast, mean cholesterol concentrations of children in the United States have not changed significantly over the past 2 decades. Comparison of trends in mean cholesterol concentrations for children in the Bogalusa Heart Study between 1973 and 1988 suggest little change over this time period (7, 31). This finding is corroborated by results from the first National Health and Nutrition Examination Survey (NHANES I; 32) and the Lipid Research Clinics (LRC) Study (22) conducted in the

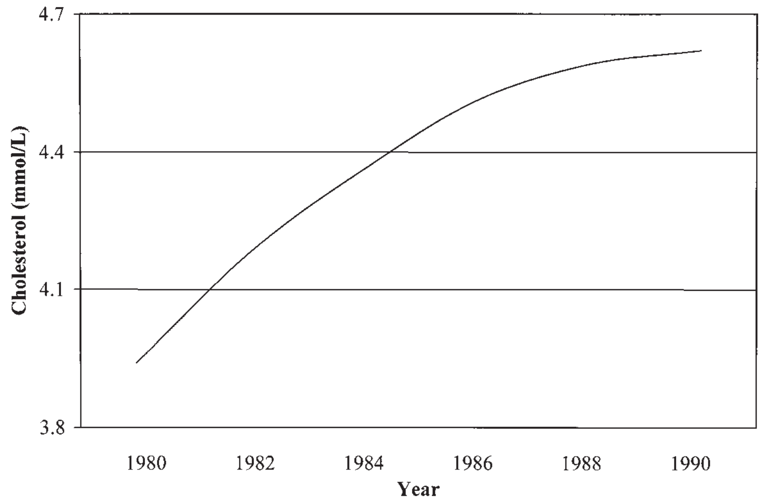

FIGURE 2. Mean serum cholesterol concentrations in Spanish children. Serum cholesterol concentrations were derived by compiling mean concentrations from all epidemiologic studies in Spanish children during the 1980s. Adapted from reference 27.

1970s, the Muscatine (33) and NHANES II (34, 35) studies of the mid-1980s, and most recently NHANES III (36). In summary, with respect to total serum cholesterol concentrations in children, these data show a dramatic and progressive rise in both Japan and Spain compared with the United States and strongly support the concept that the rise in measured cholesterol concentrations is a true concern.

We next examined the contribution of LDL and HDL cholesterol to total cholesterol concentrations in each country. An example of these differences is illustrated in **Figure 3**, in which relatively large studies from each country are compared. Although full lipid profile data in children are not as widely available as information on total cholesterol concentrations, available data indicate that in both Japan and Spain the higher total cholesterol concentrations of these children (compared with US children) are due to higher concentrations of LDL cholesterol, with smaller contributions from HDL cholesterol.

Changes in weight

Obesity is implicated as a significant risk factor for cardiovascular disease in adults and is often positively correlated with serum total and LDL-cholesterol concentrations (37, 38). Data from all 3 nations indicate an increase in weight-for-height among children over the past 2 decades. US data from NHANES I, II, and III indicate an increase of ≈2% per decade in children's BMI (39–41). Children in Spain and Japan are experiencing a slower rate of increase, <1% per decade (10, 11, 42, 43). Still, differences in BMI between 10-y-old children in the 3 countries are small (**Figure 4**).

Although comparative data linking childhood activity levels and obesity are not available, trend data do suggest an increase

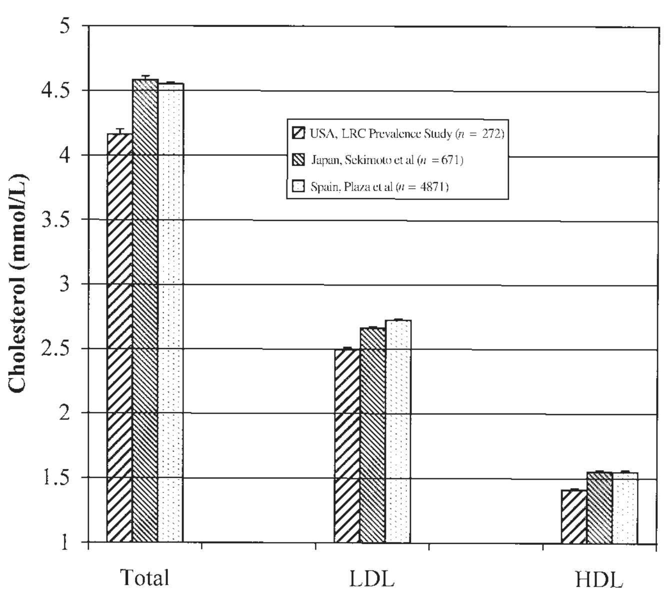

FIGURE 3. Mean (±SE) plasma lipid profiles of 5–9-y-olds in 3 countries. Data were taken from random population studies of 5–9-y-old children conducted in the 1980s in the United States (22), Japan (25), and Spain (27). LRC, Lipid Research Clinics.

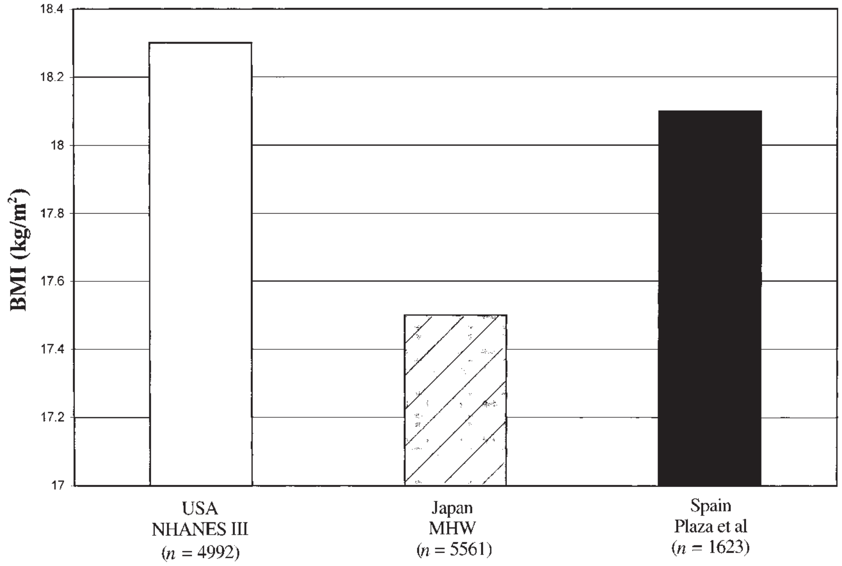

FIGURE 4. A comparison of BMIs calculated from heights and weights of 10-y-old children as reported in national surveys conducted in the United States (41), Japan (30), and Spain (43). NHANES, National Health and Nutrition Examination Survey; MHW, Ministry of Health and Welfare.

in sedentary lifestyles among children in all 3 countries. A 1990 study in Japan noted a 30% increase in the number of hours that boys aged 10–15 y spent viewing television between 1985 and 1990 (44). US children appear to have the most sedentary lifestyles; the average US child aged 6–11 y watches 3.5 h of television daily (45), compared with ≈2 h/d for Japanese children of the same age. Comparative data for Spain are not available, although anecdotal reports and a study by a major national newspaper in Spain suggest a similar decrease in physical activity. Thus, it is not likely that differences in degrees of adiposity or physical activity among children in the 3 countries are major reasons for the differences in cholesterol concentrations. We next examined the contribution of dietary modifications to changes in children's cholesterol concentrations.

Changes in diet

In comparisons of food availability data and CAD risk factors, estimated total energy intake, the percentage of energy as fat (specifically saturated fat), and the intake of animal protein have all been associated with both an increase in adiposity and an increase in serum cholesterol concentrations. As the food supply has expanded over the past 25 y, the per capita energy supply has increased 14% in Japan, 16% in the United States, and 25% in Spain (**Figure 5**). However, the contribution of total fat to total energy intake has increased substantially more than has the increase in the energy supply. In Japan between 1955 and 1989 the quantity of total fat available for human consumption increased 3-fold, from 20 to 59 g, but the quantity of saturated fat available increased >8-fold, from 3 to 23 g (29).

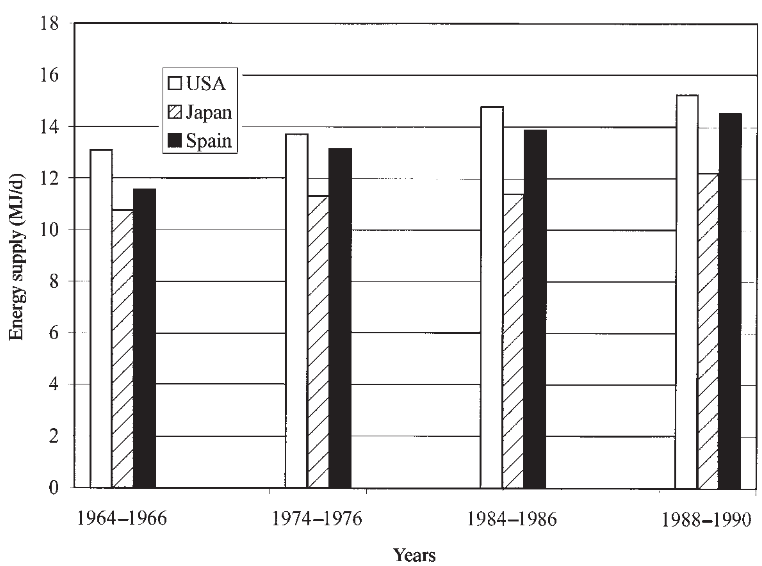

FIGURE 5. Annual available daily per capita energy supply in the United States, Japan, and Spain. Data from the Food and Agriculture Organization of the United Nations (46, 47).

TABLE 1
A comparison of the annual available daily per capita protein supply in the United States, Japan, and Spain from 1964 to 1990[1]

	1964–1966	1979–1981	1988–1990
		g/d	
United States	66.6	67.8	71.1
Japan	27.6	45.2	53.0
Spain	33.0	52.7	71.1

[1] Data from the Food and Agriculture Organization of the United Nations (46, 47).

Among 5-y-old Japanese boys, the percentage of energy from fat increased from 12.6% in 1952 to 32% in 1987 (48). Between 1964 and 1990 the estimated total fat intake in Spain increased 1.5-fold, with intakes of dairy products and meat (significant contributors of saturated fat to the Spanish diet) rising 1.3- and 1.6-fold, respectively, between 1958 and 1991 (49, 50).

Cross-sectional comparisons of data from the 3 countries also show trends toward dietary patterns associated with a higher incidence of cardiovascular disease. Interestingly, although the estimated intake of red meat products has tripled in Japan (on the basis of food availability data) from 4.0 g per capita in 1964–1966 to 12.1 g in 1988–1990, consumption still remains less than one-half of that in Spain (29.2 g) and less than one-third of that in the United States (38.8 g) (46, 47). It is assumed that similar patterns apply to children. In light of this lower consumption of saturated fat and red meat, it is striking that cholesterol concentrations among children in Japan have surpassed those of US children and are approaching those of Spanish children. The supply of total animal protein in Spain has almost doubled from 1965 to 1990, as in Japan, with only a small increase in the United States (**Table 1**). Because saturated animal fat intake closely correlates with animal protein intake, it is certain that saturated fat has also substantially increased in the Spanish diet over time.

Eggs contain ≈212 mg cholesterol per serving, nearing two-thirds of the upper limit recommended for daily dietary intake. Campaigns to reduce cholesterol intakes in the United States have focused on decreasing egg consumption. Consequently, from 1964 to 1990, estimated egg intake decreased slightly in the United States, from 5.3 to 4.1 per capita per week (46, 47). In Japan during this same time period, the use of eggs increased substantially, from 3.8 to 5.9 eggs per capita per week, and in Spain consumption increased slightly, from 3.2 to 4.9 eggs per capita per week, remaining near suggested intake amounts (47, 51). Compared with other food sources, eggs supply proportionately more cholesterol in the Japanese diet than in the US and Spanish diets.

Studies of food intake patterns indicate that sources of dietary fat for US children are predominantly dairy products, snack foods, and red meat products (1, 52). Consumption of high-fat snack foods and foods from fast-food restaurants account in large part for this high fat intake.

Although few data on snack food availability and consumption are available for Japan and Spain, the sales of processed and fast foods in both countries are growing rapidly. In Japan, Fukuba (53) reports a 14.3% increase in the portion of household food expenditures spent on processed foods between 1963 and 1988 and Murata (54) noted a 183% increase in the consumption of processed foods between 1970 and 1985. Fukuba also noted that the number of meals consumed at restaurants increased markedly, with an increase in fried and thereby higher-fat foods.

In Spain, the number of self-service vending machines almost doubled between 1976 and 1990, whereas the percentage of sugar and sweets in the diet increased more than one-third between 1958 and 1990 (55). Although it is not clear whether these foods are also high in fat, they may contribute to increased energy intake.

Data in **Table 2** summarize recent dietary surveys of children in all 3 countries. Japanese children consume ≈10% (10.3%) less energy than do US children and >20% less energy (23.2%) than do Spanish children. Spanish children consume almost 20% (16.7%) more energy than do US children.

Of interest, Japanese children, who have the lowest energy intake, have cholesterol concentrations that approach those of Spanish children and exceed those of American children (24), whereas Spanish children, who have the highest energy intake, have the highest serum cholesterol concentrations (51). Thus, energy intake does not appear to correlate with cholesterol concentrations in this population group.

Japanese children consume less total and saturated fat and less cholesterol than do US children. In contrast, Spanish children have the highest fat intakes, with especially high intakes of saturated fat (up to 18% of total energy) and cholesterol (>450 mg/d).

Serum cholesterol predictions with use of the Hegsted equation

Using the dietary fat and cholesterol ranges discussed above, we applied the most recent version of the Hegsted equation (21) in a novel way. This equation was developed initially in metabolic ward studies to predict changes in blood cholesterol concentrations in Caucasians of European descent as a function of diet manipulation in individuals (**Table 3**). Although the formula may not apply to children, we hypothesized that changes would nonetheless parallel the direction of those in adult males. For our

TABLE 2
Daily dietary intakes of 5–10-y-old children in the United States, Japan, and Spain[1]

	Energy	Total fat	Saturated fat	Polyunsaturated fat	Cholesterol
	mJ	*% of energy*	*% of energy*	*% of energy*	*mg*
United States	9.2–9.3	36	13	5–6	285–332
Japan	8.0–8.5	26–32	12[2]	8[2]	231[3]
Spain	10.7–10.9	43	16–18	6	476–517

[1] Data for the United States were from references 7 (*n* = 284) and 52 (*n* = 4361); data for Japan were from references 29 (*n* = 5561) and 24 (*n* = 62); and data for Spain were from references 51 (*n* = 1373) and 28 (*n* = 116). 1 MJ = 239 kcal.

[2] Saturated fat and total unsaturated fat intake in Japan were calculated from per capita intake of animal fat and vegetable fat, respectively (29, 53); polyunsaturated fat intake was calculated to be one-half of total unsaturated fat (56).

[3] Calculated from Food and Agriculture Organization food supply data on per capita intake of eggs (47).

TABLE 3
Differences in children's blood cholesterol concentrations: predictions from the Hegsted equation[1]

	Predicted difference in cholesterol	Actual difference in cholesterol[2]
	mmol/L	
Japan vs United States	−0.20 to −0.32	0.08 to 0.39
Spain vs United States	0.40 to 0.64	0.31 to 0.57

[1] With use of dietary measurements in US children as baseline values for blood cholesterol concentration and fat intake (7), cholesterol concentrations were predicted for Spanish and Japanese children by using the most recent version of the Hegsted Equation (21): Δ Chol (mmol/L) = $(2.10\ \Delta S - 1.16\Delta P + 0.067\Delta C) \times 0.02586$, where Δ Chol (mmol/L) = difference in serum cholesterol (mmol/L), ΔS = difference in percentage of energy from dietary saturated fat/d, ΔP = difference in percentage of energy from dietary polyunsaturated fat/d, and ΔC = difference in dietary cholesterol (mg/d); to convert mmol/L cholesterol to mg/dL, divide by 0.02586. Dietary data for Spanish and Japanese children were from Table 2.

[2] Based on differences in cholesterol values between countries as shown in Figure 1.

approach, dietary parameters of US children, from Table 2, were used as baseline control values for dietary cholesterol and fat intakes. Dietary data available for Japanese and Spanish children (Table 2) were then introduced to predict cholesterol concentrations based on calculated ranges of differences in intakes of saturated fat, polyunsaturated fat, and cholesterol. With use of this equation, Spanish children were predicted to have blood cholesterol concentrations 0.40–0.64 mmol/L higher than those of US children. This closely matches the actual measured differences. In contrast, calculations using current dietary fat intake of Japanese children predicted that Japanese children should have cholesterol concentrations 0.20–0.32 mmol/L lower than those in US children, whereas actual measurements were 0.08–0.39 mmol/L higher. Similar quantitative results were obtained by using the Keys equations (57) (data not shown).

DISCUSSION

The failure of dietary data to predict expected relations with blood cholesterol concentrations in Japanese children raises several issues. First, potential differences in analytic methods may affect comparisons of trend data between nations, eg, differences in the years and time period of data collection, the lack of data for some population age groups, collection of fasting compared with nonfasting blood samples, analytic differences in blood analysis, and differences in dietary collection protocols. Thus, there is a need to standardize international methods for data collection, analysis, and reporting. Also, because data on the effects of nutrition-gene interactions and their effect on plasma lipid concentrations are only beginning to emerge, collaborative studies in which data collection methods are standardized and in which dietary, anthropometric, biochemical, and genetic data are collected simultaneously are needed to answer the questions raised by this analysis. Another potential confounder is suggested by reports that birth weight, breast-feeding, and the introduction of weaning food may influence later expression of cardiovascular disease risk factors, a factor that might influence differences in cholesterol concentrations between populations (58–60). Further studies should include measurement of these variables.

Data comparing serum lipid concentrations of white and Japanese children are limited. Several migrant studies in young adults examined serum lipid differences between Japanese immigrants in California and persons living in Japan (61, 62). These studies showed markedly higher total cholesterol, LDL-cholesterol, and triacylglycerol concentrations in the Japanese Americans than in the Japanese. Differences in serum lipids corresponded to differences in intake of animal fat and simple carbohydrates, suggesting specific dietary factors as important determinants of changes in serum lipids and lipoproteins in these populations. Srinivasan et al (63) compared serum lipids between Japanese and white adolescents (aged 12–18 y) and found total cholesterol, LDL-cholesterol, and triacylglycerol concentrations to be higher in the Japanese than in the white teens. In this study, all lipid measurements were performed in the same US laboratory according to the Lipid Research Clinics protocol, but few dietary data were included in these comparisons. Also, given the age group selected for this study it was not clear whether the higher lipid values in the Japanese adolescents were due to genetic or environmental factors or were the result of differences in adolescent sexual maturation processes. The data presented herein on prepubertal children in different populations support the concept that measured differences in children's serum cholesterol in different population settings are valid.

Moreover, what emerges from this analysis are several questions about the relation of various risk factors to serum cholesterol concentrations in children. Traditionally, Japan and other countries have had higher intakes of vegetable and plant products not commonly available in the United States and Europe (eg, seaweed-derived foods). It is possible that some of these food ingredients have a direct blood cholesterol–lowering effect by directly affecting pathways that regulate whole-body cholesterol metabolism. Soy protein, plant sterols, dietary fiber, rice oil, oryzanol, and other ingredients in traditional diets are being studied to assess their cholesterol-lowering ability and pathways for regulating whole-body cholesterol metabolism. A theoretical example might be an algae or plant component that inhibits hydroxymethylglutaryl-CoA reductase, with resultant higher activities of the LDL receptor and lower plasma LDL-cholesterol concentrations (64). Increased consumption of ingredients more typical of a Western diet would presumably be associated with decreased consumption of these food products along with their putative cholesterol-lowering compounds.

It is also possible that there are differences in genetic response to diet between population groups. Where genetic backgrounds vary, dietary effects may not fully account for differences observed. For example, Spanish populations have a low prevalence of the apolipoprotein E4 isoform (65). Humans carrying this allele are at higher risk of atherosclerosis, tend to have higher total and LDL-cholesterol concentrations, and have an exaggerated postprandial lipid response with an increase in triacylglycerol-rich particles after meals compared with subjects carrying alleles producing the apolipoprotein E3 and E2 isoforms (66–69).

To date, though, few or no data are available to suggest which genes might predict that different populations will have different blood lipid responses to specific nutrients because of variations in genes regulating lipid metabolism. Several countries in transition to a Western diet (eg, Korea, Thailand, and India) are reporting rapid increases in CAD and higher prevalence rates of hypercholesterolemia than in the United States; yet persons in these countries still consume lower amounts of total and saturated fat than do North Americans (26, 70). Of additional concern, when Japanese or North American Indian populations become overweight, their frequency of hyperlipidemia, diabetes, and other risk factors for cardiovascular disease is substantially higher than that of whites in Europe or North America (71–73).

A testable hypothesis is that increasing dietary total and saturated fat (and cholesterol intake) in populations not previously exposed to such intakes will lead to greater and more adverse changes in blood lipid profiles than in populations long adapted to Western diets by genetic selection or other mechanisms.

Whatever the mechanistic explanation or explanations for the rapid westernization of children's cholesterol concentrations in countries that are adapting the dietary and other lifestyle habits of northern Europe and the United States, it seems prudent to introduce healthy lifestyle programs through schools and other resources to circumvent the possibility that some of these adverse habits will allow populations with previously low rates of CAD to catch up to the United States and Europe. On the basis of the apparent differences in pathways leading to higher blood cholesterol concentrations in Japan than in Spain, we suggest that more research be directed toward determining nutrient–atherosclerosis risk factor interactions in distinct populations. With an understanding of the pathophysiologic pathways responsible for the development of adverse risk factors, appropriate population-specific intervention measures can be designed and implemented.

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