Original Article

Interaction between genetic and dietary factors affecting cardiovascular risk

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Socio-economic development and progressive urbanization has been accompanied by an increase in the rates of cardiovascular disease (CVD) in developing countries. The cause of this increase is multifactorial. It is very likely that changes in lifestyle (particularly diet and physical activity) play an important role. The evidence that some ethnic groups may be at particular risk when exposed to an urban environment suggests that genetic factors may also be involved. This situation is exemplified by the experience of Chinese, Malays and Asian Indians in Singapore, where Asian Indians have three times the rates of myocardial infarction compared to Chinese despite exposure to a similar environment. However, genetic factors do not seem to explain the differences between ethnic groups either. Rather, it appears that a complex interplay of environmental and genetic factors give rise to these ethnic differences. Some genetic variants appear to identify subgroups of the population that are mal-adapted to an urban lifestyle. For example, a high fat diet is associated with higher serum triglyceride and lower HDL-cholesterol concentrations (a more atherogenic phenotype) in those with the TT genotype at position -514 of the LIPC locus while those with the CC or CT genotypes have lower serum triglyceride and higher HDL-cholesterol concentration (a less atherogenic phenotype) under the same dietary conditions. These types of findings may provide the basis for personalized lifestyle modification therapy that will optimize the benefits of such therapy for the individual concerned.

Key words: Key Words: genetic polymorphisms for cardiovascular risk, hepatic lipase, blood lipids, atherogenic phenotype and genotype, Chinese, Malays, Asian Indians

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the world today. The rates of CVD in many developed countries, such as the United States of American and parts of Western Europe, have reached a plateau and, in many instances, have begun to decline. However, in most developed countries, which are experiencing economic growth and rapid urbanization, the rates of CVD are only beginning to rise. The rise of CVD in developing countries is particularly important because the populations of these countries encompass two-thirds of the world's population. In fact, despite lower rates of CVD, more CVD deaths occur in developing than in developed countries.[1]

In part, the rise in CVD mortality that accompanies socio-economic development can be attributed to a greater proportion of older persons in the population.[2] The aging population occurs for at least two reasons. Firstly, there has been a reduction in deaths from disorders resulting from malnutrition and infection, which remain the major causes of morbidity and mortality in many developing countries today. This allows the population to live to ages at which they become susceptible to the chronic diseases, such as CVD, that form the major cause of death in developed countries.[3] Secondly, reduced fertility rates are often seen as part of socio-economic development. This has resulting in the 'greying' of the population in most developed countries.

As important, if not more important, is the change in lifestyles that has accompanied urbanization. Two of the greatest changes that have occurred relate to the diet and physical activity. Urbanization has seen a shift from more traditional diets to more "westernized diets" and a marked decrease in physical activity. These changes have resulted in a rise in the prevalence of obesity and the metabolic abnormalities that accompany it, such as glucose intolerance, hypertension and dyslipidemia. Modification of each of these risk factors by pharmaceutical agents has been shown to reduce the risk of CVD. However, the attendant costs and potential adverse effects of drug therapy mean that lifestyle modification remains the cornerstone of CVD prevention.

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Cardiovascular disease in developing countries-lessons from Singapore

We will provide a little history perspective on CVD in Singapore. Singapore is a small country in South East Asia that has undergone rapid socio-economic development over the last 40 years. Today, it is completely urbanized. Along with this rapid growth, the mortality and morbidity associated with CVD increased rapidly from the 1950's and has stabilized in the 1990s at a level that exceeds that in some developed nations including the United States of America. We believe that the lessons learnt in Singapore will be applicable to many countries in Asia as they urbanize.

The first lesson from the Singapore experience is that Asians do not enjoy special protection from CVD. For many years, CVD has been thought of as a 'Western' disease. Asians, particularly those of oriental descent, were thought to be protected from CVD. However, studies in migrant populations have shown clearly that Asians, who move into an urban environment, experience a dramatic rise in CVD risk. This has been demonstrated in Japanese immigrants to the United States[4] and Chinese immigrants to Singapore.[5] Each of these groups experience higher rates of CVD than their counterparts in their native countries. In Singapore, the rates of CVD in the predominantly Chinese population has reached, and surpassed those in the United States. Thus, it seems likely that Asians will experience the same rise in CVD seen in Western countries as a consequence of the social changes that are sweeping the world.

The second lesson is that specific ethnic groups in Asia may be at particularly high risk for developing CVD in an urban environment. The Singapore population comprises three ethnic groups (Chinese, Malay and Asian Indian) who live in a relatively uniform, highly urbanized environment. All three ethnic groups have experienced urbanization at the same time. However, Asian Indians experienced a three-fold higher rate of CVD than Chinese.[6,7] Asian Indian Immigrants to the United Kingdom experience high rates of CVD, even higher than their Caucasian counterparts.[8] Even in India, Indians living in an urban environment experience a high rate of CVD.[9] This suggests that it is the lifestyle changes associated with urbanization, as opposed to migration per se, that will drive the epidemic of CVD that is occurring in Asia today. The implications of these findings are profound.

While the rates of CVD rises in the rest of Asia towards that seen in developed countries, there may be an accelerated increase leading to even greater mortality and morbidity from CVD for the large population that lives on the Indian subcontinent.

The third lesson is that an understanding of the pathophysiologic basis of these ethnic differences may provide some insight into the approach we need to take to reduce the morbidity and mortality associated with CVD in the future. Urbanization results in an increase in the prevalence of CVD risk factors. Singapore has seen an increase in the prevalence of diabetes mellitus from 4.6% in 1984 to 8.4% in 1992 and 9.0% in 1998.[10] The age-standardized prevalence of hypertension increased from 22.5% in 1992 to 26.6% in 1998.[10] It seems likely that the increase in the prevalence of known CVD risk factors are at least partially responsible for the rise in CVD observed in the last several decades. Furthermore, the levels of the risk factors differ between ethnic groups which may explain some of the ethnic differences in CVD risk. Asian Indians, the highest risk group, exhibit a higher prevalence of diabetes mellitus than Chinese and Malays.[11] They also have higher serum triglyceride (TG) concentrations and lower high density lipoprotein cholesterol (HDL-C) concentrations than Chinese. Both high serum TG concentration[12] and low serum HDL-C[13] concentration are known to be independent risk factors for CVD. Compared to Chinese, Malays have high serum TG concentration, low HDL-C concentration (intermediate between Chinese and Asian Indians) and high serum low density lipoprotein cholesterol (LDL-C) concentration. The remainder of this paper will focus on these lipid parameters.

Based on the observation that Chinese, Malays and Asian Indians in Singapore eat different foods in their diets, and since dietary intake, particularly dietary fat, is a major determinant of serum lipid concentrations, it had been hypothesized that dietary differences between the ethnic groups could explain the ethnic differences in serum lipids observed in Singapore. This hypothesis was tested in a large random sample of Singaporeans using a food frequency questionnaire that had been developed and validated in the Singapore population.[14] It was found that despite the differences in the taste and appearance of food between ethnic groups, the macronutrient contents were remarkably similar between ethnic groups. There were small, but statistically significant, differences in the proportion of calories from dietary fat between ethnic groups but these differences were small amounting to <1% between ethnic groups (Table 1). The same was true of the various classes of dietary fatty acids. However, adjustment for dietary intake failed to explain the ethnic differences in serum lipids in our population.

It is tempting, when comparing ethnic groups, to think that genetic differences could explain differences between ethnic groups. Indeed, differences in the frequencies of particular genetic variants between ethnic groups could explain some of the differences observed. For example, genetic variation at the apolipoprotein E (*APOE*) locus represents an important determinant of serum LDL-C concentration explaining as much as 10% of the variation of this lipid parameter in some populations. Three common variants (ε2, ε3 and ε4) have been studied most extensively. The ε3 allele is the common allele and is associated with intermediate serum LDL-cholesterol concentration while the ε2 allele is associated with low serum LDL-C concentration and the ε4 allele is associated with high serum LDL-C concentration. We have examined these genetic variants in the Singapore population.[15] We confirmed that the associations between the various alleles and serum LDL-C concentration were the same in the Singapore population as in other populations i.e the ε2 allele was associated with lower LDL-C concentration and that the ε4 allele with higher LDL-C concentration. Furthermore, the E4 allele was almost twice as common in Malays as in Chinese or Asian Indians. We believe that this difference in allele frequency may contribute to the higher serum LDL-cholesterol

Table 1. Selected dietary intake by gender and ethnic group in Singapore

	Females			Males		
	Chinese	Malay	Indian	Chinese	Malay	Indian
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
energy (kcal)	[a]1812 (606)	[a]1902 (641)	[b]2081 (710)	2337 (777)	2340 (779)	2358 (704)
% fat	[a]26.8 (5.4)	[b]27.9 (5.4)	[c]28.2 (5.4)	[a]26.5 (5.4)	[b]27.6 (6.4)	27.2 (5.4)
%sfa	[a]10.1 (2.5)	[b]11.6 (2.9)	[b]11.5 (2.9)	[a]10.4 (2.5)	[b]11.8 (3.2)	[b]11.3 (3.0)
%mufa	[a]9.3 (2.3)	[a]9.1 (2.3)	[b]8.0 (2.3)	[a]9.2 (2.3)	[a]9.0 (2.6)	[b]8.1 (2.2)
%pufa	[a]5.6 (2.2)	[b]5.1 (2.2)	[c]6.2 (2.6)	[a]4.9 (1.7)	[b]4.4 (1.7)	[c]5.5 (2.2)
cholesterol (mg)	[a]222 (114)	[a]236 (122)	[b]197 (115)	[a]294 (148)	[a]295 (164)	[b]244 (141)

Data represent estimated means calculated using analysis of covariance. Different prefixes for each value indicates statistically significant differences between ethnic groups (P<0.01). TC/HDL, total cholesterol:HDL cholesterol ratio; % fat, % energy taken as fat; % sfa, % energy taken as saturated fatty acids; % mufa: % energy taken as monounsaturated fatty acids; % pufa, % energy taken as polyunsaturated fatty acids. Adapted from Ref. (14).

concentration observed in this ethnic group. However, adjustment for this genetic variant still failed to explain the ethnic differences in serum LDL-C concentration in our population. If genetic variation alone accounted for the ethnic differences, then there had to be other loci or other variants involved.

Examination of genetic variants associated with HDL-C concentration suggested to us that it was likely to be more complex than that. Cholesterol ester transfer protein (CETP) facilitates the transfer of cholesterol esters from HDL to other lipoprotein particles in exchange for triglycerides. Genetic variation at this locus has been found to be associated with variation of serum CETP activity and HDL-C concentration.[16] Of the known genetic variants, the TaqIB polymorphism is common and has been studied most extensively. There is a significant body of data showing that the B2 allele is associated with decreased CETP activity and increased serum HDL-C concentration.[17-25] When we examined this polymorphism in our population, we also found that the presence of the B2 allele was associated with increased HDL-C concentration in men and women from all three ethnic groups.[26] Contrary to our expectations, the B2 allele was more common in Asian Indians who had the lowest serum HDL-C concentration and lower in Chinese and Malays, who had higher serum HDL-C concentration. This suggested to us that genetic differences alone were unlikely to explain the differences between ethnic groups.

We have further refined our hypothesis based on the following observation. Although relationships between dietary changes and serum lipid changes are well founded and predictable for groups, a striking variability in the response of serum cholesterol to diet between subjects was reported.[27-29] In some individuals, plasma cholesterol levels dramatically decrease following consumption of a low fat diet, while they remain unchanged in others.[28-31] It has been shown, in elegant studies in non-human primates, that the serum lipoprotein response to dietary manipulation has a significant genetic component.[32-34] Several variants a various genetic loci seem to modulate the associated between dietary fat and serum lipid concentrations.[35]

As an example, we have examined the -514C>T polymorphism at the hepatic lipase (nee *LIPC*) locus. Presence of the T allele is associated with elevated serum HDL-C concentration in many studies.[36-40] This was also the case in Singapore.[41] More recently, investigators from the Framingham Offspring Study have shown that this polymorphism modulated the association between dietary fat intake and serum HDL-C concentration.[42] In those with the TT genotype, high dietary fat intake was associated with low HDL-C concentration whereas in those with the CC genotype, the opposite was true. The investigators suggested that the TT genotype may identify a group of individuals who are maladapted to a high fat diet in relation to CVD risk. The findings in Singapore were similar. As in other populations, the T allele was associated with elevated HDL-C concentration. In addition, our findings replicated those of the group in Framingham. We found that a high fat diet had an adverse effect on the serum lipid profile in the form of hypertriglyceridemia in all three ethnic groups and that this occurred primarily in those with the TT genotype (Fig. 1). In addition, our findings in Asian Indians replicated those in Framingham in relation to dietary fat and low HDL-C concentration.

In no way are we suggesting that these findings explain the ethnic differences in serum lipids in Singapore. Rather, these findings highlight an important issue. It is important to realize that ethnicity is a construct that encompasses both genetic and cultural (e.g language, religion, diet) differences.[43,44] Interactions like the one described in the preceding paragraph suggest that chronic diseases such as CVD are the consequence of a complex interplay between environmental and genetic factors and that genetic variation can multiply the effects of lifestyle factors on disease risk. If we are truly going to understand the pathogenesis of chronic disease in various ethnic groups, one must look beyond issues of race and consider the cultural differences together with the genetic differences between ethnic groups.

Gene-diet interactions-implications for future therapy

These findings may also have implications for the treatment of dyslipidemia through dietary modification. Recent years have seen a large number of popular dietary strategies emerged for weight reduction. One of the most hotly debated areas has been associated with high fat low carbohydrate diets epitomized by the Atkins diet, as opposed

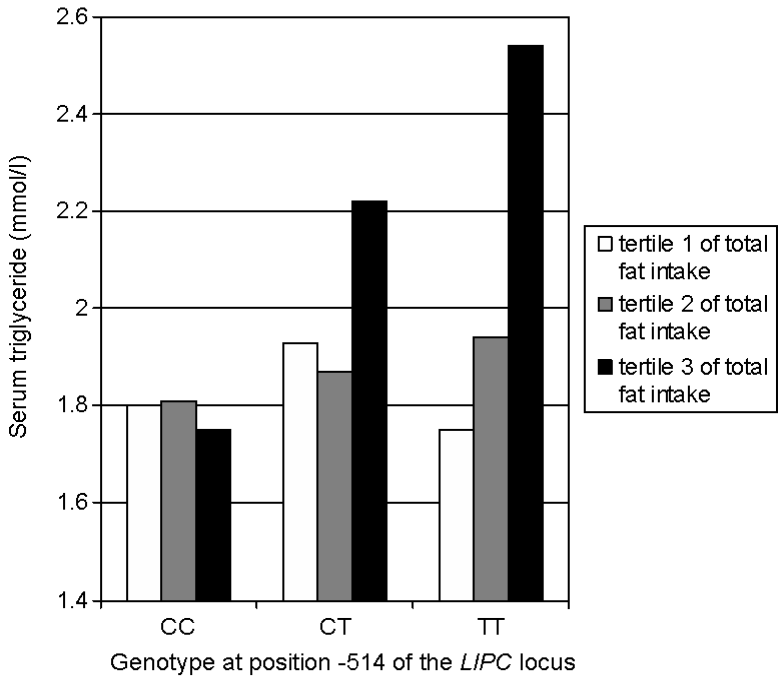

Figure1. Modification of the effect of -514C>T polymorphism on plasma triglyceride (TG) concentration depending on the total fat intake (tertiles) in the Singaporean population. Mean values of serum triglyceride concentrations were adjusted for ethnic group, gender, age, body mass index, tobacco smoking, alcohol consumption, physical exercise, diabetes, energy, carbohydrates and proteins. *P* value for total fat tertile*-514C>T polymorphism interaction = 0.005.

to the low fat high carbohydrate diets, of which the Dean Ornish diet is a prominent example. Randomized controlled trials have now shown that the high fat diets do result in significant weight loss, at least in the short term.[45,46] Some of the differences in the results achieved with these diets pertain to the effects of the diets on serum TG concentrations and HDL-C concentrations. The presence of gene-diet interactions such as the one between the -514C>T polymorphism at the LIPC locus, dietary fats and serum lipids suggest that this will be an ongoing debate, until we recognize that perhaps some persons (those with the CC genotypes), might do better on a high fat diet whereas other, those with the TT genotype, may fare better on a low fat diet such as that recommended by Dr Ornish. While one hesitates, based on currently available data, to recommend a diet that is as high in saturated fat as the Atkins diet, we should certainly be entertaining the possibility of a Mediterranean type diet[47] which is moderately high in total fat (at least compared to the diet in Singapore), but enriched in monounsaturated fatty acids rather than saturated fatty acids, for those in the former group. It is important to note that these hypotheses, derived from epidemiologic studies, need to be proven in prospective interventional trials.

Conclusion

In conclusion, our data suggest that CVD results from a complex interplay of environmental and genetic factors and the study of CVD risk in human population must take all of these into account. Common, one diet for all, strategies to reduce CVD through dietary modification are likely to work for the majority of persons. However, a significant proportion of persons may respond differentially to various types of lifestyle modification. Individualization of lifestyle modification that takes into account a person's phenotype (e.g obesity, plasma lipids, blood pressure), current environmental exposure (e.g diet, alcohol intake) and genotype may offer an opportunity for the rational prescription of therapeutic lifestyle modification that will optimize the benefits for that individual.

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