Functional foods for coronary heart disease risk reduction: a meta-analysis using a multivariate approach\textsuperscript{1–3}

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ABSTRACT

Background: It has been difficult to identify the appropriate bioactive substances for the development of new functional foods associated with coronary heart disease, because the results of many clinical studies are contradictory.

Objective: The objective of this study was to use the multivariate statistical approach known as principal component analysis (PCA) followed by a mixed model to process data obtained from a meta-analysis aimed at evaluating simultaneously the effect of ingestion of 1 of 3 types of bioactive substances (n–3 fatty acids, soluble fibers, and phytosterols) on 1 or more of 4 biomarkers (plasma total cholesterol, triacylglycerol, LDL cholesterol, and HDL cholesterol).

Design: Five independent variables (number of patients per study, dose, age, body mass index, and treatment length) and 4 dependent variables (percentage change in blood total cholesterol, LDL, HDL, and triacylglycerol) from 159 studies and substudies were organized into a matrix. The original values were converted to linear correlation units, which resulted in a new matrix.

Results: Two principal components were enough to explain 63.73\% and 84.27\% of the variance in the independent and dependent variables, respectively. Phytosterols and soluble fibers had a hypocholesterolemic effect, whereas n–3 fatty acids lowered triacylglycerol and increased total, LDL, and HDL cholesterol. The PCA and mixed model showed that this behavior was independent of dose, number of patients per study, age, and body mass index but was associated with treatment length.

Conclusions: PCA is useful for summarizing available scientific information in examinations of health claims for foods and supplements.

KEY WORDS n–3 Fatty acids, phytosterols, soluble fibers, cholesterol, multivariate analysis, functional foods

INTRODUCTION

The role of plasma lipids in the etiology of atherosclerosis and coronary heart disease has been well defined. A high plasma concentration of total cholesterol, triacylglycerol, and LDL cholesterol and a low plasma concentration of HDL cholesterol are considered important risk factors for the expression of coronary disease (1), and these plasma indexes or biomarkers must be jointly considered in the assessment of risk for populations (2).

Several studies have shown that the ingestion of bioactive substances—such as certain types of n–3 fatty acids (linoleic, eicosapentaenoic, and docosahexaenoic acids), soluble fibers (guar gum, psyllium, pectin, and oat products), and phytosterols (stanols and sterols)—may have a positive and significant lipidemic effect (3–5). However, reported contradictory results impair the choice of one or more substances for the development of new foods that could promote a reduction in the risk of coronary heart disease in humans (6–11). For the development of such foods, known as functional foods (12–14), in addition to satisfying all criteria necessary for the formulation of a regular food, one must also assess their functional efficiency on the basis of alterations in biomarkers.

Statistical techniques normally adopted in a meta-analysis, such as general regression models, summarize important information; however, they deal with one variable at a time. Multivariate approaches are statistical procedures capable of promoting data reduction or structural simplification, sorting and grouping, investigating the dependence among variables, predicting, and hypothesis testing. These approaches have been widely used in several areas of research such as medicine, sociology, business, education, psychology, and sports (15). In addition to being very efficient tools, especially in the study of correlations involving a large number of variables and sample units, these approaches have rarely been applied in nutritional research, despite this being an area in which multivariate correlation studies are essential.

The objective of this study was to present the multivariate statistical approach known as principal component analysis (PCA) followed by a mixed model to process data obtained from a meta-analysis aimed at evaluating simultaneously the effect of ingestion of 1 of 3 types of bioactive substances (n–3 fatty acids, soluble fibers, and phytosterols) on 1 or more of 4 biomarkers (plasma total cholesterol, triacylglycerol, LDL cholesterol, and HDL cholesterol).

SUBJECTS AND METHODS

Study characteristics

Studies of the effects of some n–3 fatty acids, phytosterols, and soluble fiber on blood total cholesterol, LDL-cholesterol, and triacylglycerol (guar gum, psyllium, pectin, and oat products), and phytosterols (stanols and sterols)—may have a positive and significant lipidemic effect (3–5). However, reported contradictory results impair the choice of one or more substances for the development of new foods that could promote a reduction in the risk of coronary heart disease in humans (6–11). For the development of such foods, known as functional foods (12–14), in addition to satisfying all criteria necessary for the formulation of a regular food, one must also assess their functional efficiency on the basis of alterations in biomarkers.
HDL-cholesterol, and triacylglycerol concentrations in adults were identified by a computerized literature search of the Internet [Web of Science, Elsevier, and MEDLINE (National Library of Medicine, Bethesda, MD)] of articles primarily published (96%) from January 1990 to April 2003 and by examining their respective cited reference sources. The full texts were obtained from the Library of the Institute of Chemistry of the University of São Paulo (USP), Brazil, and from the Louise M Darling Biomedical Library of the Center for Health Sciences, University of California. Only published trials reported in English were considered. Studies were selected for analysis according to the criteria shown in Table 1. For this meta-analysis, studies involving supplementation with more than one type of functional ingredient and studies that applied more than one dose or intervention time were partitioned to be treated as substudies. The dependence of these specific studies and substudies was considered in the mixed model.

### Specification of the variables

In the present meta-analysis, 4 dependent variables (percent- change in cholesterol, LDL cholesterol, HDL cholesterol, and triacylglycerol) and 5 independent variables [number of patients per study, dose, age, body mass index (BMI), and treatment length] were obtained from 159 studies and substudies that were described in detail by the respective authors (Table 2) cited in the text.

The change in biomarkers (Δ%) was calculated according to the following equation:

\[
\Delta \% \text{ Biomarker} = \frac{\left( T_1 - T_0 \right)}{T_0} \times 100
\]

\( T_1, T_0, P_1, \) and \( P_0 \) were the final and initial blood concentrations of the specific biomarker for the experimental and the placebo groups, respectively. The number of patients per study was obtained from the total number of individuals included in the study or substudy, with ≈50% corresponding to the experimental and 50% to the placebo groups. Dose was considered as the functional ingredient in its pure form and was reported in grams. Age (y) and BMI (kg/m²) were obtained from the mean for the experimental and placebo groups at baseline. The treatment length variable was computed with respect to the effective period of intervention, excluding both the adaptive and the washout periods in the crossover studies. Studies whose variables could not be included in this classification were not considered for this meta-analysis.

In general, the studies showed closely similar patterns concerning the form of bioactive substance ingestion, sex, experimental design, subject’s baseline healthy conditions (cholesterol < 8 mmol/L and triacylglycerols < 3 mmol/L), diet (energy ≈2500 kcal, cholesterol =300 mg, and total fat ≈30% of energy), moderate practice of physical exercise, alcohol consumption, smoking habit, and use of mild drugs or other nutritional supplements, which were normally discontinued a few months before or maintained without changes during the intervention. Similarities in lifestyles allowed the conclusion that alterations observed in the biomarkers resulted basically from the nutritional interventions.

### Statistical analysis

PCA was the multivariate technique applied to assess the association between the 4 dependent variables and the 5 independent variables and to categorize the studies and substudies according to the plane generated by the main components. PCA is only a descriptive statistical procedure, which does not involve any supposition about variance homogeneity. It is a simple and adequate descriptive technique to handle quantitative variables. The data matrices for independent variables (159 × 5) and for dependent variables (159 × 4), expressed in different units (g, kg/m², y, d, and %), were prepared by adopting the variables as columns and the studies and substudies as rows. First, statistical standardization was performed to obtain relativized data to which the multivariate technique was applied. The original values were converted into linear correlation units to form a new matrix, which was used as the base for PCA. The grouping
variables were designated as n–3 fatty acids, soluble fiber, and phytosterols. Correlations between the variables of all selected studies and substudies were used, with the variables and “studies and substudies” being grouped as a function of similarities.

With respect to the variables, the number of factors obtained should be determined by the number of eigenvalues >1.0 (91). Eigenvalues correspond to vectors capable of holding part of the variation observed when the original values (4 and 5) are reduced into the principal components. The studies and substudies were plotted graphically on the two-dimensional plane generated by the variables. A mixed model was fitted using 2 principal components of the dependent variables as response. All calculations were performed by using STATISTICA software (version 6; Statsoft Inc, Tulsa, OK), except those in the mixed model, for which SAS software (SAS Institute Inc, Cary, NC) was used.

RESULTS

Study characteristics

The studies reported the effect of 3 different bioactive substances—n–3 fatty acids, phytosterols, and soluble fibers—on the percentage change in cholesterol, LDL cholesterol, HDL cholesterol, and triacylglycerol under different experimental conditions (Table 3). With this initial approach, it was possible to observe that the general dietary interventions promoted average net reductions in cholesterol, LDL cholesterol, and triacylglycerol of 3.57%, 3.88%, and 11.50%, respectively, and a net age net reductions in cholesterol, LDL cholesterol, and triacylglycerol.

Multivariate analysis

The eigenvalues obtained by PCA for the independent and dependent variables are presented in Tables 4 and 5, respectively. They were arranged in decreasing order, indicating the importance of the respective factor in explaining the variation of the data. On the basis of the decision criteria recommended by Piggot and Sharman (91), 2 factors (eigenvalues > 1.0) were selected and the factor coordinates of the variables, based on correlations for each one, are presented in Table 6. Two principal components were enough to explain 63.73% and 84.27% of the variance in the independent and dependent variables, respectively. The linear correlations between the dependent and independent variables, including the principal components PCD1 and PCD2 (first and second principal components for dependent variables) and PCI1 and PCI2 (first and second principal components for independent variables), are presented in Table 7. The correlations were low. The correlation between treatment length and the percentage change in cholesterol, LDL cholesterol, PCD1, and PCD2 and the correlation between PCI1 and PCI2 were significantly different from zero. The vectors relative to the centered and reduced variables, selected as active in this meta-analysis, were located on the circumference and are graphically represented in Figures 1 and 2.

The distribution of the 159 studies and substudies on the plane generated by the variables is shown in Figures 3 and 4. The contribution of BMI and age to the first principal component and of treatment length and number of patients per study to the second principal component are shown in Figure 1. The dose variable did not present a high correlation with the 2 principal components discussed in this study. Considering the dependent variables, the
influence of the percentage change in LDL cholesterol, choles-
terol, HDL cholesterol, and triacylglycerol on the first principal
component and the influence of triacylglycerol on the second
principal component are shown in Figure 2.

The mixed-model analysis was performed for the first 2 de-
pendent principal components. The final equations are presented
in Table 8. In the initial models, the bioactive substances (n−3 fatty acids, phytosterols and soluble fibers) were included as a
fixed effect, studies as a random effect, and PCI1 and PCI2 as well
as the interaction between type of study and independent prin-
cipal components as exploratory variables. The mixed-model
analysis showed that the bioactive substances and PCI2 had a
statistically significant effect. The interaction effects and the
main effect of the first independent principal component were
removed from the model because none of them were statistically
significant at a 0.05 level of significance. A multiple compari-
sions Tukey’s test was applied to compare the 3 intercepts
corresponding to the type of study. For the first dependent prin-
cipal component, P values adjusted with the Tukey-Kramer test
were as follows: phytosterols versus soluble fibers (P = 0.2310),
n−3 fatty acids versus phytosterols (P < 0.0001), and n−3 fatty
acids versus soluble fibers (P < 0.0001). This result indicates
that the intercept for phytosterols and soluble fibers is equal
and both variables are different from the intercept for n−3 fatty
acids. For the second dependent principal component, P
values adjusted with the Tukey-Kramer test were as follows:
n−3 fatty acids versus phytosterols (P = 0.7843), n−3 fatty
acids versus soluble fibers (P = 0.1022), and phytosterols
versus soluble fibers (P = 0.0154). The conclusion is that the
intercept for n−3 fatty acids and phytosterols is equal and
both of them are different from the intercept for soluble fibers.
A residual analysis was performed and it did not show any
major departures from the assumptions, which indicated that
the model was appropriate for the data.

### Table 7

<table>
<thead>
<tr>
<th>Variable</th>
<th>Δ%Cholesterol</th>
<th>Δ%Triacylglycerol</th>
<th>Δ%HDL cholesterol</th>
<th>Δ%LDL cholesterol</th>
<th>PCD1</th>
<th>PCD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients per study</td>
<td>0.069</td>
<td>0.003</td>
<td>−0.060</td>
<td>0.132</td>
<td>−0.078</td>
<td>−0.140</td>
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<tr>
<td>Dose</td>
<td>0.105</td>
<td>0.073</td>
<td>0.061</td>
<td>0.046</td>
<td>−0.070</td>
<td>−0.008</td>
</tr>
<tr>
<td>Age</td>
<td>−0.028</td>
<td>0.001</td>
<td>−0.163</td>
<td>−0.067</td>
<td>0.018</td>
<td>−0.115</td>
</tr>
<tr>
<td>BMI</td>
<td>0.035</td>
<td>−0.099</td>
<td>0.011</td>
<td>0.051</td>
<td>−0.119</td>
<td>0.084</td>
</tr>
<tr>
<td>Treatment length</td>
<td>0.189</td>
<td>−0.040</td>
<td>0.041</td>
<td>0.261</td>
<td>0.201</td>
<td>0.325</td>
</tr>
<tr>
<td>PCI1</td>
<td>0.088</td>
<td>−0.049</td>
<td>−0.058</td>
<td>0.098</td>
<td>−0.132</td>
<td>−0.102</td>
</tr>
<tr>
<td>PCI2</td>
<td>−0.074</td>
<td>−0.016</td>
<td>0.006</td>
<td>−0.156</td>
<td>0.056</td>
<td>0.238</td>
</tr>
</tbody>
</table>

1 Δ change.
2 P < 0.05.
3 P < 0.01.
DISCUSSION

Why submit the data obtained by this meta-analysis to multivariate statistical analysis?

It is impossible to use the simple ordering of information to reach the objective of this study. Multivariate analysis presents several alternative statistical procedures that permit a simplified structure of the data without relevant loss of information, which transforms an expressive number of original variables into a smaller number of new noncorrelated variables (15).

Regression models and univariate analysis have often been used in a statistical approach to a meta-analysis, which indicates important correlations between independent and dependent variables. However, many of these variables are correlated and could be substituted by principal components. Multivariate techniques are able to identify such correlations, taking into account a "p" number of variables of interest, with the same weight and at the same time, expressing these correlations graphically. It can be said that techniques such as PCA for quantitative variables present a complete picture of the study, the visual
analysis of which contributes substantially to the interpretation of the results.

What information can be obtained from the reduction of factors and from grouping in multivariate analysis?

The data presented in Table 3 agree with those presented in other studies, which take into account the net effect of the experimental group. In a meta-analysis, Bucher et al (92) investigated the effects of dietary and supplemental intake of n-3 fatty acids on coronary heart disease. They observed that the anti-lipidemic effect was limited to an average 20% reduction in triacylglycerol concentrations; no effect on LDL- or HDL-cholesterol concentrations was observed. According to Quílez et al (93), over the past decade the possibility of using phytosterols as ingredients in functional foods has led to numerous studies of mechanisms such as increased fatty acid oxidation and inhibition of hepatic fatty acid synthesis byproducts of fermentation as short-chain fatty acids (94). The hypolipidemia caused by n-3 fatty acids and phytosterols as a consequence of the different way in which these 3 bioactive substances act on human metabolism. Different mechanisms are responsible for the cholesterol-lowering effect of free and esterified phytosterols, such as competition for solubilization in dietary mixed micelles, cocry statsis with cholesterol to form insoluble mixed crystals, and interference with hydrolysis processes by lipases and cholesterol esterases (95). Evidence suggests that some soluble fibers bind bile acids or cholesterol during the intraluminal formation of micelles. The resulting reduction in the cholesterol content of liver cells leads to an up-regulation of the LDL receptors and thus an increased clearance of LDL cholesterol. Soluble fibers could also promote the inhibition of hepatic fatty acid synthesis byproducts of fermentation as short-chain fatty acids (94). The hyperlipidemia caused by n-3 fatty acid diets is well established and has been associated with various hepatic mechanisms such as increased fatty acid oxidation and inhibition of hepatic fatty acid synthesis.

**Table 8**

<table>
<thead>
<tr>
<th>Equation</th>
<th>P</th>
<th>Equation</th>
<th>P</th>
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<tbody>
<tr>
<td>Mixed model for first PCD&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n-3 Fatty acids</td>
<td>PCD&lt;sub&gt;1&lt;/sub&gt; = -1.6301&lt;sup&gt;d&lt;/sup&gt; - 0.2224 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.0001&lt;sup&gt;d&lt;/sup&gt;</td>
<td>PCD&lt;sub&gt;1&lt;/sub&gt; = -1.6329 - 0.2291 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>(0.2011) (0.1022)</td>
<td></td>
<td>(0.2031) (0.1031)</td>
<td></td>
</tr>
<tr>
<td>Phytosterol</td>
<td>PCD&lt;sub&gt;1&lt;/sub&gt; = 0.9935&lt;sup&gt;d&lt;/sup&gt; - 0.2224 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.0001&lt;sup&gt;d&lt;/sup&gt;</td>
<td>PCD&lt;sub&gt;1&lt;/sub&gt; = 0.8233 - 0.2291 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>(0.1744) (0.1022)</td>
<td></td>
<td>(0.1428) (0.1031)</td>
<td></td>
</tr>
<tr>
<td>Soluble fibers</td>
<td>PCD&lt;sub&gt;1&lt;/sub&gt; = 0.5156&lt;sup&gt;d&lt;/sup&gt; - 0.2224 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.0325&lt;sup&gt;d&lt;/sup&gt;</td>
<td>PCD&lt;sub&gt;1&lt;/sub&gt; = 0.8233 - 0.2291 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>(0.2326) (0.1022)</td>
<td></td>
<td>(0.1428) (0.1031)</td>
<td></td>
</tr>
<tr>
<td>Mixed model for second PCD&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-3 Fatty acids</td>
<td>PCD&lt;sub&gt;2&lt;/sub&gt; = 0.4057&lt;sup&gt;d&lt;/sup&gt; + 0.2396 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.8081&lt;sup&gt;d&lt;/sup&gt;</td>
<td>PCD&lt;sub&gt;2&lt;/sub&gt; = 0.1409 + 0.2564 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>(0.1867) (0.0949)</td>
<td></td>
<td>(0.1198) (0.0912)</td>
<td></td>
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<tr>
<td>Phytosterol</td>
<td>PCD&lt;sub&gt;2&lt;/sub&gt; = 0.2132&lt;sup&gt;d&lt;/sup&gt; + 0.2396 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.1958&lt;sup&gt;d&lt;/sup&gt;</td>
<td>PCD&lt;sub&gt;2&lt;/sub&gt; = 0.1409 + 0.2564 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>(0.1620) (0.0949)</td>
<td></td>
<td>(0.1198) (0.0912)</td>
<td></td>
</tr>
<tr>
<td>Soluble fibers</td>
<td>PCD&lt;sub&gt;2&lt;/sub&gt; = -0.5659&lt;sup&gt;d&lt;/sup&gt; + 0.2396 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.0125&lt;sup&gt;d&lt;/sup&gt;</td>
<td>PCD&lt;sub&gt;2&lt;/sub&gt; = -0.5724 + 0.2564 PCl&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>(0.2160) (0.0949)</td>
<td></td>
<td>(0.2151) (0.0912)</td>
<td></td>
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</table>

<sup>1</sup> SE of the coefficient in parentheses. PCl<sub>1</sub>, second principal component for independent variables. Intercepts with different superscript letters are significantly different. P < 0.05.

<sup>2</sup> Before the multiple comparisons Tukey’s test applied to compare the 3 intercepts corresponding to the type of study.

<sup>3</sup> After the multiple comparisons Tukey’s test applied to compare the 3 intercepts corresponding to the type of study.

<sup>4</sup> The intercept is significantly different from zero.

<sup>5</sup> The PCl<sub>1</sub> coefficient is significantly different from zero.
The percentage changes in cholesterol, LDL cholesterol, and HDL cholesterol were negatively correlated with the first principal component, whereas triacylglycerol made a positive contribution or that nutritional interventions that resulted in a reduction in the blood concentrations of triacylglycerol caused a considerable increase in LDL cholesterol, total cholesterol, and HDL cholesterol (Figures 2 and 4). This information should be printed on the labels of these functional foods because they can be purchased directly by consumers in supermarkets without medical supervision. In a study conducted in 6 hypertriglyceridemic patients supplemented with fish-oil concentrate, a 35% reduction in triacylglycerol was observed, which was accompanied by a 25% increase in LDL cholesterol, which suggested that n−3 fatty acids may enhance the propensity of VLDL cholesterol to be converted to LDL cholesterol (97). This could be a problem for those patients with modest elevations in triacylglycerol, in whom the elevation in LDL cholesterol impedes them from achieving their desired LDL-cholesterol concentration (8).

In summary, phytosterols and soluble fibers have a significant hypcholesterolemic effect, whereas n−3 fatty acids decreased triacylglycerol and increased total cholesterol, LDL cholesterol, and HDL cholesterol. The PCA and mixed models were able to show that this behavior is independent of dose, number of patients per study, age, and BMI but is associated with treatment length.

How should the results of this meta-analysis be used for the development of a functional food aimed at reducing the risk factors for coronary heart disease?

On the basis of the information generated by PCA and mixed models, the most adequate alternative for further studies should be the use of mixtures of the 3 bioactive substances to explore the maximum reduction of cholesterol, LDL cholesterol, and triacylglycerol with a maximum increase in HDL cholesterol. Other aspects of these 3 bioactive substances beside the hypolipidemic effect should be considered when developing function foods. For example, the major benefit of eating fiber-rich foods, including soluble fibers, may be a change in dietary pattern, resulting in a diet that is lower in saturated and trans unsaturated fats and cholesterol and higher in protective nutrients such as unsaturated fatty acids, minerals, folate, and antioxidant vitamins. Soluble fibers could promote slower absorption of macronutrients and increased satiety, which results in an overall lower energy intake (94). In addition, the contribution of n−3 fatty acids to the reduction in risk of coronary heart disease is mainly due to their effect at the vascular level. Eicosanoids synthesized from eicosapentaenoic acid are less potent in their ability to cause platelet aggregation or an inflammatory response than are corresponding eicosanoids derived from arachidonic acid (3, 83, 98, 99). Additional benefits of fish oils include improvements in endothelial function, better arterial elasticity, and modulation of inflammatory markers (100).

Conclusions

Although no health claims have been authorized on the basis of meta-analyses alone, they may be applied as supporting evidence for them. The multivariate statistical analysis applied in this study, PCA, showed correlations between 3 bioactive substances (n−3 fatty acids, soluble fibers, and phytosterols) and 4 blood biomarkers for coronary heart disease graphically. On the basis of these results, a more interesting proposal will be to develop further research that involves mixtures of these substances. The mixtures could be applied both for the purpose of developing new foods and for individual dietary planning, which will provide consumers with dietary alternatives capable of positively affecting plasma biomarkers and thus contribute to the control of coronary heart disease risk factors.

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