Inter-relationships between Arteriosclerotic Risk Factors: A Meta-Analysis

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--- Abstract ---

This study was performed to clarify the overall inter-relationships between the arteriosclerotic risk factors, including smoking, alcoholic consumption, obesity, serum cholesterol and triglyceride levels, high density lipoprotein, and systolic and diastolic blood pressure using a meta analysis method. The subjects of this study were included in 24 primary studies reported in Korea since 1980, which concerned arteriosclerotic risk factors. The results show that smoking is significantly associated with total cholesterol ($\bar{R} = .04$), triglyceride ($\bar{R} = .10$) and HDL-cholesterol ($\bar{R} = -.06$). Alcohol consumption is also significantly and positively associated with all three serum lipid parameters: cholesterol ($\bar{R} = .04$), triglyceride ($\bar{R} = .08$) and HDL-cholesterol ($\bar{R} = .10$). The effect of smoking and alcohol consumption on cholesterol levels were found to be almost equal. However, smoking has a predominant effect on triglyceride, whereas, alcohol consumption exerts an influence primarily on the HDL-cholesterol level. Obesity was positively correlated with cholesterol ($\bar{R} = .25$) and triglyceride ($\bar{R} = .21$), however, it was negatively correlated with HDL-cholesterol ($\bar{R} = -.14$). It appears that the serum lipid parameter, which shows strongest correlation with obesity, is the total cholesterol level. Obesity also showed a significant correlation with systolic ($\bar{R} = .19$) and diastolic blood pressure ($\bar{R} = .13$). Blood pressure was also positively correlated with cholesterol ($\bar{R} = .18$) and triglyceride ($\bar{R} = .26$), however, it correlated negatively with HDL-cholesterol ($\bar{R} = -.23$). In conclusion, the overall inter-relationships between the arteriosclerotic risk factors; smoking, alcohol consumption, obesity, serum lipid level and blood pressure were all found to be significant.

Key Words: Meta analysis, arteriosclerotic risk factor

INTRODUCTION

Arteriosclerosis is a major risk factor of coronary heart disease and cerebrovascular disease. According to representative data, arteriosclerotic changes of the coronary artery are responsible for approximately 48% of deaths in U.S.A (Center for Disease Control, 1984). In Korea, the mortality rate from chronic degenerative disease has increased recently as a result of an increment in the old population since the 1970s. It has been postulated that arteriosclerotic coronary artery disease is now the major cause of death in Korea.¹

It is believed that a variety of lifestyle and physiological factors play pathophysiological roles in the arteriosclerotic deterioration of blood vessels.² This study shows that lifestyle variables such as alcohol consumption, smoking, lack of exercise and stress are risk factors for arteriosclerosis. Similarly, physiological variables such as obesity, high serum lipid level (cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol) and high blood pressure are also reported to be risk factors.³,⁴ It has been reported that the death rate in U.S.A. between 1968 and 1976 was reduced by some 62.5%, which was attributed to overall reductions in population serum cholesterol (30%), smoking rate (24%) and hypertension (8.5%).³ Statistics of this type account for the importance attached to risk factors when treating arteriosclerosis.

Each of these risk factors predisposes the individual to arteriosclerosis, but risk factors acting in concert alter risk substantially because of their combined effects, are considered to be multiplicative. Therefore, persons with a number of risk factors are considered as high risk subjects. For this reason, the inter-relationships between risk factors is as important as investigating the independent effects of individual risk factors. We approached this issue by retrospectively
verifying and systematically analyzing data collected during previously published research studies into the inter-relationships between risk factors. Several studies have reported relationships among arteriosclerotic risk factors, but results have often been inconsistent. Attempts have been made in Korea to clarify the relationship between serum lipid level and lifestyle-related variables such as alcohol consumption and smoking. Therefore, we performed a meta-analysis of the Korean published literature to identify the overall inter-relationship between arteriosclerotic risk factors, and included both life-style and physiological variables.

MATERIALS AND METHODS

Research design

This study involved a meta-analysis of primary studies which concerned the inter-relationships between arteriosclerotic risk factors.

Sample

We searched for research reports which had been published after 1980 in Korea and extracted data concerning the relationships between arteriosclerotic risk factors such as alcohol consumption, smoking, obesity, serum lipid level and blood pressure. All papers were sourced from respected Korean journals dealt with subjects of this type (The Korean Journal of Internal Medicine, Korean Journal of Preventive Medicine, and The Korea Circulation Journal). Finally 24 studies that satisfied the following criteria were included in the meta-analysis: (1) Studies were performed to examine relationships between arteriosclerotic risk factors: smoking, alcohol consumption, serum lipid level, obesity, and blood pressure, (2) statistical data for calculating effective size was provided directly by the respective study, (3) studies were reported after 1980, and (4) the subjects of all studies were Korean.

Procedures

Measurement: The variables extracted from each report included author, year of publication, sample size, independent variable, dependent variable, etc, for a complete list refer to Appendix 1-4. If more than one tool had been used for measurement, then the most frequently used technique was selected for consistency.

Calculation of effect size: The magnitude of the effect size of outcome variable (r) was calculated using a Meta-Analysis Program developed by Song (Appendix 1-4). The effect size can be defined in the term of a standardized mean difference and calculated from the following expression: \( d = \frac{M_c - M_e}{\text{SD}_p} \) where \( M_c \) is the mean value of control group, \( M_e \) is the mean value of experimental group, and \( \text{SD}_p \) is the standard deviation of control and experimental group. The correlation coefficient, \( r \), which is unaffected by the units of measurement, may be used for assessing the effect size. Actually, the \( d \) and \( r \) value can be thought of as being equivalent to each other, the relationship between them is expressed by following formula:

\[
\begin{align*}
    r &= d/\sqrt{d^2 + 1/pq} \quad \text{or} \quad r = d/\sqrt{d^2 + \text{num}/N^2}
\end{align*}
\]

Song suggested that the binominal effective size display (BESD) introduced by Rosenthal and Rubin reflected the degree of effectiveness of a treatment. Indeed, the BESD is expressed by the correlation coefficient \( r \) which signified a ratio of events occurrence (or a ratio of event nonoccurrence) in the control and experimental groups. A meta-analysis can be used for analyzing treatment effects as well as clarifying the overall relationships between variables since \( d \) and \( r \) are equivalent to each other. In this study, we calculated the effect size using \( r \) and other statistical values such as mean, standard deviation, t-test, p value, F-test and \( \chi^2 \).

Data analysis techniques: First of all, we tested for homogeneity using a Meta-Analysis Program developed by Song. If homogeneity was established, the effect sizes \( (r) \) calculated from each study were combined. Then, the statistical significance and the 95% confidence interval for the combined effect size (\( \bar{R} \)) were computed. Hedges and Olkin suggested that the effect size upon a population could be overestimated when the sample size is small, which means that a larger sample size provides a better basis for estimating the effect size upon a population. Therefore, we calculated mean values by adding inverse value of variance to the effect size of outcome variables.
RESULTS

Meta-analysis of effect size for smoking, alcohol, and obesity upon serum lipid levels

To evaluate the effect of smoking, alcohol and obesity upon serum lipid levels, mean effect size ($\bar{R}$) was computed using the combined effect size ($r$) which was calculated from data provided in study reports (Appendix 1 and 2).

The relationship between smoking and serum lipid levels: The result of meta-analysis on the relationship between smoking and serum lipid is represented in Table 1. The overall combined correlation coefficient, of smoking and total cholesterol was calculated after testing the homogeneity of the correlation coefficients ($Q=4.83$, $p=.31$). $\bar{R}$ in this case was 0.04 which implied a relatively small, however, this was statistically significant ($U=5.38$, $p=.02$). The combined effect size of $d$ ($\bar{D}$) which was converted from $\bar{R}$ was 0.09. Five studies were included in this analysis.

Correlation coefficients of smoking and triglyceride were also homogeneous ($Q=1.70$, $p=.63$). $\bar{R}$ was 0.10 and statistically significant ($U=24.56$, $p=.0000$). $\bar{D}$ was 0.20, and 4 studies were included in this analysis.

Therefore, it can be suggested that the overall relationship between smoking and triglyceride is significantly positive.

$\bar{R}$ of smoking and HDL-cholesterol was calculated after testing the homogeneity of the correlation coefficients ($Q=1.70$, $p=.43$), found to be $-0.06$ and statistically significant ($U=6.22$, $p=.01$). $\bar{D}$ was $-0.11$ which implies a relatively small. Five studies were included in this analysis. This result suggests that the overall relationship between smoking and HDL-cholesterol is significantly negative.

The relationship between alcohol consumption and serum lipid levels: The result of meta-analysis upon the relationship between alcohol consumption and serum lipid is represented in Table 2. $\bar{R}$ for alcohol consumption and total cholesterol was calculated after testing the homogeneity of the correlation coefficients ($Q=7.78$, $p=.26$) and found to be 0.04 which implied a relatively small. And this was statistically significant ($U=7.47$, $p=.006$). $\bar{D}$ was 0.08 and 7 studies were included in this analysis.

Correlation coefficients of alcohol consumption and triglyceride were homogeneous ($Q=2.95$, $p=.57$), found to be 0.08 and statistically significant ($U=20.21$, $p=.000$). This result showed that the relationship between alcohol consumption and triglyceride is

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* Independent variables, †Dependent variables, $^1$Combined effect size of $r$, $^2$Combined BESD, $^3$Combined effect size of $d$, $^4$95% confidence interval of $\bar{R}$, $^5$Significance test for $\bar{R}$, $^6$Homogeneity test for the $r$ values of individual study.

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* Independent variables, †Dependent variables, $^1$Combined effect size of $r$, $^2$Combined BESD, $^3$Combined effect size of $d$, $^4$95% confidence interval of $\bar{R}$, $^5$Significance test for $\bar{R}$, $^6$Homogeneity test for the $r$ values of individual study.
inter-relationships between arteriosclerotic risk factors

Table 3. Results of meta-analysis: The Relationships between Obesity with Serum Lipid and Blood Pressure

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<tr>
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<td>.36</td>
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</table>

* Independent variables, † Dependent variables, ² Combined effect size of \( r \), ³ Combined BESD, ⁴ Combined effect size of \( d \), ⁵ 95% confidence interval of \( R \), ⁶ Significance test for \( R \), ⁷ Homogeneity test for the \( r \) values of individual study.

significantly positive. \( D \) was 0.16 and 4 studies were included in this analysis.

Correlation coefficients for alcohol consumption and HDL-cholesterol were also homogeneous \( (Q=5.19, p=.16) \), found to be 0.10 and statistically significant \( (U=28.63, p=.0000) \). These results show that alcohol consumption and HDL-cholesterol are significantly and positively correlated. \( D \) was 0.20 and 4 studies were included in this analysis.

The relationship between obesity and serum lipid levels: The result of meta-analysis upon the relationship between obesity and serum lipids is represented in Table 3. \( R \) of obesity and total cholesterol were also calculated after testing for homogeneity of the correlation coefficients \( (Q=10.82, p=.07) \). \( R \) in this case was 0.25 and statistically significant \( (U=273.03, p=.0000) \). \( D \) was 0.51 and 9 studies were included in this analysis.

The correlation coefficients of obesity and triglyceride were homogeneous \( (Q=3.66, p=.06) \), found to be 0.21 and statistically significant \( (U=67.63, p=.0000) \). This shows that the relationship between obesity and triglyceride is significantly positive. \( D \) was 0.44 and 7 studies were included in this analysis.

Correlation coefficients of obesity and HDL-cholesterol were also homogeneous \( (Q=5.21, p=.27) \), found to be -0.14 and statistically significant \( (U=28.58, p=.0000) \). This result demonstrates that the relationship between obesity and HDL-cholesterol is significantly negative. \( D \) was -0.28 which implies relatively small and 6 studies were included for this analysis.

Meta-analysis of effect size for obesity and serum lipids upon blood pressure

To evaluate the effects of obesity and serum lipid levels upon blood pressure, the mean effect size \( (\bar{R}) \) was computed using the combined effect size \( (r) \) which was determined from the data provided in study reports (Appendix 3 and 4).

The relationship between obesity and blood pressure: The relationship between obesity and blood pressure as determined by meta-analysis is shown in Table 3. \( \bar{R} \) of obesity and systolic blood pressure was calculated after testing the homogeneity of the correlation coefficients \( (Q=10.79, p=.06) \). \( \bar{R} \) in this case was 0.19 and statistically significant \( (U=160.00, p=.0000) \). This result shows that the relationship between obesity and systolic blood pressure is significantly positive. \( D \) was 0.39 and 11 studies were included in this analysis.

Correlation coefficients of obesity and diastolic blood pressure was homogeneous \( (Q=2.31, p=.80) \), found to be 0.13 and statistically significant \( (U=36.95, p=.0000) \). Therefore, the relationship between obesity and diastolic blood pressure is significant. \( D \) was 0.27 and 11 studies were included in this analysis.

The relationship between serum lipids and blood pressure: The relationship between serum lipids and blood pressure as determined by meta-analysis is represented by Table 4. Blood pressure was not divided into systolic and diastolic pressure for this analysis, because most of the studies involved comparisons of serum lipid levels in normotensive and hypertensive groups. When a study examined both
systolic and diastolic blood pressure separately, the systolic blood pressure only was included in the analysis.

$\bar{R}$ of blood pressure and total cholesterol was calculated after testing the homogeneity of the correlation coefficients ($Q=11.93$, $p=.04$). $\bar{R}$ was 0.18 and statistically significant ($U=76.85$, $p=.0000$). $\bar{d}$ was 0.36 and 7 studies were included in this analysis.

Correlation coefficients of blood pressure and triglyceride were homogeneous ($Q=5.55$, $p=.14$), found to be 0.26 and statistically significant ($U=67.37$, $p=.0000$). This result suggests that the relationship between blood pressure and triglyceride is significantly positive. $\bar{d}$ was 0.53 and 4 studies were included in this analysis. Cholesterol exhibited less effect on blood pressure than triglyceride (0.18 : 0.26). However, this difference was not statistically significant.

Correlation coefficients of blood pressure and HDL-cholesterol were also homogeneous ($Q=2.86$, $p=.41$). $\bar{R}$ in this case was $-0.23$ and statistically significant ($U=25.84$, $p=.0000$). The result demonstrates that the relationship between blood pressure and HDL-cholesterol is significant. $\bar{d}$ was $-0.48$ and 6 studies were included in this analysis.

**DISCUSSION**

Our results show that smoking is significantly and positively associated with serum cholesterol and triglyceride. In other words, cholesterol and triglyceride levels are increased by smoking. The difference between the high cholesterol ratio of the smoking (CBESD2=0.52) and nonsmoking groups (CBESD1=0.48) was 4% which was relatively small, but was statistically significant with a sample size of 500. The difference between the high triglyceride ratio of the smoking (CBESD2=0.55) and nonsmoking groups (CBESD1=0.45) was 10%. The mean sample size was 438. There was a significant tendency for the HDL-cholesterol level to be lower in smokers. The difference between the high HDL-cholesterol ratio of the smoking (CBESD2=0.47) and nonsmoking groups (CBESD1=0.53) was 6% and statistically significant (mean sample size: 500).

Alcohol consumption was positively associated with serum cholesterol, triglyceride and HDL-cholesterol. The difference between the high cholesterol ratio of the alcohol consuming (CBESD2=0.52) and non-consuming groups (CBESD1=0.48) was 4%, which was a relatively small though significance result, mean sample size 798. The difference between the high triglyceride ratio of the alcohol consuming (CBESD2=0.54) and nonconsuming groups (CBESD1=0.46) was 8%, mean sample size 695. The difference between the high HDL-cholesterol ratio of the alcohol consuming (CBESD2=0.55) and nonconsuming groups (CBESD1=0.45) was 10%, mean sample size 438.
Inter-relationships between Arteriosclerotic Risk Factors

Drinking (CBESD2 = 0.55) and nonconsuming groups (CBESD1 = 0.45) was 10%, which was also statistically significant, mean sample size 695.

Fig. 1 shows the effect of smoking and alcohol consumption on serum lipid parameters. The effects of smoking and alcohol consumption on cholesterol levels were similar. However, smoking had a predominant effect on triglyceride level, and alcohol consumption exerted greatest influence on the HDL-cholesterol level, but these differences were not statistically significant. Park et al.14 also showed that alcohol intake was positively related to HDL-cholesterol and concluded that it is the most significant independent positive variables for HDL-cholesterol. Similar results on the positive relationship between alcohol and HDL-cholesterol levels have been reported in other countries.31,32 It has been proposed that alcohol might increase HDL-cholesterol levels by inhibiting hepatic microsomal enzyme induction or suppressing cholesteryl ester transfer protein activity.14,31

Obesity is significantly associated with all three lipid parameters: cholesterol, triglyceride, and HDL-cholesterol. The results show that obesity is positively correlated with cholesterol and triglyceride, and negatively correlated with HDL-cholesterol. This result suggests higher cholesterol and triglyceride levels along with lower HDL-cholesterol level in the obese group. The difference between the high cholesterol ratio of the obese and non-obese groups was 25% which demonstrates a relatively large induced effect. Since the mean sample size was 1100, this value probably reflects the situation in the population at large. The difference between the high triglyceride ratio of the obese and non-obese group was 21%, mean sample size 731. On the other hand, the difference between high HDL-cholesterol ratio of the obese and non-obese groups was 14%, mean sample size 872. Fig. 1 also shows the degree of correlation between obesity and serum lipid parameters. It appears that the serum lipid variable shows the strongest correlation with obesity is cholesterol level, then triglyceride and HDL-cholesterol in that order. However, this difference was not statistically significant.

Obesity was significantly and qualitatively associated with both of systolic and diastolic blood pressure. The mean sample size in this case was 1052, which is probably large enough to reflect the general population. The difference between the high blood pressure ratio of the obese and non-obese groups was 19% for systolic blood pressure, and 13% for diastolic blood pressure. However, these differences were not statistically different.

Blood pressure was significantly associated with all three lipid parameters, cholesterol, triglyceride, and HDL-cholesterol. The results indicate that blood pressure is positively correlated with cholesterol and triglyceride, and negatively correlated with HDL-cholesterol. The difference between the high cholesterol ratio of the hypertensive and normotensive groups was 18%, mean sample size 540. The difference between the high triglyceride ratio of the hypertensive and normotensive groups was 26% and the difference between the high HDL-cholesterol ratio of the hypertensive and normotensive groups was 23%. The mean sample sizes involved in the triglyceride and HDL-cholesterol analysis with respect to blood pressure were 136 and 133, respectively. A comparison of the effect of these serum lipid parameters on blood pressure is presented in Fig. 1.

In conclusion, the overall inter-relationship of the arteriosclerotic risk factors, smoking, alcohol consumption, obesity, serum lipid level and blood pressure were significant in all cases, though in most cases the overall effect sizes were relatively small. However, the effect sizes for correlation between obesity and cholesterol as well as blood pressure and triglyceride showed medium. The degree of association between serum lipid levels and smoking and alcohol consumption was significant but relatively minor.

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