the rehabilitation of stroke patients and evolution of the level of their functional impairment. Nonetheless, we believe that our findings contribute to a better understanding of the prognosis of stroke patients and of stroke predictors in Japanese who are considered to be at higher risk of stroke than are people in other countries.

## Conclusions

Our findings confirm the importance of primary prevention of stroke, because Japanese are characterized by a larger proportion of hemorrhagic stroke and thereby a higher fatality rate after stroke. The maintenance of good nutrition may be important to improve the long-term prognosis after stroke. In addition, management of hypertension and atrial fibrillation is considered to be useful to avoid early death after cerebral infarction.

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# Editorial Comment

## Trends in Stroke Mortality

Stroke is a serious public health problem leading to long-term disabilities, recurrence, and death. Therefore, the prognosis of outcome is investigated in several epidemiological studies in recent years. Stroke mortality varies from country to country; an increase in mortality was observed in Eastern European countries, except in Poland, whereas mortality declined in other European population.[1] Biological, clinical, environmental, and social factors may interact to facilitate or interfere with recovery from stroke.[2] Barker and Lackland[3] have demonstrated that within Britain and the United States there are geographic variations in poststroke mortality that are not correlated with differences in adult lifestyle. In particular, these authors found a higher stroke mortality in areas of England and Wales characterized in the past by poor living standards. Hardie and coworkers,[4] in a population-based study in Australia, have found that the direct effects of initial stroke and cardiovascular diseases are the major causes of death after first-ever stroke.

The present study examines the 10-year prognosis, causes, and risk factors of death after first stroke in a Japanese cohort. A total of 1261 subjects, aged >=40 years and living in Hisayama on Kyushu Island in southern Japan, were enrolled

and followed from 1961 to 1987. When neurological symptoms were suspected, the patient underwent clinical and diagnostic examinations including lumbar puncture, cerebral angiography, and brain imaging. The 82.6% of patients who died underwent autopsy. To elucidate the risk factors for death, the authors have collected several clinical data: alcohol consumption, smoking habits, glucose intolerance, serum total cholesterol, body mass index, hypertension, and abnormal ECG findings. Multivariate statistical analysis indicated that age, lower body mass index, and hemorrhagic stroke were significant risk factors for death. The article describes differences between the presented findings and those obtained in previous studies from other authors. As concerns potential limitations of the study, the severity of the index stroke was not taken into account in the evaluation of risk factors for fatality.

Prospective studies on defined populations allow examination of patients representative of a broad range of cases including severe as well as very mild stroke. Therefore, these studies may better individuate and analyze parameters that may influence functional recovery, degree of disability, and stroke mortality. However, future studies have to consider in the employed statistical models also other variables related to the standards of medical care and rehabilitation, psychiatric complications, type of discharge, quality of life, and socioeconomic status.

Depression has been found to be a frequent psychiatric complication of stroke also in long-term survivors. The relationship between depression and location of brain damage is disputed, but several studies suggest that depression may impair long-term recovery in activities of daily living after stroke and can adversely affect resumption of social activities.[5] Can mood disorders influence long-term mortality after stroke?

The role of comorbidity for recovery is debatable, however; for example, the Framingham study has demonstrated that ischemic stroke associated with atrial fibrillation leads to recurrence, higher disability, and more frequent death. Therefore, the medical care standard, including the possibility of having adequate pharmaceutical treatments for concomitant diseases, can explain some differences in mortality trends in different countries and in different geographic areas in the same country.

According to several trials,[2,6] home care appears to be a fruitful intervention. The familiar settings and the resumption of previous activities are probably to prompt motivation; task- and context-oriented rehabilitation approaches may improve activities of daily living, social relationships, motor dexterity, and walking. Can the benefits from a long-term personalized assistance at home reduce mortality after stroke?

To have a good understanding of the factors affecting epidemiological trends in stroke mortality as well as in long-term functional recovery, population-based studies can play a fundamental role if they are well planned considering the above-mentioned parameters, also taking into account the subtypes and the severity of cerebral vascular damages and the level of disability after the acute phase.

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# Insulin-mediated effects of alcohol intake on serum lipid levels in a general population: The Hisayama Study

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## Abstract

To determine whether the beneficial effects of alcohol on lipid concentrations are mediated by insulin levels, we performed a cross-sectional analysis in 2103 nondiabetic men and women aged 40 to 79 years from a general Japanese population in Hisayama. The multivariate-adjusted sum of fasting and 2-hour postloading insulin levels and the insulin resistance index significantly decreased with elevating alcohol intake levels in men ($P < 0.01$ for the trend) but not in women. No dose-response relations between alcohol intake and glucose levels were observed. In both sexes, high-density lipoprotein cholesterol (HDLC) significantly increased with elevated alcohol intake ($P < 0.01$), whereas total cholesterol and low-density lipoprotein cholesterol (LDLC) were inversely correlated with alcohol intake ($P < 0.01$). In contrast, triglycerides (TGs) levels in men showed a J-shaped relation to alcohol dose, with moderate drinkers (10–29 g/d) having the lowest levels. Estimates using regression models indicated that for men, 10% of the alcohol-induced increase in HDLC and 2% of the alcohol-induced decrease in LDLC were insulin mediated. It was also estimated for male subjects that 36% of the reduction in TGs due to low to moderate alcohol intake was mediated by low levels of insulin and that this insulin-mediated pathway reduced the positive alcohol-TG relation by 13% in cases of moderate to heavy drinking. Our data suggest that regular alcohol consumption dose-dependently increased insulin sensitivity among male nondiabetics, but the insulin-mediated beneficial effects of alcohol on lipid concentrations were relatively small. 

*Keywords:* Alcohol; Lipids; Insulin; Epidemiology; Population

## 1. Introduction

Most epidemiologic studies have reported that moderate alcohol consumption is associated with decreased incidence of coronary heart disease [1]. The beneficial effects of alcohol consumption on serum lipid levels have been proposed as one of the major plausible explanations for this association: A positive linear relation has been demonstrated between alcohol intake and high-density lipoprotein cholesterol (HDLC) level [2,3], whereas a negative linear relation was shown between alcohol intake and low-density lipoprotein cholesterol (LDLC) level [4]. Insulin resistance and compensatory hyperinsulinemia are known to be associated with decreased HDLC, increased triglycerides (TGs), hypertension, obesity, and glucose intolerance, thereby increasing the risk of coronary heart disease [5,6]. Although the acute effects of alcohol ingestion on insulin resistance or insulinemia remain controversial [7–12], several recent epidemiologic studies have shown that regular alcohol consumption is associated with lowered insulin levels [3,13–16]. Furthermore, in an experimental study in which atherosclerosis-prone obese rats were exposed to long-term alcohol intake, fasting insulin levels were decreased and pancreatic β-cell hyperplasia was reduced, suggesting that sensitivity to insulin was increased by chronic alcohol intake [17]. Based on these findings, Razay et al [3] and Facchini et al [18] hypothesized that the beneficial effects of alcohol on lipid concentrations—especially HDLC—are mediated by alcohol-induced reductions in insulin level and thus that insulin plays a central role in the link between moderate alcohol consumption and the risk of coronary heart disease. To our knowledge, however, there has been no report evaluating the relationships between regular alcohol intake and serum lipid levels while also accounting for insulin levels. Furthermore, these

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positive effects of alcohol on lipid concentrations have mainly been demonstrated in individuals with low to moderate alcohol consumption but are less clear in cases of large alcohol intake [3,14,16].

The purpose of this study was to explore the relationships between habitual alcohol consumption and surrogate measures of insulin resistance among nondiabetic subjects based on a survey of a general Japanese population in Hisayama. In addition, we examined the degree to which insulinemia mediated the effect of alcohol consumption on the concentration of each lipid.

## 2. Methods

### 2.1. Study population

A prospective population survey of cardiovascular disease and its risk factors was initiated in 1961 in Hisayama Town, which is a sub-rural community adjacent to Fukuoka City, a metropolitan area on Kyushu Island of Japan. In 1988, as a part of the study, a cross-sectional diabetes survey of Hisayama residents was conducted. Details of this survey have been published previously [19]. Briefly, of all 3227 residents aged 40 to 79 years based on the town registry, 2587 (80.2%) consented to take part in the examination. Of these, 2480 (1073 men and 1407 women) underwent a comprehensive assessment including a fasting 75-g oral glucose tolerance test (OGTT). A total of 297 subjects (161 men and 136 women) were excluded because they took hypoglycemic agents or met the 1998 World Health Organization criteria for diabetes [20] based on the OGTT, and two subjects with missing information on insulin level were excluded. An additional 78 ex-drinkers (66 men and 12 women) were excluded because they might have been advised to abstain from drinking due to pre-existing medical conditions or risks. The final study group comprised 2103 subjects (845 men and 1258 women).

### 2.2. Clinical evaluation and laboratory measurements

All participants attended the Hisayama Health Center. Alcohol consumption was assessed by a self-administered questionnaire, which was completed in advance and was checked by trained nurses. Participants answered items on the frequency of their habitual alcohol intake over the last year and the kinds and amounts of alcoholic beverages customarily consumed. These measurements were converted into daily amounts of alcohol (g/d) and were classified using five categories: no (0 g/d), light (<10 g/d), moderate (10–29 g/d), borderline (30–49 g/d), and heavy (≥50 g/d) alcohol intake. The questionnaire also investigated previous medical history, with items on diabetes and hypertension, current medical treatment, physical activity, and smoking habits. Physical activity was defined as present or not based on whether respondents exercised daily during their leisure time. Smoking habits were classified as currently habitual or not.

A dietary survey was also conducted using the semiquantitative food frequency method [21]. Dietitians checked a self-administered questionnaire on food intake over the last year by showing the respondents food models of actual size. Nutritional intake was calculated using the fourth revision of the Standard Tables of Food Composition in Japan [22,23].

Body height and weight were measured in light clothing without shoes, and body mass index (BMI) (kg/m$^2$) was calculated as an indicator of obesity. Abdominal girth at the umbilical level and hip circumference at 5 cm below the spinae iliaca anterior superior were measured and used to calculate the waist-to-hip ratio. Before the OGTT, sitting systolic and diastolic blood pressures were measured three times after a rest of at least 5 minutes by a standard mercury sphygmomanometer with a standard cuff. The average of three measurements was used for data analysis. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive agents.

The fasting 75-g OGTT was performed between 8 AM and 10:30 AM. Before and 120 minutes after ingestion of the carbohydrate solution, blood samples were obtained for laboratory measurements. These specimens were analyzed within 24 hours after venipuncture in the central study laboratory (Japan Medical Laboratory Inc., Fukuoka, Japan), which participates in the Centers for Disease Control Lipid Standardization Program. The plasma glucose levels were determined by the glucose oxidase. Serum insulin levels were determined by a commercial double-antibody, solid-phase radioimmunoassay. Fasting total cholesterol, HDLC, and TG levels were measured enzymatically using an autoanalyzer. The measurement of HDLC was performed after the precipitation of very low-density lipoprotein (VLDL) and low-density lipoprotein with dextran sulfate and magnesium. LDLC concentrations were calculated using the Friedewald formula. Serum γ-glutamyl transpeptidase was measured using Orlowsky's method with modifications, and the serum uric acid level was measured using Morgenstern's method. The relative insulin resistance index was calculated for each subject as the product of fasting insulin (mU/L) and fasting plasma glucose (mmol/L) divided by 22.5, as described by Matthews et al [24].

### 2.3. Statistical analysis

The sum of the fasting and 2-hour postloading insulin concentrations was used as an index of insulinemia. Serum insulin and plasma glucose values were transformed into logarithms to improve the skew, and the geometric means were determined. The relationships between alcohol consumption and relevant factors were tested by linear regression analysis or Mantel-Haenszel chi-square test as appropriate. Multivariate-adjusted mean values of insulin, glucose, and lipids were estimated by the covariance method, and the trends in crude and multivariate-adjusted mean values of these variables among groups were tested by multiple regression analysis.

To determine the extent to which alcohol-lipid relations were mediated by insulin levels, multiple linear regression models were obtained for alcohol with covariates, and insulin was added to the model. If insulin played a role in the biological pathways through which alcohol affects lipid concentrations, the association with alcohol in the model would be expected to change as insulin was added. This would occur because the insulin-mediated portion of the alcohol-lipid relationship would be associated with insulin rather than alcohol.

## 3. Results

Mean values or frequencies of potential relevant factors are presented by alcohol intake levels for men in Table 1. Nondrinkers (0 g/d) were significantly older than current drinkers. Mean systolic and diastolic blood pressures and the frequency of hypertension significantly increased with elevating alcohol intake, but an opposite effect was observed for antihypertensive medication. Body weight and BMI did not change by alcohol intake, whereas mean values for the waist-to-hip ratio significantly increased with elevating alcohol consumption. No dose-response relationships were observed between alcohol intake and the frequencies of impaired glucose tolerance and physical activity, whereas the frequency of smoking habits and the mean values of γ-glutamyl transpeptidase and uric acid increased with elevating alcohol intake. Total energy intake (excluding that from alcoholic beverages) and saturated fatty acid intake remained unchanged across alcohol intake levels. Women showed the same tendencies as men for all relevant factors but three: Women showed no dose-response relationships for the frequency of antihypertensive medication and the mean waist-to-hip ratio, and their total energy intake was significantly decreased with elevating alcohol intake (Table 2).

For men, the crude mean values of serum insulin and the insulin resistance index significantly decreased with elevating alcohol consumption ($P < 0.05$) (Table 3). These tendencies did not change even after adjustment for age, BMI, waist-to-hip ratio, physical activity, smoking habits, hypertension, antihypertensive medication, total energy intake, and saturated fatty acid intake ($P < 0.01$). In contrast, no dose-response relationship was observed between alcohol consumption and fasting glucose. The crude 2-hour post-loading plasma glucose level showed a significant relationship with alcohol intake levels ($P < 0.05$), but this relation was not significant after adjustment for other relevant factors. These relations were not seen in women (Table 4).

For men, crude and multivariate-adjusted serum HDLC concentrations significantly increased with elevating alcohol intake ($P < 0.01$), whereas total cholesterol and LDLC levels showed inverse dose-response relationships with alcohol intake ($P < 0.01$) (Table 3). In contrast, TG values demonstrated a J-shaped relation, with moderate drinkers having the lowest levels; significant differences were seen between moderate drinkers, nondrinkers, and heavy drinkers after adjustment for other variables ($P < 0.05$). The same tendencies were observed for women, with the exception of total cholesterol (Table 4).

Table 5 presents crude and multivariate-adjusted mean values of serum lipid concentrations by serum insulin quartiles in each sex. In both sexes, crude mean values of total cholesterol, LDLC, and TG significantly increased with elevating insulin levels, whereas an opposite relation was seen for HDLC. After adjustment for other variables, these relations did not change for total cholesterol, LDLC, or TG, but the significant relation between LDLC and insulin disappeared.

Table 1
Mean values or frequencies of potential cardiovascular risk factors and selected laboratory variables by daily alcohol consumption in 845 nondiabetic men from the Hisayama study, 1988

| | Alcohol intake (g/d) | | | | | |
|---|---|---|---|---|---|---|
| Variables | 0 ($n$ = 300) | <10 ($n$ = 54) | 10–29 ($n$ = 195) | 30–49 ($n$ = 155) | ≥50 ($n$ = 141) | $P$ value for trend |
| Age, y | 58 | 55 | 54 | 57 | 53 | <0.01 |
| Systolic blood pressure, mm Hg | 128 | 134 | 133 | 138 | 138 | <0.01 |
| Diastolic blood pressure, mm Hg | 76 | 81 | 83 | 83 | 83 | <0.01 |
| Hypertension, % | 32 | 39 | 47 | 52 | 52 | <0.01 |
| Antihypertensive medication, % | 34 | 43 | 37 | 35 | 14 | <0.01 |
| Body weight | 59.1 | 60.1 | 62.8 | 59.2 | 60.5 | ns |
| BMI, kg/m$^2$ | 22.6 | 22.9 | 23.3 | 22.7 | 22.5 | ns |
| Waist/hip ratio | 0.908 | 0.919 | 0.921 | 0.923 | 0.929 | <0.01 |
| Impaired glucose tolerance, % | 19 | 15 | 20 | 30 | 23 | ns |
| Physically active, % | 21 | 32 | 27 | 25 | 19 | ns |
| Current smoker, % | 47 | 43 | 46 | 57 | 56 | <0.05 |
| γ-Glutamyl transpeptidase, mU/mL | 22 | 25 | 35 | 56 | 64 | <0.01 |
| Uric acid, μmol/L | 330 | 351 | 363 | 355 | 369 | <0.01 |
| Total energy intake, kcal/d | 1766 | 1702 | 1798 | 1725 | 1625 | ns |
| Saturated fatty acid intake, g/d | 13.7 | 12.5 | 14.1 | 13.6 | 13.2 | ns |

*Abbreviations:* BMI, body mass index; ns, not significant.

Table 2
Mean values or frequencies of potential cardiovascular risk factors and selected laboratory variables by daily alcohol consumption in 1258 nondiabetic women from the Hisayama study, 1988

| Variables | Alcohol intake (g/d) | | | | P value for trend |
|---|---|---|---|---|---|
| | 0 ($n$ = 1142) | <10 ($n$ = 51) | 10–29 ($n$ = 45) | ≥30 ($n$ = 20) | |
| Age, y | 57 | 53 | 55 | 54 | <0.05 |
| Systolic blood pressure, mm Hg | 129 | 126 | 133 | 144 | <0.01 |
| Diastolic blood pressure, mm Hg | 75 | 75 | 79 | 86 | <0.01 |
| Hypertension, % | 32 | 27 | 33 | 70 | <0.05 |
| Antihypertensive medication, % | 40 | 29 | 53 | 57 | ns |
| Body weight, kg | 51.3 | 52.1 | 51.7 | 51.4 | ns |
| BMI, kg/m$^2$ | 22.9 | 22.7 | 22.9 | 23.3 | ns |
| Waist/hip ratio | 0.908 | 0.895 | 0.920 | 0.912 | ns |
| Impaired glucose tolerance, % | 21 | 12 | 24 | 15 | ns |
| Physically active, % | 13 | 16 | 13 | 10 | ns |
| Current smoker, % | 5 | 14 | 27 | 50 | <0.01 |
| γ-Glutamyl transpeptidase, mU/mL | 16 | 19 | 22 | 82 | <0.01 |
| Uric acid, μmol/L | 256 | 266 | 278 | 335 | <0.01 |
| Total energy intake, kcal/d | 1565 | 1546 | 1462 | 1454 | <0.05 |
| Saturated fatty acid intake, g/d | 12.7 | 13.1 | 12.1 | 13.1 | ns |

*Abbreviations:* BMI, body mass index; ns, not significant.

Table 6 shows the standardized partial regression coefficients of alcohol based on 1 SD interval (22.4 g) for lipid concentrations in the base models with covariates and with the addition of insulin along with the percent changes of the coefficients between these models by sex. The covariates of the base models were age, BMI, waist-to-hip ratio, physical activity, smoking habits, hypertension, antihypertensive medication, total energy intake, and saturated fatty acid intake. In the base models for men, alcohol was significantly related to HDLC with a standardized partial regression coefficient of 0.0446 ($P < 0.01$); namely, HDLC increased by 0.0446 mmol/L with increasing 1 SD of alcohol intake a day. Adding insulin to the model decreased the coefficient to 0.0402 ($P < 0.01$), suggesting that 10% of the alcohol-induced increase in HDLC level was mediated by insulinemia. Only 2% of the alcohol-induced decrease in LDLC was mediated by insulin. The relation between alcohol and TG levels was J-shaped but was not statistically significant in quadratic models (data not shown). In the linear model, the coefficient of alcohol for TG levels increased by 38% (from 0.0310 to 0.0428) after adding insulin to the model. This suggests that the insulin-mediated biological pathway reduced the positive relation between alcohol and TGs by 38%. We next performed the same analyses in two subgroups: non- to moderate drinkers and moderate to heavy drinkers. Among non- to moderate drinkers, the coefficient of alcohol for TGs was negative (−0.0799, $P = 0.11$) in the base model; after inclusion of insulin in the model, it became less negative (−0.0508, $P = 0.29$), showing a 36% decrease in slope. Among moderate to heavy drinkers, the positive coefficient of alcohol increased by 13%, from 0.0669 to 0.0757 ($P < 0.01$ for both) after adding insulin. These results suggested that for non- to moderate drinkers, 36% of the TG-lowering effect of alcohol was mediated by insulin, whereas the insulin-mediated pathway reduced the positive alcohol–TG relation by 13% in moderate to heavy drinkers.

When the insulin resistance index was included in the models in place of insulin, the patterns of change in the coefficients for alcohol were the same as for the models including insulin, but these changes were less pronounced. In women, changes in these coefficients were trivial.

## 4. Discussion

### *4.1. Associations of alcohol with glucose and insulin metabolism*

Among nondiabetic men with alcohol consumption habits ranging from abstinence to 50 g or more of alcohol per day, we found a significantly inverse relationship between the amounts of habitual alcohol consumption and serum insulin concentrations even after adjustment for major factors known to be associated with insulin levels (ie, age, BMI, waist-to-hip circumference ratio, physical activity, smoking, hypertension, antihypertensive medication, total energy intake, and saturated fatty acid intake). The relationship seemed to be linear, but fasting and postload glucose levels did not show any apparent change across alcohol intake levels, implying that regular alcohol consumption improves insulin sensitivity. These findings were supported by the fact that the insulin resistance index was inversely correlated with alcohol intake levels. On the other hand, we did not find these associations in women, probably because of the small number of female drinkers, especially those who consumed borderline to heavy amounts of alcohol.

Previous findings on the acute effects of alcohol ingestion on glucose and insulin metabolism are inconsistent. Several clinical studies have shown that alcohol had no effect on insulin or glucose response to a glucose challenge [7] or that alcohol worsened glucose tolerance [8,12]. In contrast, the chronic effects of alcohol consumption on glucose metabolism and insulin resistance/insulinemia would seem to be quite different from the

Table 3
Crude and multivariate-adjusted mean values of insulin, glucose, and lipid concentrations by daily alcohol consumption in 845 nondiabetic men from the Hisayama study, 1988

| Variables | Alcohol intake (g/d)[a] 0 ($n$ = 300) | <10 ($n$ = 54) | 10–29 ($n$ = 195) | 30–49 ($n$ = 155) | ≥50 ($n$ = 141) | $P$ value for trend |
|---|---|---|---|---|---|---|
| Insulin,[b] pmol/L | | | | | | |
| Crude | 229 | 238 | 222 | 222 | 189 | <0.05 |
| Adjusted | 239 | 240 | 211 | 220 | 184 | <0.01 |
| Insulin resistance index | | | | | | |
| Crude | 1.49 | 1.36 | 1.53 | 1.33 | 1.27 | <0.05 |
| Adjusted | 1.54 | 1.35 | 1.42 | 1.33 | 1.29 | <0.01 |
| Fasting glucose, mmol/L | | | | | | |
| Crude | 5.51 | 5.46 | 5.56 | 5.64 | 5.57 | ns |
| Adjusted | 5.51 | 5.46 | 5.55 | 5.63 | 5.58 | ns |
| Postload glucose, mmol/L | | | | | | |
| Crude | 5.84 | 5.99 | 6.30 | 6.42 | 6.32 | <0.05 |
| Adjusted | 5.88 | 6.00 | 6.28 | 6.35 | 6.33 | ns |
| Total cholesterol, mmol/L | | | | | | |
| Crude | 5.20 | 4.95 | 5.13 | 4.90 | 4.90 | <0.01 |
| Adjusted | 5.24 | 4.96 | 5.09 | 4.93 | 4.87 | <0.01 |
| HDL cholesterol, mmol/L | | | | | | |
| Crude | 1.21 | 1.14 | 1.26 | 1.33 | 1.39 | <0.01 |
| Adjusted | 1.20 | 1.14 | 1.27 | 1.34 | 1.37 | <0.01 |
| LDL cholesterol, mmol/L | | | | | | |
| Crude | 3.36 | 3.17 | 3.21 | 2.90 | 2.72 | <0.01 |
| Adjusted | 3.36 | 3.17 | 3.19 | 2.93 | 2.74 | <0.01 |
| Triglycerides, mmol/L | | | | | | |
| Crude | 1.25 | 1.24 | 1.23 | 1.25 | 1.52 | <0.01 |
| Adjusted | 1.31 | 1.25 | 1.18 | 1.25 | 1.47 | <0.05 |

*Abbreviations:* ns, not significant; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Values were adjusted for age, body mass index, waist/hip ratio, physical activity, smoking, hypertensive state, antihypertensive medication, total energy intake, and saturated fatty acid intake.

[b] Insulin = the sum of fasting and 2-hour postloading insulin concentrations.

acute effects. In previous epidemiologic studies, a consistent negative correlation between alcohol consumption and insulin levels has been observed [25–27], although these findings were not explored in detail. Recently, several cross-sectional epidemiologic studies have indicated that moderate amounts of alcohol intake reduced insulin levels, but their results differed with respect to the effects of larger amounts of alcohol [3,13–16]. Kiechl et al [14] have shown in 820 healthy nondiabetic Italian men and women that serum insulin concentration and insulin resistance index dose-dependently decreased with increasing amounts of alcohol beyond 100 g a day. These findings were in accord with the findings in our study. Conversely, in men and women in east England [3,15] and in selected subjects of the Normative Aging Study [16], U-shaped relations between alcohol consumption and insulin concentrations were observed, with the lowest insulin concentrations occurring in subjects who consumed moderate amounts of alcohol (about 10–30 g/d). The use of different methods of excluding diabetic subjects (OGTT or disease history only), the effects of other factors related to insulin, or genetic differences among the subjects might have contributed to these discrepant results.

### 4.2. Association of alcohol intake with lipids

Our data showed that chronic alcohol consumption and TG levels assumed a J-shaped relation and that chronic alcohol consumption was associated with higher concentrations of HDLC and lower concentrations of LDLC. Long-term consumption of low to moderate amounts of alcohol might restrain TG levels mainly due to peripheral breakdown of VLDL by the actions of lipoprotein lipase in adipose tissue, whereas heavy drinking could increase TGs due to disturbed metabolism of free fatty acids and increased production of VLDL in the liver [28], resulting in a J-shaped relation between TG concentration and alcohol consumption. On the other hand, our study showed a positive correlation between serum insulin and TG levels. It is known that hyperinsulinemia increases the production of circulating TGs by causing the production of VLDL particles in the liver [29]. Insulin resistance also decreases the activity of lipoprotein lipase [30], leading to decreased peripheral breakdown of VLDL in adipose tissue and thereby to an increase in serum TG concentration. Thus, moderate alcohol intake could decrease TG levels through its beneficial effect on insulin resistance or insulinemia. Our findings from the multiple regression models suggest that, for men, 36% of the TG-lowering effect of low to moderate alcohol consumption is mediated by decreased insulin levels and that this beneficial insulin-mediated effect of alcohol reduces the alcohol-induced increase in TG levels by 13% in cases of moderate to heavy drinking.

Similarly, HDLC increases through several pathways in response to chronic alcohol consumption. The alcohol-

Table 4
Crude and multivariate-adjusted mean values of insulin, glucose, and lipid concentrations by daily alcohol consumption in 1258 nondiabetic women from the Hisayama study, 1988

| Variables | Alcohol intake (g/d)[a] 0 ($n$ = 1142) | <10 ($n$ = 51) | 10–29 ($n$ = 45) | ≥30 ($n$ = 20) | $P$ value for trend |
|---|---|---|---|---|---|
| Insulin,[b] pmol/L | | | | | |
| Crude | 239 | 240 | 211 | 220 | ns |
| Adjusted | 256 | 273 | 256 | 248 | ns |
| Insulin resistance index | | | | | |
| Crude | 1.50 | 1.53 | 1.58 | 2.01 | ns |
| Adjusted | 1.62 | 1.66 | 1.63 | 1.74 | ns |
| Fasting glucose, mmol/L | | | | | |
| Crude | 5.40 | 5.35 | 5.49 | 5.69 | <0.05 |
| Adjusted | 5.39 | 5.39 | 5.49 | 5.64 | <0.05 |
| Postload glucose, mmol/L | | | | | |
| Crude | 6.44 | 6.26 | 6.83 | 6.31 | ns |
| Adjusted | 6.31 | 6.23 | 6.76 | 6.20 | ns |
| Total cholesterol, mmol/L | | | | | |
| Crude | 5.54 | 5.21 | 5.35 | 4.78 | ns |
| Adjusted | 5.57 | 5.30 | 5.39 | 5.02 | ns |
| HDL cholesterol, mmol/L | | | | | |
| Crude | 1.34 | 1.42 | 1.38 | 1.43 | <0.05 |
| Adjusted | 1.32 | 1.38 | 1.37 | 1.47 | <0.01 |
| LDL cholesterol, mmol/L | | | | | |
| Crude | 3.67 | 3.32 | 3.42 | 2.57 | <0.01 |
| Adjusted | 3.70 | 3.40 | 3.45 | 2.83 | <0.01 |
| Triglycerides, mmol/L | | | | | |
| Crude | 1.03 | 0.95 | 1.05 | 1.54 | <0.01 |
| Adjusted | 1.07 | 1.03 | 1.07 | 1.47 | <0.05 |

*Abbreviations:* ns, not significant; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Values were adjusted for age, body mass index, waist/hip ratio, physical activity, smoking, hypertensive state, antihypertensive medication, total energy intake, and saturated fatty acid intake.

[b] Insulin: the sum of fasting and 2-hour postloading insulin concentrations.

induced increase in the activity of lipoprotein lipase enhances the synthesis of HDLC from the products of VLDL catabolism in adipose tissue [28]. Alcohol also reduces the activity of hepatic TG lipase, which is responsible for the removal of HDL from the circulation [31]. In addition, alcohol could augment production of apolipoprotein A-I in the liver, which is a constituent part of HDL particles in the periphery [32]. On the other hand, insulin resistance or hyperinsulinemia affects the activities of adipose tissue lipoprotein lipase [33] and increases the amount and thus the activities of hepatic TG lipase [34]; these changes may result in an inverse association between insulin and HDLC levels, as seen in our subjects. Thus, alcohol intake could increase HDLC levels through its beneficial effects on insulin resistance/insulinemia. According to our findings from the multiple regression analysis, however, this insulin-mediated pathway could not have been responsible for more than 10% of the observed association between alcohol and HDLC.

It is known that acetaldehyde, an intermediate product of alcohol catabolism, modifies LDL in the circulation and increases its removal rate, leading to a reduction of plasma LDLC levels [4]. In our subjects, the crude significant relationship between insulin and LDLC levels disappeared after adjustment for other relevant factors. This was compatible with previous findings that measures of insulin resistance were not directly associated with LDLC levels [14]. These findings, together with findings from our regression analysis, suggest that the effect of alcohol on LDLC levels is not mediated by insulin.

### 4.3. Limitations

The primary limitation of this study is that our study subjects were restricted those who did not have diabetes, and consequently the full spectrum of insulin resistance was not explored. We performed this selection to exclude subjects with failing β cells and for comparability with related reports in which subjects with diabetes were also excluded. The effects of alcohol on insulin resistance and lipid concentration differ between diabetic and normal subjects; it is known that large amounts of alcohol deteriorate glucose and insulin metabolism in diabetes [35]. Thus, the insulin-mediated effects of alcohol on lipid concentrations should be examined separately in diabetic and normal subjects. Further studies are needed to elucidate this issue for subjects with diabetes.

The second limitation is that, like all studies dealing with alcohol, the present study is subject to possible biases, such as under-reporting of alcohol consumption. That this under-reporting does not seem to occur in Japan might be due to the tolerance toward alcohol use in Japanese society [36]. In the present study, alcohol-related variables such as

Table 5
Crude and multivariate-adjusted mean values of lipid concentrations by insulin level from the Hisayama study, 1988

A. 845 non-diabetic men

| Variables | Quartile of insulin[a] level (pmol/L)[b] ≤165 ($n$ = 289) | 166–252 ($n$ = 196) | 253–380 ($n$ = 186) | ≥381 ($n$ = 174) | $P$ value for trend |
|---|---|---|---|---|---|
| Total cholesterol, mmol/L | | | | | |
| Crude | 4.88 | 4.99 | 5.26 | 5.24 | <0.01 |
| Adjusted | 4.93 | 5.00 | 5.25 | 5.21 | <0.01 |
| HDL cholesterol, mmol/L | | | | | |
| Crude | 1.35 | 1.28 | 1.23 | 1.17 | <0.01 |
| Adjusted | 1.32 | 1.28 | 1.24 | 1.19 | <0.01 |
| LDL cholesterol, mmol/L | | | | | |
| Crude | 3.02 | 3.08 | 3.27 | 3.19 | <0.05 |
| Adjusted | 3.05 | 3.08 | 3.26 | 3.19 | ns |
| Triglycerides, mmol/L | | | | | |
| Crude | 1.03 | 1.21 | 1.48 | 1.69 | <0.01 |
| Adjusted | 1.12 | 1.22 | 1.43 | 1.53 | <0.01 |

B. 1258 non-diabetic women

| Variables | Quartile of insulin level (pmol/L) ≤165 ($n$ = 253) | 166–252 ($n$ = 319) | 253–380 ($n$ = 351) | ≥381 ($n$ = 335) | $P$ value for trend |
|---|---|---|---|---|---|
| Total cholesterol, mmol/L | | | | | |
| Crude | 5.36 | 5.45 | 5.52 | 5.68 | <0.01 |
| Adjusted | 5.42 | 5.47 | 5.53 | 5.55 | <0.01 |
| HDL cholesterol, mmol/L | | | | | |
| Crude | 1.43 | 1.35 | 1.35 | 1.28 | <0.01 |
| Adjusted | 1.39 | 1.33 | 1.33 | 1.30 | <0.01 |
| LDL cholesterol, mmol/L | | | | | |
| Crude | 3.50 | 3.62 | 3.64 | 3.75 | <0.01 |
| Adjusted | 3.56 | 3.63 | 3.64 | 3.61 | ns |
| Triglycerides, mmol/L | | | | | |
| Crude | 0.85 | 0.96 | 1.03 | 1.28 | <0.01 |
| Adjusted | 0.95 | 1.04 | 1.11 | 1.26 | <0.01 |

*Abbreviations:* HDL, high-density lipoprotein; LDL, low-density lipoprotein; ns, not significant.

[a] Insulin: the sum of fasting and 2-hour postloading insulin concentrations.

[b] Values were adjusted for age, body mass index, waist/hip ratio, physical activity, smoking, hypertensive state, antihypertensive medication, total energy intake, and saturated fatty acid intake.

hypertension, γ-glutamyl transpeptidase, and uric acid showed clear dose-response relationships with alcohol consumption, suggesting that the reliability of self-reported alcohol intake in our study was high and that the frequency of deliberate reporting of lower-than-actual consumption was relatively low.

Finally, we did not have information on treatment for dyslipidemia among our subjects. This limitation would likely contribute to underestimation of the relationship between alcohol intake and lipid concentrations. Compared with Caucasian populations, however, Japanese are characterized by lower cholesterol levels, lower incidence of coronary heart disease, and less pronounced association between hyperlipidemia and cardiovascular disease [37]. Thus, treatment for dyslipidemia was not prevalent in Japan at the time of the present study (1988). Although awareness and treatment of dyslipidemia have increased in Japan over the last decade, only 4.9% of dyslipidemic Hisayama residents were receiving treatment in 1993, 5 years after the survey used for the present study. We therefore conclude that dyslipidemia treatment did not seriously affect the present findings.

## 5. Conclusion

Because relative hyperinsulinemia is considered to be a risk factor for cardiovascular disease through a variety of possible mechanisms other than lipoprotein metabolism or blood pressure [38], the finding of an independent inverse relation of alcohol intake to insulin levels could reflect additional mechanisms by which alcohol may lower the risk of cardiovascular disease. However, the insulin-mediated effects of habitual alcohol intake on lipid concentrations were suggested to be modest, and the biological mechanism for the inverse relationship between alcohol intake and insulin levels is still unknown. Further studies are needed to clarify this issue.

Table 6
Standardized partial regression coefficients of daily alcohol consumption for lipid concentrations in general linear models from the Hisayama study, 1988

| Model | HDL-C | LDL-C | Log TG |
|---|---|---|---|
| 845 nondiabetic men | | | |
| Base model[a] | 0.0446* | −0.1513* | 0.0310** |
| Base model + adjustment for insulin | 0.0402* | −0.1477* | 0.0428† |
| Change, % | −10 | −2 | +38 |
| Base model + adjustment for IRI | 0.0425* | −0.1517* | 0.0402* |
| Change, % | −5 | 0 | +30 |
| 1258 nondiabetic women | | | |
| Base model | 0.0812* | −0.250* | 0.0969** |
| Base model + adjustment for insulin | 0.0793* | −0.249* | 0.1030** |
| Change, % | −2 | 0 | +6 |
| Base model + adjustment for IRI | 0.0790* | −0.252* | 0.1032* |
| Change, % | −3 | 0 | +7 |

*Abbreviations:* HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; IRI, insulin resistance index.

*$P < 0.01$; **$P < 0.05$.

[a] The base model was adjusted for age, body mass index, waist/hip ratio, physical activity, smoking, hypertensive state, antihypertensive medication, total energy intake, and saturated fatty acid intake.

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CLINICAL SCIENCE

# Risk factors for age related maculopathy in a Japanese population: the Hisayama study

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**Aims:** To examine the risk factors for age related maculopathy (ARM) in a sample Japanese population.

**Methods:** In 1998, a cross sectional community survey was conducted among residents of Hisayama. A total of 596 men and 886 women living in Hisayama, Japan, aged 50 years or older consented to participate in the study. Each participant underwent a comprehensive examination that included an ophthalmic examination. The presence of ARM was determined by grading from fundus examination by indirect ophthalmoscopy, slit lamp examination, and colour fundus photographs. Using these cross sectional data, logistic regression analyses were performed to determine the risk factors for ARM. The following 10 possible risk factors were used: age, cataract, hypertension (history), hypertension (history or examination), diabetes, hyperlipidaemia, current smoker, alcohol intake, BMI, and WBC.

**Results:** ARM was detected in 19.5% of men and 14.9% of women. Men were found to have a significantly higher prevalence of ARM than women. Multiple logistic regression analysis showed that age and hypertension (history or examination) were significantly associated with ARM in men, whereas only age was a significant risk factor for ARM in women.

**Conclusions:** This study suggests that higher age and male sex are relevant risk factors for ARM in Japan. In addition, hypertension is a relevant risk factor in men.

Age related maculopathy (ARM) is a major cause of blindness and severe vision loss in older people in developed countries.[1] With the ageing population, ARM will become an increasing public health problem in the future. Therefore, it is crucial to identify risk factors for ARM to enhance understanding of the disease. Several risk factors for ARM have been investigated in population based[2–8] and case-control studies.[9–11] The risk factors examined include refractive error,[9] iris colour,[2] cataract,[3 4] hypertension,[5] atherosclerosis,[6] current smoker,[7] alcohol intake,[8] white blood cell count,[10] and sunlight.[11] To the best of our knowledge, however, no population based studies have assessed risk factors for ARM in Japan.

We have already reported the prevalence of early and late stage ARM in a representative Japanese community, Hisayama (the Hisayama study).[12] In this study, we investigate the important factors that contribute to ARM, using cross sectional data.

## PATIENTS AND METHODS

### Study population

A prospective population based follow up study of cardiovascular diseases has been carried out since 1961 in Hisayama.[13 14] The population of the town is approximately 7500, and it has been shown to be demographically representative of Japan based on the national census.[15] As part of the follow up survey, we performed a health examination, including an eye examination, of Hisayama residents aged 50 years or older in 1998. Of the 3054 residents in that age group, 1844 (60.4%) consented to participate in the study. Of these, 349 subjects underwent the health examination at home, while 13 subjects refused to participate in the ophthalmic examination. Ultimately, 1482 individuals (596 men and 886 women, 44.3% of the male population and 51.9% of the female population in that age group) underwent the ophthalmic examination.

### Ophthalmic examination and definition of age related maculopathy

The methods of the ophthalmic examination and the definition of ARM were described in detail previously.[12] Briefly, each participant underwent a comprehensive ophthalmic examination, including lens grading using a slit lamp, stereoscopic fundus examination using indirect ophthalmoscopy, and examination with a slit lamp biomicroscope with a "Superfield lens" (Volk, Mentor, OH, USA) after pupil dilatation with 1.0% tropicamide and 10% phenylephrine. Forty five degree fundus photographs were taken using a Topcon "non-mydriatic" TRC NW-5 fundus camera (Topcon, Tokyo) and Fujichrome slide film (Sensia II Fujifilm Co, Tokyo). The photographs were taken using a previously described method with a minor modification.[16] Briefly, photographs were taken of a field centred horizontally and vertically on a point midway between the temporal edge of the optic disc and the fovea. The photographic image included the area above and below the temporal arcades and the areas just nasal to the disc and temporal to the macula. The 35 mm slide transparencies were mounted in clear plastic sheets and graded at Kyushu University by two experienced graders (Y Oshima and T Ishibashi).

The presence of ARM was based on the grading of fundus examinations by indirect ophthalmoscopy, slit lamp, and colour fundus photographs. Two experienced ophthalmologists, without knowledge of clinical information, examined all the participants following the International ARM Epidemiological Study Group grading protocol and the grids of the Wisconsin Age Related Maculopathy Grading system.[17 18] ARM was classified as either early or late stage. Early stage ARM was defined by the presence of drusen (soft distinct and soft intermediate) or retinal pigment epithelium (RPE) pigmentary abnormalities within the grid in the absence of late stage ARM in either eye. Late stage ARM was further divided into neovascular age related macular degeneration (AMD), also termed "wet AMD," and geographic atrophy of the retinal pigment epithelium (RPE) in the absence of neovascular AMD,

**Table 1** Age specific prevalence of early and late age related maculopathy by sex, the Hisayama Study, 1998

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Population | No. (%) | | Population | No. (%) | |
| Age | at risk | Early ARM | Late ARM | at risk | Early ARM | Late ARM |
| 50–59 | 154 | 19 (12.3) | 1 (0.7) | 284 | 34 (12.0) | 0 (0.0) |
| 60–69 | 231 | 43 (18.6) | 2 (0.9) | 335 | 41 (12.2) | 0 (0.0) |
| 70–79 | 178 | 36 (20.2) | 2 (1.1) | 212 | 40 (18.9) | 1 (0.5) |
| 80+ | 33 | 12 (36.4) | 1 (3.0) | 55 | 16 (29.1) | 0 (0.0) |
| Total | 596 | 110 (18.5) | 6 (1.0) | 886 | 131 (14.8) | 1 (0.1) |

**Table 2** Mean values or frequencies of risk factors for age related maculopathy by sex, the Hisayama Study, 1998

| | Men | | Women | |
|---|---|---|---|---|
| Risk factor | Non-ARM (n=480) | ARM (n=116) | Non-ARM (n=754) | ARM (n=132) |
| Age (year) (SD) | 65 (9) | 68 (9)** | 64 (9) | 68 (10)** |
| Cataract (%) | 61.3 | 68.1 | 65.5 | 75.0* |
| Hypertension (history) (%) | 30.4 | 42.2* | 32.0 | 31.1 |
| Hypertension (history or examination) (%) | 51.3 | 63.8* | 47.0 | 51.5 |
| Diabetes (%) | 19.6 | 16.4 | 10.1 | 13.6 |
| Hyperlipidaemia (%) | 44.2 | 40.5 | 59.7 | 58.3 |
| Current smoker (%) | 34.8 | 33.6 | 4.5 | 4.6 |
| Alcohol intake (%) | 65.8 | 61.2 | 13.4 | 9.9 |
| Body mass index (kg/m²) (SD) | 23.1 (3.0) | 23.2 (2.9) | 23.1 (3.3) | 23.0 (3.6) |
| White blood cells (×10³/l) (SD) | 6.3 (1.7) | 6.0 (1.4) | 5.5 (1.3) | 5.3 (1.4) |

**p<0.01, ARM v non-ARM. *p<0.05, ARM v non-ARM.

also termed "dry AMD." Neovascular AMD included serous or haemorrhagic detachment of the RPE or sensory retina, and the presence of subretinal or sub-RPE haemorrhages or subretinal fibrous scar tissue. Dry AMD was characterised by sharply edged, roughly round or oval areas of RPE hypopigmentation, with clearly visible choroidal vessels. The minimum area of geographic atrophy was a circle 175 μm in diameter or larger.

The methods used to assess ARM were described in detail previously.[12] Briefly, two experienced graders, masked to subject information, assessed the ARM. The analysis included people with gradable photographs of either eye providing the clearest macular characteristics detected by stereoscopic eye examination. Interobserver and intraobserver variability were analysed using kappa statistics. The level of agreement was moderate to substantial for most features.

### Data collection

We defined the presence of cataract by whether the subject had nuclear or cortical senile lens changes or a history of cataract surgery in either eye. We adopted the definition of cataract used in the Health and Nutrition Examination Survey (HANES).[19] Briefly, the lens was evaluated by slit lamp and then by the direct ophthalmoscopy with a +20 dioptre lens. Opacities observed with both instruments and decreased lucency of the nucleus observed with a slit lamp was noted by two experienced graders. For the purposes of this study, cataract cases included people with a past history of cataract surgery.

Blood pressure was measured three times after resting for at least 5 minutes in the sitting position. The average of the three measurements was used for the analysis. Hypertension was defined as systolic blood pressure = 140 mm Hg, diastolic blood pressure = 90 mm Hg, or current use of antihypertensive medication. A history of hypertension was obtained using a standard questionnaire. Blood samples were collected from the antecubital vein after an overnight fast. After taking the fasting blood specimen, a 75 g oral glucose tolerance test was performed with a 75 g glucose equivalent carbohydrate load (Trelan G; Shimizu Pharmaceutical Inc, Shimizu, Japan). Diabetes was defined as a fasting plasma glucose level = 7.0 mmol/l or a 2 hour postloading glucose level = 11.1 mmol/l, in addition to a medical history of diabetes. The total cholesterol and serum triglyceride levels were determined enzymatically using an autoanalyser (TBA-80S; Toshiba Inc, Tokyo, Japan), and hyperlipidaemia was defined as a total cholesterol level = 5.7 mmol/l, serum triglyceride level = 1.7 mmol/l, or the current use of antihyperlipidaemic medication. Information on smoking habits, and alcohol intake was obtained using a standard questionnaire, and these factors were classified into either current habitual use or non-use. Body height and weight were measured in light clothing without shoes, and the body mass index (BMI) was calculated as the weight in kilograms divided by the height in metres squared. White blood cell counts (WBC) were determined using a Coulter counter (STKS; Coulter Inc, USA).

### Statistical methods

We defined a subject as having ARM if the subject had early or late stage ARM in at least one eye. We considered the following 10 possible risk factors for ARM: age, cataract, hypertension (history), hypertension (history or examination), diabetes, hyperlipidaemia, current smoker, alcohol intake, BMI, and WBC. Age, BMI, and WBC were treated as continuous variables and the others as categorical variables. Each categorical variable was coded as either 1 or 0 depending on the presence or absence of the factor, respectively. The association of the variables with ARM was assessed using Student's $t$ test for the continuous variables and the Pearson $\chi^2$ test for the categorical variables. Logistic regression analysis was performed to determine risk factors for ARM using odds ratio

**Table 3** Crude and age adjusted odds ratios of risk factors for ARM by sex, the Hisayama Study, 1998

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Crude | | Age adjusted | | Crude | | Age adjusted | |
| Risk factor | OR† | 95%CI‡ | OR† | 95%CI‡ | OR† | 95%CI‡ | OR† | 95%CI‡ |
| Age | 1.04** | 1.01 to 1.06 | | | 1.04** | 1.02 to 1.06 | | |
| Cataract | 1.35 | 0.88 to 2.08 | 1.05 | 0.66 to 1.70 | 1.58* | 1.04 to 2.41 | 1.17 | 0.74 to 1.86 |
| Hypertension (history) | 1.67* | 1.10 to 2.54 | 1.55† | 1.02 to 2.37 | 0.97 | 0.65 to 1.44 | 0.83 | 0.55 to 1.25 |
| Hypertension (history or examination) | 1.68* | 1.10 to 2.55 | 1.58* | 1.04 to 2.42 | 1.20 | 0.83 to 1.74 | 0.96 | 0.65 to 1.42 |
| Diabetes | 0.80 | 0.47 to 1.38 | 0.80 | 0.46 to 1.37 | 1.41 | 0.81 to 2.44 | 1.30 | 0.75 to 2.27 |
| Hyperlipidaemia | 0.86 | 0.57 to 1.30 | 0.95 | 0.62 to 1.44 | 0.95 | 0.65 to 1.38 | 0.94 | 0.64 to 1.37 |
| Current smoker | 0.95 | 0.62 to 1.46 | 1.01 | 0.65 to 1.55 | 1.01 | 0.42 to 2.45 | 1.13 | 0.46 to 2.77 |
| Alcohol intake | 0.82 | 0.54 to 1.24 | 0.91 | 0.59 to 1.39 | 0.52 | 0.28 to 1.05 | 0.58 | 0.32 to 1.07 |
| Body mass index | 1.01 | 0.94 to 1.08 | 1.04 | 0.96 to 1.11 | 0.99 | 0.93 to 1.04 | 1.00 | 0.94 to 1.06 |
| White blood cells | 0.86 | 0.76 to 1.09 | 0.89 | 0.77 to 1.01 | 0.88 | 0.76 to 1.02 | 0.87 | 0.75 to 1.01 |

†OR: odds ratio ‡CI: confidence interval. **p<0.01; *p<0.05.

**Table 4** Stepwise multivariate logistic analysis of risk factors for ARM by sex, the Hisayama Study, 1998

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| Risk factor | Estimated coefficient | OR† | 95%CI‡ | | Estimated coefficient | OR† | 95%CI‡ | |
| Age | 0.029 | 1.03** | 1.01 to 1.06 | | 0.040 | 1.04** | 1.02 to 1.06 | |
| Hypertension (history or examination) | 0.456 | 1.58* | 1.03 to 2.41 | | | | | |

†OR: odds ratio ‡CI: confidence interval. **p<0.01; *p<0.05.

estimates with 95% confidence intervals. Furthermore, a stepwise multivariate regression analysis was performed, with p value less than 0.05 being required for entering the model and remaining there. The SAS software package (SAS Institute, Cary, NC, USA) was used to perform the statistical analyses.[20] A two sided p value less than 0.05 was considered statistically significant.

## RESULTS

Of the 1482 subjects examined, 248 had ARM. Of the subjects with ARM, most (97.2%) had early stage ARM. Table 1 shows the age specific prevalence of early and late stage ARM by sex. Early stage ARM significantly increased with advancing age in both sexes. In both sexes, about one third of the subjects aged 80 years or older had ARM. In each age group, the prevalence of ARM was consistently higher in men than in women, and after adjusting for age, men were found to have a significantly higher prevalence of ARM than women (odds ratio (OR), 1.32; 95% confidence interval (CI), 1.01 to 1.72).

We compared the distribution of possible risk factors in subjects with and without ARM by sex (Table 2). The subjects with ARM were older than those without ARM, in both sexes ($p<0.01$). Cataracts were more frequent in those with ARM, in women ($p<0.05$). Of the 320 men with hypertension, 154 (48.1%) had used of antihypertensive medications, while 221 of 422 (52.4%) women with hypertension had used antihypertensive medications. In men, the subjects with ARM were diagnosed with hypertension from history or examination more frequently ($p<0.05$).

The results of the crude and age adjusted logistic regression analyses of risk factors for ARM are shown in Table 3. In the crude analysis, age and hypertension either diagnosed from history or diagnosed from examination were significantly associated with ARM in men, while age and cataract were significantly associated with ARM in women. After adjusting for age, hypertension either diagnosed from history or from examination remained a significant risk factor in men, while no factor was significant in women.

The stepwise multivariate regression analysis showed that age and hypertension diagnosed from examination were significantly associated with ARM in men, whereas only age was a significant risk factor for ARM in women (Table 4).

## DISCUSSION

To our knowledge, this is the first study to investigate the prevalence and risk factors of ARM in Japan, using a population based sample. The results show that age is significantly associated with ARM in both sexes, and hypertension is an additional risk factor in men.

There have been inconsistent results on the association between hypertension and ARM in previous studies.[5 19 21 22] Some studies found a positive association with increased blood pressure,[19 21] while others did not.[22] In the Framingham Eye Study, the prevalence of ARM progressively increased with the duration of systemic hypertension.[5] We found that hypertension diagnosed from either history or examination remained a significant risk factor in men, and that hypertension increased the risk of ARM by 59% in the multivariate regression analysis. The exact aetiology of ARM is unclear, but patients with ARM are reported to have prolonged filling of the choroidal capillaries, probably due to thickening of Bruch's membranes and decreased perfusion of the choroidal capillaries.[6 23 24] These findings suggest that long standing hypertension promotes atherosclerotic changes in the choroidal vessels, which might consequently decrease choroidal blood flow, thus resulting in an increased risk of ARM.

In our Japanese subjects, ARM was more prevalent among men than women. Yuzawa *et al* have also reported that exudative AMD was more prevalent in men than in women in patients visiting ophthalmology departments in Japan.[25] By contrast, ARM is more prevalent in women than in men in Western countries.[26 27] The reason for this difference is not clear. Some studies have reported racial differences in the prevalence of ARM,[27 28] which might explain the discrepancy between studies conducted in Japan and Western countries, and genetic or environmental factors might be the cause. However, we should mention the possibility of ascertainment bias since less than half of the available population consented to be studied (1482/3054 = 48.5%). The higher prevalence of

ARM in men might be the result of an ascertainment bias, because working men were less likely than women to enrol in the study unless they had visual symptoms.

The Beaver Dam Eye Study[3] reported that nuclear sclerotic cataracts were associated with early stage ARM in a cross sectional population based study. However, cataracts were not associated with the incidence and progression of ARM in a 5 year follow up study.[39] Sperduto *et al* found that the incidence of ARM increased with the presence of cortical lens changes and decreased with nuclear sclerosis.[4] Our data showed that the prevalence of both ARM and cataracts increased with age. Statistical analysis demonstrated that cataracts were significantly associated with ARM in both sexes, but the association was not significant after adjusting for age. Therefore, in our study, cataract is not considered an independent risk factor for ARM. Further investigation based on anatomical classification of cataract, which was not available in our study, would help clarify the relation between cataracts and ARM in more detail.

Although smoking is considered a risk factor for AMD in some studies,[7 30 31] we failed to find a significant association between smoking and ARM. In the Beaver Dam Eye Study, there was no association between smoking and early stage ARM, but there was a significant association between smoking and exudative AMD.[7] Smoking might promote the development and progression of subretinal neovascularisation, and different stages of ARM might have different aetiologies.[7] In our study, smoking was not associated with ARM, possibly because there were too few subjects with late stage ARM.

Several factors limit the interpretation of the results of this study. Firstly, many previous studies have examined risk factors for AMD (late stage ARM). However, we could not examine the risk factors for early and late stage ARM separately, because of the small number of subjects with late stage ARM. Secondly, the rate of participation in the examination was low. As a result of the participation rate, the study is probably subject to selection bias, which could have influenced the results. Hypertension and late stage ARM resulting in impaired vision would have been major motivations for men to participate. Consequently, the study might have examined a higher proportion of hypertensive and visually impaired men than it would have done from a representative sample.

In conclusion, our population based study in a sample Japanese population suggests that the prevalence of ARM is significantly higher in men than in women, that age is significantly associated with ARM in both sexes, and that hypertension is an additional risk factor in men. Additional prospective studies will help clarify the causal relations between hypertension and ARM.

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# Analysis of hospital charges for ischemic stroke in Fukuoka, Japan

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**Abstract**

*Objectives:* Stroke is a heavy economic burden on individuals, society, and health services in Japan, where health expenditures are rising rapidly. The objective of the present study was to examine medical services and demographic factors associated with increased inpatient charges for ischemic stroke in Japan. *Subjects and methods:* The study subjects were 316 patients with a principal diagnosis of acute ischemic stroke who were discharged from the National Kyushu Medical Center Hospital from 1 July 1995 through 31 June 1999. Demographic, clinical, and administrative data were retrospectively collected from medical records and the hospital Clinical Financial Information System (CFIS). The influence of social and medical factors on total charges was analyzed using the stepwise multiple regression model. *Results:* Among the total subjects, the mean (median) length of hospital stay (LOHS) was 33 (30) days (range, 2–155 days). The mean (median) hospital charge per patient was US $9020 ($7974) with a range of $336–54 509. The distribution of charges was 42% for fundamental, 17% for injection therapies, 13% for radiological test, 11% for other laboratory examinations, 3% for drugs, and 3% for operations. Stepwise multiple regression analysis revealed that LOHS was the key determinant of the hospital charge (partial $R^2 = 0.5993$, $P = 0.0001$). Operations ($P = 0.0001$) and angiography ($P = 0.03$) were also independent but less contributory determinants of the hospital charge. *Conclusions:* LOHS was strongly, positively associated with inpatient charges for ischemic stroke in Japan. This implies that significant charge reductions are more likely to rely on shortening LOHS, which probably can be achieved by altering reimbursement policies.


*Keywords:* Ischemic stroke; Hospital charge; Medical cost; Length of hospital stay; Medical insurance system

## 1. Introduction

In Japan, stroke affects approximately 140 000 individuals, and the expenditure for stroke is approximately 1900 billion yen (US $158.3 billion)

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each year, 70% of which is attributed to inpatient cost [1]. Ischemic stroke mainly occurs in elderly individuals and accounts for approximately 70% of total stroke [2]; its high mortality, high hospitalization, and chronic disability rates place a heavy burden on health care finance. The steady increase in the number of elderly Japanese will undoubtedly have implications for future expenditures on ischemic stroke in health service and health finance.

A number of studies have investigated resource utilization for stroke patients in Western countries [3–28]. However, the relationship between stroke and medical expenditures has not been fully investigated in Japan, where the health insurance system, practice patterns, and costs are distinct from those in Western countries. Japan has achieved universal health care coverage by making compulsory enrollment in one of the health insurance programs based on employment or residence and by mandating insurers to provide minimum coverage, including a wide range of health care benefits. Health insurance in Japan covers almost all medical treatment and fees for medical providers. Some previous studies conducted outside Japan have demonstrated that hospital costs for stroke patients were strongly correlated with length of hospital stay (LOHS) [4,18,26]. On the other hand, several studies have reported that the Japanese LOHS was the longest among the developed countries because the insurance system in Japan provided hospitals with little economic incentive to reduce LOHS [29–34]. There have been no reports on the economy of stroke since Takahashi's study in 1988 [35], which reported the contributory predictors were the average medical cost per day of the first month, the patients' place of residence, and age. However, this study was limited to patients from a farming community and clinical data were not included.

In Japan, the charges for health service are strictly regulated by the government; the charges for all the medical procedures, services, diagnostic tests, and drugs are set under guidelines established by the Ministry of Health, Labor and Welfare. In 1995, the Japanese government began to monitor LOHS in major hospitals and encourage doctors to shorten it. In the present study, we examined those medical services and demographic factors that were associated with inpatient charges for ischemic stroke just after introduction of the new LOHS monitoring system in Japan. An improved knowledge of the determinants of hospital charges for ischemic stroke will enhance our understanding of the health care needs for stroke victims, and assist in the planning of cost-effective programs for stroke treatment and prevention.

## 2. Subjects and methods

The study was conducted at the National Kyushu Medical Center Hospital in Fukuoka city (population = 1.33 million), which is one of the main general emergency care centers of Kyushu Island in the southern region of Japan. The hospital is equipped with 650 short-term care beds and 50 psychiatric beds. It is operated by the Ministry of Health, Labor, and Welfare of Japan and serves as a facility for teaching and medical research. Using International Classification of Diseases (ICD-9-CM) primary diagnosis codes, 502 consecutive patients with a principal diagnosis of acute ischemic stroke (ICD-9 code = 434.0, 434.1, 434.9), who were discharged from 1 July 1995 through 31 June 1999, were selected. The onset of stroke is generally followed by immediate hospitalization, and patients are usually started on a regimen of highly expensive drugs, injections, and imaging tests—including brain computerized tomography (CT) and magnetic resonance imaging (MRI)—upon hospital admission. Thus, hospital charges are likely to be confounded by potential differences in the preadmission process between patients who are admitted to the National Kyushu Medical Center directly and those who are transferred from the other hospitals. Accordingly, among the total of 502 patients, 186 who were transferred from other hospitals were excluded and the remaining 316 patients were eligible for the present study. All 316 were evaluated morphologically using CT and/or MRI at the National Kyushu Medical Center Hospital.

Information on inpatient charges was retrospectively collected from the Clinical Financial Information System (CFIS), a national database

sponsored by the Ministry of Health and Welfare. The inpatient total charges consisted of fundamental charges as well as charges for radiological tests, other laboratory examinations, injection therapies, drugs, operations, board, extra room, and others. Demographic data, insurance status, and clinical data were retrospectively taken from medical records and the CFIS. The demographic characteristics included sex and age at admission. Clinical data consisted of principal diagnosis, severity of stroke, bed use (intensive care unit or ward bed), LOHS, comorbid conditions (hypertension, diabetes mellitus, cancer, and ischemic heart disease), and whether or not cerebral angiography, surgery, or autopsy were performed. Insurance status was determined by ascertaining the kind of insurance that covered the inpatient charges of the subject. Health insurance programs in Japan are of two main types: Employee Health Insurance, which covers employees and their dependents, and Community Health Insurance, which covers the remaining population, including the self-employed. The severity of stroke was assessed by a modified version of the Scandinavian Stroke Scale [36]. The maximum score was 46 points, with lower scores indicating a more severe level of stroke. Outcomes on discharge were classified as in-hospital death, discharge to a rehabilitation facility, or discharge to home.

The differences in total charges among levels of relevant factors were tested using the Wilcoxon rank-sum test. Since the distribution of financial data was skewed to the right, the values of these variables were log-transformed, and geometric means were calculated from the exponent of the mean log-transformed values. The associations of social and medical factors with patient charges were analyzed using a multiple linear regression model. The appropriate regression models were selected using a stepwise multiple regression procedure. The level of statistical significance required for the addition of variables to the model was $P < 0.05$, and that for retention in the model was $P < 0.15$. All analyses were conducted using STATISTIC ANALYSIS SYSTEM (SAS) software, version 6.12 for WINDOWS. All statistical tests were two-sided, and values of $P < 0.05$ were considered to indicate statistical significance.

Medical charges were also shown in American dollars for comparison with other studies; one dollar was considered equal to approximately 120 Japanese yen.

Table 1
Background characteristics of 316 patients with acute ischemic stroke

| Factor | All patients (N = 316) | |
|---|---|---|
| | Number | % |
| *Age (year)* | | |
| 20–39 | 6 | 1.9 |
| 40–64 | 103 | 32.6 |
| 65–92 | 207 | 65.5 |
| *Sex* | | |
| Male | 187 | 59.2 |
| Female | 129 | 40.8 |
| *Insurance status* | | |
| Community health insurance | 174 | 55.1 |
| Employee health insurance | 142 | 44.9 |
| *Severity score on admission* | | |
| 0–19 | 45 | 14.2 |
| 20–39 | 175 | 55.4 |
| 40–46 | 96 | 30.4 |
| *Bed use* | | |
| Ward bed | 249 | 78.8 |
| Intensive care unit | 67 | 21.2 |
| *LOHS (days)* | | |
| 1–29 | 139 | 44.0 |
| 30–59 | 156 | 49.4 |
| 60–155 | 21 | 6.6 |
| *Comorbid condition* | | |
| Hypertension | 210 | 66.5 |
| Diabetes mellitus | 83 | 26.3 |
| Ischemic heart disease | 11 | 3.5 |
| Cancer | 9 | 2.8 |
| Cerebral angiography | 76 | 24.0 |
| Surgery | 17 | 5.4 |
| Autopsy | 5 | 1.6 |
| *Outcome* | | |
| In-hospital death | 15 | 4.7 |
| Discharged to home | 166 | 52.5 |
| Discharged to rehabilitation facilities | 135 | 42.7 |

## 3. Results

The characteristics of 316 patients are shown in Table 1. Age ranged from 20 to 92 years with a mean of 68, and men (59%) exceeded women in number. Fifty-five percent of patients had Community Health Insurance, and the others had Employee Health Insurance. Among the 316 patients, 249 (79%) were admitted to the general ward and the other 67 (21%) were admitted to the intensive care unit. On admission, 45 patients (14%) had severe stroke and 96 (30%) had mild stroke. LOHS showed a wide variation ranging from 1 to 155 days with a mean (median) of 33 (31) days. Approximately two-thirds of the patients had comorbid conditions of hypertension, and one fourth had diabetes. Cerebral angiography was performed on 24% of the patients, and operation was done on 5% of the patients. Fifteen patients (5%) died in the hospital, and five of them underwent autopsy. Forty three percent of the patients were discharged to rehabilitation facilities, and 53% were directly discharged to their home.

The mean and median hospital charges per patient were 1 097 498 yen ($9146) and 968 925 yen ($8074), respectively, with a range of 132 030 yen ($1100) to 6 541 100 yen ($54 509). The distribution of charges is presented in the Fig. 1. Forty-two percent of the charges were attributed to fundamental charges, 13% were associated with radiological tests, including X-ray, CT, MRI and cerebral angiography, 11% were associated with other laboratory examination and diagnostic tests, 17% were for injection therapies, 3% were for drugs, and 3% were for operations.

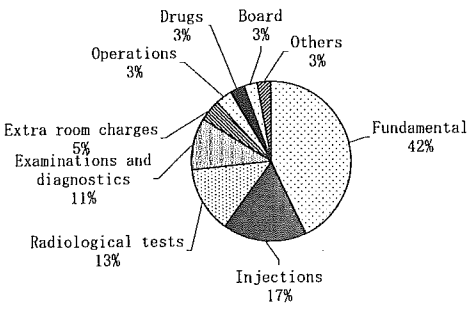


Fig. 1. Distribution of hospital charges for 316 patients of acute ischemic stroke in the National Kyushu Medical Center of Japan.

Table 2 shows the crude mean values of total charges according to the contributory factors. Total charges were significantly increased in patients who were older ($P = 0.03$) or who had had a stroke of greater severity ($P = 0.0001$). The higher total charge was also associated with increased LOHS ($P = 0.0001$). The patients with diabetes ($P = 0.03$) as well as those who underwent surgery ($P = 0.0001$) and angiography ($P = 0.0001$) had higher total charges. The total charge was also significantly increased in patients who were discharged to rehabilitation facilities ($P = 0.0001$). However, there were no significant differences in total charge between patient groups divided according to sex, insurance status, bed use, or comorbid conditions of hypertension, ischemic heart disease, or cancer. Multivariate analysis was then carried out using relevant factors that were significant in the univariate analysis (Table 3). In the stepwise regression model, LOHS ($P = 0.0001$), surgery ($P = 0.0001$) and angiography ($P = 0.03$) were found to be significant predictors of hospital charge. LOHS was the key determinant of hospital charge for ischemic stroke, since it accounted for 60% of the variance in total charges. Age, severity at admission, diabetes, and outcomes did not independently influence total charges.

## 4. Discussion

The most prominent finding of this study was that LOHS was the key contributor to increased total charge, and it accounted for 60% of the variance in total charge. The average LOHS for our patients was 33 days, considerably longer than that of American studies [4,10,37,38], which reported average LOHS values of 6–11.6 days. The long LOHS in our study was similar to that of a Canadian study [28], in which the major factor determining stroke expenditures was family support. A plausible explanation for the longer average LOHS for Japanese ischemic stroke patients compared with the American patients is considered to be the difference in the economic incentives built into the payment systems. The

Table 2
Crude mean values of hospital charges for 316 patients with acute ischemic stroke by levels of contributory factors[a]

| Factor | Crude hospital charges | | |
|---|---|---|---|
| | Mean (US $) | 95% CI | *P*-value [b] |
| *Age (year)* | | | |
| <65 | 7430 | 6713–8223 | 0.03 |
| 65 and over | 8134 | 7557–8755 | |
| *Sex* | | | |
| Male | 8183 | 7573–8841 | 0.31 |
| Female | 7470 | 6805–8200 | |
| *Insurance status* | | | |
| Community health insurance | 8213 | 7579–8899 | 0.29 |
| Employee health insurance | 7499 | 6862–8196 | |
| *Severity score on admission* | | | |
| 0–19 | 9433 | 7813–11 390 | 0.0001 |
| 20–39 | 9671 | 8525–10 971 | |
| 40–46 | 7226 | 6739–7749 | |
| *Bed use* | | | |
| Ward bed | 7608 | 7717–8134 | 0.05 |
| Intensive care unit | 9000 | 7313–10 237 | |
| *LOHS (days)* | | | |
| 1–29 | 5498 | 5141–5879 | 0.0001 |
| 30–59 | 9629 | 9038–10 259 | |
| 60–155 | 19 403 | 16 328–23 057 | |
| *Hypertension* | | | |
| Yes | 7906 | 7131–8765 | 0.98 |
| No | 7840 | 7285–8436 | |
| *Diabetes mellitus* | | | |
| Yes | 9205 | 8595–9858 | 0.03 |
| No | 7460 | 6651–8369 | |
| *Ischemic heart disease* | | | |
| Yes | 8950 | 8422–9510 | 0.20 |
| No | 7848 | 5699–10 808 | |
| *Cancer* | | | |
| Yes | 8451 | 5931–12 041 | 0.77 |
| No | 7868 | 7405–8360 | |
| *Surgery* | | | |
| Yes | 15 249 | 11 917–19 513 | 0.0001 |
| No | 7594 | 7160–8053 | |
| *Angiography* | | | |
| Yes | 9936 | 8827–11 183 | 0.0001 |
| No | 7327 | 6855–7831 | |
| *Outcomes* | | | |
| In-hospital death | 5929 | 4561–7707 | 0.0001 |
| Discharged to home | 6975 | 6446–7547 | |
| Discharged to rehabilitation facilities | 9461 | 8869–10 325 | |

[a] All values show charges per case in American dollars. One dollar equals approximately 120 Japanese yen.
[b] The difference was tested by the Wilcoxon rank-sum test.