We investigated the relation between albuminuria and life-style factors in 5670 people, ages 40 years and over, who participated in a health screening survey of a local workforce. The degree of albuminuria showed piecewise log-linear relationships with alcohol consumption and cigarette smoking, with changes in slope (and 95% confidence interval) corresponding with 5 (2, 8) g of alcohol/day and 10 (6, 14) cigarettes/day. After adjusting for age, gender, ethnicity, and other life-style variables, relative risks (95% confidence interval) of slight albuminuria for people consuming >32 g of alcohol/day compared with nondrinkers, and for cigarette smokers compared with nonsmokers, were 1.74 (1.02, 2.98) and 1.37 (1.01, 1.88), respectively. However, there was no significant effect of exercise. We conclude that slight albuminuria is significantly associated with cigarette smoking and heavy alcohol consumption, consistent with its role as an index of risk of cardiovascular disease.

Indexing Terms: hypertriglyceridemia  • cardiovascular disease  • risk factors

We previously reported reference values and principal associations of slight albuminuria in 5670 people of ages 40 years and over who participated in a health screening survey of a local workforce (1). The degrees of albuminuria showed piecewise log-linear relationships with diastolic blood pressure and body mass index, log-linear relationships with hypertriglyceridemia and hypercholesterolemia, and a negative log-linear relationship with high-density lipoprotein cholesterol. These findings are consistent with the role of slight albuminuria as a predictor of macrovascular disease in nondiabetic subjects (2).

Other factors known to influence urinary albumin excretion are cigarette smoking (3–6), strenuous exercise (7, 8), and alcohol intake (9). However, no previous studies have investigated these factors simultaneously in the same population. Because smoking, alcohol consumption, and physical activity are likely to be associated with each other, we report here their effects on albuminuria, controlling for any interrelationships by using a multiple-regression model.

Subjects and Methods

Study Population

The study population comprised 5670 individuals, 4106 men and 1564 women, ages 40–78 (median 49) years, who participated in a health screening survey of a New Zealand workforce (response 67%). Participants were 78.8% European, 7.7% Maori, 11.7% Pacific Islander, and 1.8% Asian, distributed among 40 companies in Auckland and Tokoroa. Participants gave informed consent, and procedures followed were in accordance with the Ethical Committee of Auckland University.

The study design and recruitment methods are described in detail elsewhere (10). Briefly, all participants underwent a 75-g oral glucose tolerance test; blood samples were collected after an overnight fast and 2 h after the glucose load. Seventy-nine participants were classified as having diabetes mellitus on the basis of 2-h plasma glucose concentrations ≥11.1 mmol/L, according to World Health Organization (WHO) criteria for epidemiological surveys (11) (mean urinary albumin: 12.4 mmol/L; 95% confidence interval: 9.7, 15.6), and 102 participants reported a past history of diabetes mellitus (mean urinary albumin: 11.0 mmol/L; 95% confidence interval: 8.9, 13.5).

Alcohol consumption, cigarette smoking, and exercise habits were determined from a questionnaire. Participants indicated their typical alcohol consumption in numbers of glasses, cans, and bottles of beer, spirits, fortified wine, and table wines, during the 3 months before the interview. These were converted to grams of absolute alcohol per day by using a standard conversion table (12). Mean alcohol intakes (95% confidence interval) in European, Maori, Pacific Island, and Asian men were 8.3 (7.89, 8.69), 6.8 (5.74, 8.16), 4.3 (3.57, 5.08), and 2.6 (1.75, 3.73) g/day, respectively. Similarly, mean alcohol intakes in women were 3.2 (2.96, 3.50), 3.3 (2.41, 4.38), 0.6 (0.47, 0.82), and 0.4 (0.06, 0.77) g/day, respectively. Urinary alcohol metabolites were not measured.

Participants reported their cigarette smoking habits as current smoker, ex-smoker, or never smoked regularly. Current smokers also reported the number of cigarettes smoked per day. Leisure-time physical activity was based on regular (at least once per week) participation in vigorous and moderate activities outside work. Vigorous activity was defined as exercise that caused sweating and hard breathing for at least 20 min per

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session on at least 3 days per week; otherwise, exercise was classified as moderate or none. Responses to questionnaires were considered confidential information.

Participants collected a first-voided early morning urine sample into a sterile container on the day of the interview, to be used for albumin estimation. Urine samples were refrigerated within 3 h of arrival at the laboratory and analyzed the same or the following day. Urine samples were cultured for infection and 203 people were excluded on this basis (mean urinary albumin: 9.0 mg/L; 95% confidence interval: 7.7, 10.6). Although we did not obtain a menstrual history, contamination of urine specimens by menses is unlikely because the women were middle-aged [mean (range) age 48 (40, 75) years] and many would have been postmenopausal at the time of the study.

Urinary albumin concentrations were determined by an immunoturbidimetric assay (Cambridge Life Sciences, Cambridge, UK) that had a linear standard curve for 0–165 mg/L albumin concentrations and detected as little as 2 mg/L. Participants were assigned to the following groups: no albuminuria (≤28 mg/L for men, ≤29 mg/L for women), slight albuminuria (29–299 mg/L for men, 30–299 mg/L for women), and clinical albuminuria (≥300 mg/L). These cutoff values for slight albuminuria in men and women were determined from the population described in the current study (1).

Statistical Methods

Urinary albumin concentrations and reported alcohol consumption were converted to log values for calculations because of their positively skewed frequency distribution; the results are presented as geometric means (the exponential of the mean of the log-transformed data) and associated 95% confidence intervals. We used multiple linear-regression analysis to assess the joint effects of variables associated with albuminuria. Relative risks, controlled for possible confounding effects, and associated 95% confidence intervals were determined by the Mantel–Haenszel method (13). These statistical analyses were performed with SAS (Research Triangle Park, NC) statistical software.

Piecewise linear models were fitted to log-transformed values of urinary albumin concentrations and number of cigarettes smoked per day and to daily alcohol consumption to obtain estimates of the points at which a significant change of slope occurred and their associated 95% confidence intervals (14). The 24 people with clinical albuminuria (3 of whom had diabetes mellitus) were excluded from the regression analysis, because their numbers were small and their urinary albumin concentrations highly influential. Study numbers vary for different analyses because of missing information for some studies.

The figures show “average” y-values vs x, where “average” means that smoothed y values were calculated by robust locally weighted regression (15), with 75% of the data being used for smoothing each x value. Confidence intervals were obtained by using the bootstrap technique (16) as follows: After randomly sam-

pling the study group of 5394 people with alcohol values (5422 for current cigarette smoking) and calculating the weighted regression line 1000 times, we calculated an approximate 95% confidence interval as the 2.5th and 97.5th percentiles of the 1000 bootstrapped regression estimates.

Results

Effect of alcohol consumption. After adjusting for age and gender, there was a significant difference in geometric mean (SE) total alcohol consumption between people with no albuminuria and people with slight albuminuria [13.8 (0.29) vs 17.2 (1.25) g/day (P = 0.008), respectively]. However, there was no significant difference in alcohol consumption between people with no albuminuria and people with clinical albuminuria [17.5 (4.36) g/day (P = 0.40)]. The smoothed relation between alcohol consumption and log-transformed albuminuria values appeared to be piecewise linear (Figure 1). When a piecewise linear model was fitted, there was a significant increase of the slope at a point corresponding to an alcohol consumption of 5 (95% confidence interval: 2.8) g/day.

Results were adjusted for age, gender, and ethnicity, as well as for smoking and exercise, because life-style variables are likely to be interrelated. The relative risk of slight albuminuria was significantly increased among heavy drinkers consuming >32 g/day of alcohol (Table 1). However, after further adjusting for serum triglyceride concentrations, the relative risk of slight albuminuria was no longer significant. This suggests that the effect of alcohol may have been partly mediated by hypertriglyceridemia.

Effect of smoking. After adjusting for age and gender, geometric mean (95% confidence interval) albuminuria
concentrations were significantly higher in current cigarette smokers compared with nonsmokers (5.37 (5.24–5.92) vs 4.63 (4.41–4.87) mg/L (P < 0.001), respectively). There was no significant difference between past smokers and nonsmokers (4.40 (4.26–4.65) vs 4.63 (4.41–4.87) mg/L, respectively). When a piecewise linear model was fitted to the relation between number of cigarettes smoked per day and log-transformed albuminuria values, there was a significant change of slope at a point corresponding with 10 (6–14) cigarettes/day (Figure 2). After adjusting for age, gender, and ethnicity, the relative risk of slight albuminuria remained higher among current cigarette smokers than for nonsmokers (Table 1).

Effect of leisure-time exercise. After adjusting for age and gender, geometric mean albuminuria concentrations (95% confidence interval) were significantly higher in people who reported no exercise [5.35 (5.09–5.62) mg/L] than in people who reported leisure activity at least once a week [4.66 (4.65–5.07) mg/L (P = 0.028)] or vigorous aerobic exercise for 20 min per session on at least 3 days per week [4.69 (4.35–5.03) mg/L (P < 0.003)].

However, after adjusting for ethnicity, the reduced risk of slight albuminuria among people who reported vigorous aerobic exercise was no longer significant (Table 1). This is caused by a higher prevalence of slight albuminuria among Pacific Islanders who coincidentally reported less leisure-time activity. Compared with Europeans, Pacific Islanders are more susceptible to other forms of albuminuric renal disease such as poststreptococcal glomerulonephritis and diabetes mellitus (17).

Multivariate analysis. We previously reported the effect of age, gender, body mass index, and diastolic blood pressure on urinary albumin concentrations (1) and adjusted for them in the multiple-regression model to assess the independent effects of life-style factors. The squared terms for body mass index and diastolic blood pressure were included to account for their nonlinear relationship with degree of albuminuria (1).

When all variables were entered in a stepwise manner into a multiple-regression model to assess their joint effects with (log) urinary albumin concentrations, significant regression coefficients were found for age, gender, ethnicity, body mass index, diastolic blood pressure, triglyceridemia, and current cigarette smoking (Table 2). When serum triglyceride and ethnicity variables were added to the model, alcohol consumption and physical activity, respectively, no longer had a significant effect.

If all other variables remain constant, this model predicts 14% higher urinary albumin concentrations (95% confidence interval: 8–21%) in current smokers compared with nonsmokers and ex-smokers. The net contri-

Table 1. Mantel–Haenszel Relative Risks (95% Confidence Interval) for Slight Albuminuria Associated with Alcohol Consumption, Smoking, and Leisure Time Activity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects, n</th>
<th>Adjusted for gender and age</th>
<th>Adjusted for gender, age, and ethnicity*</th>
<th>Adjusted for gender, age, ethnicity, and other factorsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Albuminuric</td>
<td>Nonalbuminuric</td>
<td>Adjusted for gender and age</td>
<td>Adjusted for gender, age, and ethnicity*</td>
</tr>
<tr>
<td>Nondrinker</td>
<td>52</td>
<td>623</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Light</td>
<td>106</td>
<td>2206</td>
<td>0.59 (0.43, 0.81)</td>
<td>0.90 (0.64, 1.25)</td>
</tr>
<tr>
<td>Moderate</td>
<td>83</td>
<td>1709</td>
<td>0.56 (0.39, 0.81)</td>
<td>1.05 (0.73, 1.51)</td>
</tr>
<tr>
<td>Heavy</td>
<td>49</td>
<td>588</td>
<td>1.05 (0.66, 1.67)</td>
<td>1.76 (1.07, 2.89)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Nonsmoker</td>
<td>104</td>
<td>1274</td>
<td>1.00</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>89</td>
<td>1760</td>
<td>1.02 (0.77, 1.35)</td>
<td>1.14 (0.86, 1.50)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>102</td>
<td>2135</td>
<td>1.69 (1.28, 2.23)</td>
<td>1.34 (1.01, 1.79)</td>
</tr>
<tr>
<td>Exercise</td>
<td>None</td>
<td>39</td>
<td>922</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate</td>
<td>143</td>
<td>2241</td>
<td>0.91 (0.71, 1.17)</td>
<td>1.05 (0.81, 1.36)</td>
</tr>
<tr>
<td>Vigorous</td>
<td>113</td>
<td>1809</td>
<td>0.63 (0.44, 0.92)</td>
<td>0.72 (0.49, 1.07)</td>
</tr>
</tbody>
</table>

* Ethnic groups were European and Asian, Maori and Pacific Islander.

b Adjusted for life-style factors other than the variable of interest, e.g., odds ratios for alcohol consumption adjusted for smoking and exercise groups.

* Alcohol consumption was light, >0–8 g/day; moderate, >8–32 g/day; or heavy, >32 g/day.

d Defined as exercise that causes sweating and hard breathing for at least 20 min per session on at least 3 days per week.

Fig. 2. Effect of current cigarette smoking on average urinary albumin concentrations

Mean and 95% confidence intervals; n = 5422
Table 2. Multiple-Regression Analysis of Variables Associated with Albuminuria

<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>SE</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.3857</td>
<td>0.0311</td>
<td>44.519</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0091</td>
<td>0.0021</td>
<td>-4.401</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.2882</td>
<td>0.0310</td>
<td>9.303</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.3735</td>
<td>0.0373</td>
<td>10.030</td>
</tr>
<tr>
<td>Diabetes status</td>
<td>0.4207</td>
<td>0.0722</td>
<td>5.823</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.0007</td>
<td>0.0052</td>
<td>0.133</td>
</tr>
<tr>
<td>(Body mass index)^2</td>
<td>0.0027</td>
<td>0.0004</td>
<td>7.026</td>
</tr>
<tr>
<td>Gender × body mass index</td>
<td>0.0224</td>
<td>0.0057</td>
<td>3.904</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.0080</td>
<td>0.0014</td>
<td>5.745</td>
</tr>
<tr>
<td>(Diastolic blood pressure)^2</td>
<td>0.0003</td>
<td>0.0001</td>
<td>4.446</td>
</tr>
<tr>
<td>Serum triglyceride</td>
<td>0.0554</td>
<td>0.0117</td>
<td>4.729</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>0.1351</td>
<td>0.0296</td>
<td>4.535</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.0011</td>
<td>0.0006</td>
<td>1.830</td>
</tr>
<tr>
<td>Vigorous exercise</td>
<td>0.0155</td>
<td>0.0289</td>
<td>0.577</td>
</tr>
</tbody>
</table>

* Data is converted: loga (urinary albumin + 1); multiple R^2 = 0.145, n = 5965.
* Ethnicity was coded as Maori and Pacific Islander = 1; European and Asian = 0.
* Diabetes status was coded 1 for participants with diabetes mellitus and 0 otherwise.
* Vigorous activity was coded 1 for participants who reported exercise that made them sweat and breathe hard for at least 20 min per session on at least 3 days per week and 0 otherwise.

Explanatory variables are centered by subtracting their average values as follows: age = 48.8 years; body mass index = 27.3 kg/m^2; diastolic blood pressure = 76.8 mmHg; serum triglyceride = 1.65 mmol/L; alcohol = 6.5 g/day.

SE, standard error of the estimate.

bution of these variables accounted for 14.5% of the variation of urinary albumin concentrations.

Discussion

Gosling and Beavers (18) reported one of the few studies of the relation between alcohol consumption and slight albuminuria. Although they found no significant association, their study population contained only 199 factory workers and they could have missed a weak relationship. In contrast, Winocour et al. (9) reported a positive relation between the albumin:creatinine ratio and alcohol intake in 10 subjects with slight albuminuria. We have now demonstrated a significant relation between albuminuria and alcohol consumption in a predominantly nondiabetic middle-aged population (Figure 1).

This relation between alcohol and slight albuminuria may have been mediated by hypertriglyceridemia. We previously demonstrated a strong relationship between slight albuminuria and triglyceride concentrations (1), and ethanol ingestion is known to cause hyperlipidemia (19). Very-low density lipoprotein triglyceride and chylomicron triglyceride concentrations are both increased after alcohol consumption, and may remain so even in the basal state. Ethanol increases plasma triglyceride concentrations by inhibiting fatty acid oxidation and gluconeogenesis, and enhancing fatty acid synthesis in the liver.

A positive association between current cigarette smoking and clinical albuminuria has been observed in a number of studies of patients with diabetes mellitus (3–6). For example, Chase et al. (6) reported a 2.8-fold increase in the relative risk of proteinuria among 359 subjects with insulin-dependent diabetes mellitus, which declined significantly on cessation of smoking. In a case-control study of 192 insulin-dependent diabetics, Mühlhauser et al. (5) reported a twofold increase in proteinuria and proliferative retinopathy in current cigarette smokers compared with nonsmokers, whereas Telmer et al. (3) found a significant increase in proteinuria among insulin-dependent diabetics who smoked >10 cigarettes per day.

In contrast, no such relation was found in other studies of diabetic (20) and nondiabetic (18) individuals, nor was a relation between albuminuria and cigarette smoking found in 1728 diabetic individuals who participated in the WHO multinational study of risk factors for microangiopathy (21).

The mechanism of tobacco-induced slight albuminuria is uncertain. Increases in heart rate and blood pressure among nondiabetic cigarette smokers have been reported (22), which may increase glomerular filtration rate and renal plasma flow. Alternatively, because cigarette smoking is associated with high amounts of carboxyhemoglobin and decreased oxygen delivery to tissues, albuminuria may be caused by hypoxia in the renal microcirculation (5). Higher insulin requirements and glycohemoglobin concentrations were found in insulin-dependent diabetic cigarette smokers than in nonsmokers (6), suggesting a direct effect of glycemic control on glomerular permeability.

We observed lower urinary albumin concentrations among healthy individuals who engage in activities that improve physical fitness (8), although this relation was no longer significant after adjusting for ethnicity (Table 1). This suggests that the relation is spurious and caused by interethnic variations in reported physical activity and prevalence of slight albuminuria.

Our observation of associations between slight albuminuria and alcohol consumption and cigarette smoking in a middle-aged workforce supports the finding of slight albuminuria as a marker of atherosclerotic risk (2, 23). The association between alcohol consumption and degree of albuminuria evident in Figure 1 also reflects similar relations reported between amounts of alcohol consumed and the risk of hemorrhagic and non-hemorrhagic stroke (24) and between alcohol consumption and the risk of myocardial infarction (25).

We conclude that the degree of albuminuria in the general population is independently associated with heavy alcohol consumption, possibly mediated by hypertriglyceridemia, and cigarette smoking. Both life-style variables have been reported previously as potent risk factors for cardiovascular disease; thus our findings further support the contention that slight albuminuria is a marker of cardiovascular risk in nondiabetic individuals.

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References