よくわかっていない。

そこで、この３つの主要なリスク要因の組合せと医療費の関係をより正確に把握するために、「大崎国保加入者コホート」の参加者を、リスクの保有状況（なし、各１つ×３、２つの組合せ×３、３つすべて）によって８つのグループに分けて、その後７年間の医療サービスの利用状況（入院日数と外来回数）および医療費を比較した。

２）対象と方法

性別、年齢、飲酒、がん・心筋梗塞・脳卒中の既往について補正の上、グループごとの医療費を算出した。リスクがないグループは、喫煙したことがなく、体格指数〔体重 kg ÷（身長 m）^{2}〕が 25.0 未満で、１日の歩行時間が１時間より長いという全ての条件を満たす者で構成される。

ベースライン調査：1994 年 10 月から 12 月までに、宮城県の大崎保健所が管轄する 14 市町（当時）に居住する、40 から 79 歳までの国民健康保険の加入者約５万 5,000 人を対象に、生活習慣に関する自己記入式アンケートを配布し、５万 2,029 人から有効回答を得た。回答率は 95%であった。

追跡調査：ベースライン調査に回答した者のうち、追跡開始以前に国民健康保険から脱退した者 774 人と、今回の研究に関連する質問への回答に不備のあった者を対象から除外した。また、結果への影響を考慮して、体格指数 20 未満のやせすぎの者、身体機能の調査で活発な運動ができないと判断された者は、分析の対象から除外した。最終的に、男性約１万 5,000 人、女性約１万 1,000 人、合計約２万 6,000 人の対象者の７年間の医療施設の利用状況（外来受診回数と入院日数）と医療費のデータを、国民健康保険利用の記録をもとに把握した。国民健康保険受給者の主な職業は、農業、自営業、主婦、年金受給者などであった。この記録によって、１人１人の受給者が利用したほぼすべての医療サービスと費用を把握することができた。７年目までの追跡調査中に、対象者の 96.7%の者が、何らかの医療サービスを利用していた。

３）研究結果

各グループの人数は、リスクなし 4,191 人、喫煙のみ 4,834 人、肥満のみ 1,962 人、運動不足のみ 4,403 人、たばこと肥満 1,646 人、たばこと運動不足 4,635 人、肥満と運動不足 2,357 人、たばこと肥満と運動不足 2,082 人であった。たばこと大量飲酒は女性の割合が低く、平均年齢、がん・心筋梗塞・脳卒中になった人の割合は、グループの間でほぼ同じであった。

リスクがないグループに比べ、リスク要因の数が２つ、３つと増えるにつれて、医療費が高くなった。１人当りの１ヶ月の医療費増加の割合は、リスク要因が１つの場合、たばこを吸ったことがあるグループでは 8.3%、過体重または肥満のグループでは 7.1%、運動不足のグループでは 8.0%であった。リスク要因が２つになった場合、たばこと肥満では

11.7%、たばこと運動不足では31.4%、肥満と運動不足では16.4%であった。さらに、たばこ、肥満、運動不足の３つのリスク要因がすべて揃ったグループでは、42.6%で、１人当り１ヶ月に１万円近く高くなった。３つのリスク要因のうち、特に、喫煙と運動、または喫煙と肥満と運動の組み合わせによる医療費への影響は、単なる足し算で増えるのではなく、相乗効果で高くなると考えられた。

４）考　察

本研究では、約２万6,000人の１人１人について、７年間にわたる医療費をほぼ正確に把握し、他の要因の影響を取り除いて、３つの主要なリスク要因の組み合わせとの関係を調べることができた。他の同様の研究では、個人の社会・経済的状態が医療サービスの利用状況に大きな影響を与えることが指摘されているが、日本の国民健康保険という制度の下では社会・経済的状態の医療費への影響は少ないものと考えられる。

身体機能スコアと医療費の関係についてはすでに報告済みであるが、今回の研究では、あまり活発に運動できない身体機能スコアが４以下の者をあらかじめ対象から除き、運動不足というリスク要因の医療費への影響をより正確に把握することができた。

本研究により、３つのリスク要因の組み合わせによって、医療費が単なる足し算以上に高くなることが示された。そのうち１つずつでも減らすように働きかけをすることで、将来の医療費が削減できること、１人１人の健康状態が改善されることが期待される。

７．飲酒と医療費

１）はじめに

日本からの報告も含め、飲酒量の多い人で死亡率が高くなることを示す研究が数多くある。少量飲酒が健康によいかどうかは、まだ決着がついていないが、大量飲酒によって、肝硬変や飲酒関連がん、脳卒中や高血圧のリスクは確実に高くなる。そのため、大量飲酒者では、医療サービスを利用することが多くなり、医療費も高くなるのではないかと考えられる。これまでの研究によれば、飲酒量が多くなると病院の外来を利用する回数が増えることに関してはほぼ一致しているが、入院に関しては多くなる、少なくなるなど結果がばらばらで一定の結論に至っていない。

そこで、飲酒と医療費の関係をより正確に把握するために、「大崎国保加入者コホート」の男性参加者を、１日当りの飲酒量によって４つのグループに分けて、その後４年間の医療サービスの利用状況（外来受診回数と入院日数）および医療費を、年齢層別に比較した。

２）対象と方法

アンケート調査では、まずお酒を飲む、飲んだことがない、飲んでいたが止めた、という３つの選択肢から回答してもらった。次に、飲む人には、どれくらいの頻度で飲むか、

1日あたりの飲酒量はどれくらいかを、お酒の種類別に尋ねた。日本酒1合は約180mlで、エタノール換算で23gになる。

ベースライン調査：1994年10月から12月までに、宮城県の大崎保健所が管轄する14市町（当時）に居住する、40から79歳までの国民健康保険の加入者約5万5,000人を対象に、生活習慣に関する自己記入式アンケートを配布し、5万2,029人から有効回答を得た。回答率は95%であった。

追跡調査：ベースライン調査に回答した者のうち、追跡開始以前に国民健康保険から脱退した者774人を対象から除外した。女性は全体的に飲酒量が少なく、飲酒量別の比較が難しかったので、この研究では男性約2万5,000人だけを対象にした。今回の研究に関連する質問への回答に不備のあった者、ベースライン時点ですでに脳卒中、心筋梗塞、肝臓病あるいはがんを発症したことがあると答えた者を、分析の対象から外した。また、お酒を止めた人は、お酒を飲まない人に比べ健康状態が悪い可能性がある。そこで、お酒を飲んでいたが止めた人も対象から外し、お酒を飲んだことがないという人だけを残した。1995年1月から1998年12月までの追跡調査で、約1万7,000人の対象者の医療施設の利用状況（外来受診回数と入院日数）と医療費のデータを、国民健康保険利用の記録をもとに把握した。国民健康保険受給者の主な職業は、農業、自営業、主婦、年金受給者などであった。この記録によって、1人1人の受給者が利用したほぼすべての医療サービスと費用を把握することができる。

3）研究結果

エタノール換算した飲酒量と、1人当りの1ヶ月分の平均入院日数と入院費用は、U字型の関連を示した。お酒を飲まないグループ（入院日数0.56日、入院費用1万3,500円）と飲酒量が最も多いグループ（入院日数0.58日、入院費用1万24,00円）で最も高く、150-299gのグループで最も低く（入院日数0.37日、入院費用9,300円）なった。年齢層別にみると、49歳以下のグループでだけ、飲酒量のより少ない1-149gのグループで最も低くなった。

一方、外来の回数と費用については、飲酒量が多いほど低くなる傾向がみられた。お酒を飲まないグループ（入院費用1万4,100円）で最も高く、飲酒量が増すにつれてだんだん低くなった。年齢層別にみると、どのグループでも、同様の傾向がみられた。

4）考　察

本研究では、1人1人の医療費をほぼ正確に把握し、年齢、たばこ、体格指数、運動量のような他の要因の影響を取り除いて、飲酒量との関係を調べることができた。

健診受診者のデータで、アンケート調査の飲酒量と実際の肝機能検査のデータとの関連性が十分に高かったことが確認され、調査の妥当性が示された。

飲酒量は、入院費用についてはU型の関連を示し、外来費用については負の関連を示した。外来をよく受診することは、健康意識の高さを反映しているとも考えられる。そのため、入院費用でみられた関連の方が、直接的な結果であるといえるであろう。

この研究では、少し飲む人は、まったく飲まない人よりも医療費が低くなった。お酒をまったく飲まないよりも少し飲むことによって、心臓や脳の血管障害や、糖尿病のリスクが下がるといわれている。その一方で、飲酒はいくつかのがんと、高血圧、肝硬変などのリスクを明らかに高くする。飲酒の複合的な健康影響を考えると、お酒を少し飲むと医療費が下がるということは、集団レベルでとらえるべきではなく、個人レベルで考えるべきであろう。

この研究では、飲酒の医療費への影響を追跡期間4年で調べたが、実際の飲酒の健康影響は、4年以上遅れて現れるものがあるかもしれない。その場合には、大量飲酒による医療費の負担増を低く見積もってしまった可能性もある。

Impact of alcohol consumption upon medical care utilization and costs in men: 4-year observation of National Health Insurance beneficiaries in Japan

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ABSTRACT

Aims The purpose of the present study was to examine the association between alcohol consumption and in-patient and out-patient care utilization and its costs, respectively.

Design and participants The present data were derived from a 4-year prospective observation of National Health Insurance beneficiaries in rural Japan. A total of 17 497 men aged 40–79 years were analysed, after excluding subjects who at the baseline reported having had at least one of four chronic diseases: stroke, myocardial infarction, liver disease and cancer. Alcohol intake was classified into five groups, not including ex-drinkers: life-long abstainers and ethanol intakes of 1–149 g/week, 150–299 g/week, 300–449 g/week, and ≥450 g/week.

Findings The hospital days and in-patient care cost showed a U-shaped relationship with alcohol consumption. In-patient cost was highest for those consuming more than 450 g/week [£74.96, 95% confidence interval (CI): 54.39, 95.52] and for life-long abstainers (£69.16, 95% CI: 62.08, 77.83), and lowest for those consuming 150–299 g/week (£51.69, 95% CI: 45.33, 58.04). In-patient use by age specific analysis also showed a U-shape at all ages, and was lowest for those consuming 1–149 g/week in youngest age group. In contrast, the number of physician visits and out-patient cost showed an inverse linear relationships with alcohol consumption.

Conclusions This study suggests that in-patient use shows a U-shaped curve and out-patient use shows an inverse linear relationship to alcohol consumption.

KEYWORDS Alcohol drinking, health care costs, health care services, prospective studies.

INTRODUCTION

Many studies have reported a J- or U-shaped relation between alcohol consumption and all-cause mortality [1,2], including Japanese populations [3–5]. In addition, excessive drinking is an established risk factor for diseases such as liver cirrhosis, alcohol-related cancers, stroke and hypertension [6].

Because excessive alcohol consumption is associated with an increased risk of mortality and adverse health consequences, it is reasonable to assume a causal association between alcohol consumption and increased usage

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and the cost of medical care. Although an inverse relationship between alcohol consumption and out-patient care use has been observed consistently among previous studies [7–14], no conclusion has been reached about the association between alcohol consumption and the utilization of in-patient care [7,10,12–20]. Previous studies have reported five major patterns regarding the association between alcohol consumption and in-patient care use—linearly positive, [18,19] J-shaped, [15,19] U-shaped, [16,17] inverse J-shaped, [10,12,20] or linearly inverse [7,10,12–14]. The inconsistency among the studies would have been attributable partly to certain study limitations; hypothetical, cross-sectional or retrospective observations, small sample sizes, subjects who had limited socio-economic status, not separating life-long abstainers from ex-drinkers.

In order to examine fully the impact of alcohol consumption on the use and cost of in-patient and out-patient care, it is necessary to follow-up a large-scale population-based cohort for a sufficiently long period during which every member has equal access to medical care services. The purpose of the present study was to examine the association between alcohol consumption and in-patient and out-patient care utilization and its costs, respectively. The impact of alcohol consumption upon health may vary depending on the diagnosis of the diseases [15,17,21] and the latter may influence the use of in-patient or out-patient care. Furthermore, out-patient care use is, in general, influenced more by patients' care-seeking behavior than by in-patient care use [11]. We therefore conducted separate analyses of in-patient and out-patient use. The present data were derived from a 4-year prospective observation of National Health Insurance (NHI) beneficiaries in rural Japan, known as the Ohsaki NHI Cohort Study [22]. The strengths of this study include a large sample size ($n = 17\,497$), coverage of almost all medical care under the NHI system, perfect monitoring of medical care utilization by linkage with claim history files and comprehensive health and life-style information for each subject at the baseline survey.

MATERIALS AND METHODS

The health insurance system in Japan

Health insurance is compulsory for everyone living in Japan, and is provided by one of two systems [22]; the first is for employees and their dependents, the second is a community-based health insurance system used mainly by farmers, the self-employed, pensioners and their dependents. This second system is called the National Health Insurance (NHI) plan and covers 35% of the Japanese population. The NHI covers almost all aspects of medical treatment, including diagnostic tests, medication, surgery, supplies and materials, payment of physicians and other personnel and most dental treatment. It also covers the home-care services provided by physicians and nurses, but not by other professionals, such as home-health aides. When medical providers treat a patient, they receive a co-payment from the patient and then file a claim with the local NHI association for reimbursement. Payment to medical providers is made on a fee-for-service basis, where the price of each service is determined by a uniform national fee schedule. The local NHI association has a peer-review system to determine the level of reimbursement.

Study setting and design

The setting and design of the Ohsaki NHI Cohort Study has been reported in detail elsewhere [22–26]. In brief, a baseline questionnaire survey was distributed to all NHI beneficiaries aged 40–79 years living in the catchment area of the Ohsaki Public Health Center, Miyagi Prefecture, Japan, between October and December 1994. This study was approved by the Tohoku University School of Medicine Ethics Committee.

The baseline survey questionnaire included socio-demographics, medical history, physical functioning and health-related life-style factors such as smoking, alcohol consumption, dietary habits and physical activity.

Trained survey personnel visited the study subjects, informing them of the study objectives and their right to decline, and asked them to complete the questionnaire if they consented. The survey personnel revisited subjects to collect the questionnaire about 1 week later. From among 54 996 eligible individuals, 52 029 (95%) responded. We excluded 774 subjects because they had withdrawn from the NHI before 1 January 1995, when we started prospective collection of NHI claim history files; thus 51 255 subjects formed the study cohort.

Study subjects

Because women in this cohort seldom drank, we limited our analysis to men ($n = 24\,574$). Of those, we excluded 1830 subjects who failed to answer some of the questions in the alcohol consumption questionnaire. We also excluded subjects who, at baseline, reported having had at least one episode of either stroke, myocardial infarction, liver disease or cancer ($n = 3361$). In a previous study it was suggested that alcohol abstainers include two distinct groups, life-long abstainers and ex-drinkers, and that ex-drinkers had worse health than life-long abstainers [27,28]. We therefore excluded ex-drinkers ($n = 1886$) from the analysis. The remaining 17 497 subjects were finally analysed.

Study variables

The impact of alcohol consumption on monthly medical care utilization and costs was examined. All life-style information was derived from the responses to the self-completed questionnaire in the 1994 baseline survey. The question on the amount of drinking by each subject was worded as: 'Do you drink alcoholic beverages?' and the subjects were asked to choose one of three options to describe their status: current drinker, former drinker or life-long abstainer. Current drinkers reported their frequency of consumption as one of four categories: almost daily, 3–4 days/week, 1–2 days/week and <1 day/week. Furthermore, they were asked which types and amounts of alcoholic beverages were consumed in a day; this information was recorded as '5 *go* or more', '4 *go*', '3 *go*', '2 *go*', '1 *go*' or 'less than 1 *go*' (a *go* is a traditional unit in Japan equal to approximately 180 mL of sake, containing 23 g of ethanol). Weekly ethanol consumption was calculated by multiplying the amount of ethanol consumed per day by the frequency of drinking per week. Alcohol intake was classified into five groups: life-long abstainers and current ethanol intakes of 1–149 g/week, 150–299 g/week, 300–449 g/week and ≥450 g/week.

Multivariate models included the following variables as covariates, as there was an association between alcohol consumption and the following variables: (1) age: continuous variable; (2) smoking status: never, ever smoked, currently smoking; (3) body mass index (BMI): weight, kg/height, m^2 (<21.0, 21.0–24.9 and ≥25.0 kg/m^2); and (4) time spent walking per day: <30 minutes, 30 minutes–1 hour, ≥1 hour.

Outcome measures

Data on medical care utilization and costs were collected prospectively for all individuals in the cohort between January 1995 and December 1998. The NHI claims history files were obtained from the Miyagi NHI Association. Claims history files included the beneficiary's ID number, the number of days and cost of out-patient care and the number of days and cost for in-patient care. Information on the diagnosis related to each episode of medical care was not available.

When a beneficiary was withdrawn from the NHI because of death or emigration, the date and reasons were recorded on the NHI withdrawal history file. From this file, survival and emigration status could be identified for all the study subjects. Both NHI claims and withdrawal history files were linked with our baseline survey data file based on the beneficiary's ID number as the key code. In order to protect the subjects' privacy, their names were deleted from the data files used for analysis.

Statistical analysis

The impact of alcohol consumption on per-month per-capita medical costs (in-patient and out-patient), hospital days and number of physician visits was examined by analysis of covariance (ANCOVA). Per-month values for each subject were calculated by dividing the accumulated values through observation by the number of months observed. We examined per-month values rather than accumulated values to avoid underestimating the medical care use and costs of the subjects who died or emigrated.

In this paper, monetary values are converted to pounds sterling (£) using an exchange rate of £1.00 = 180 Japanese Yen (2003 rate). Approximate variance formulae were used to calculate 95% confidence intervals (CI): differences at $P < 0.05$ were regarded as statistically significant. All statistical calculation was performed using SAS software (version 8.2, SAS Institute, Cary, NC, USA) [29].

RESULTS

Characteristics of the subjects

Table 1 lists the baseline characteristics of the subjects by categories of alcohol intake. The highest proportion of current drinkers (38.6%) were in the category consuming 1–149 g/week, and the proportions decreased with higher alcohol consumption. The mean age was highest for life-long abstainers, and decreased with the amount of alcohol consumed. Alcohol consumption was associated with cigarette smoking, BMI and walking time: the proportion of current smokers increased with alcohol consumption, and the proportions of those who had a BMI of more than 25.0 and those who walked for less than 30 minutes per day were greater among current drinkers consuming more than 450 g/week.

Among the subjects, 5355 men (30.6%) attended health check-ups provided by the municipality in 1995, and we compared the self-reported alcohol consumption at the baseline survey with the data from liver function tests obtained at the health check-up. Table 2 lists the mean levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT), according to the categories of self-reported alcohol consumption. A linear relationship was observed between the values from all liver function tests and the self-reported alcohol consumption level (*P* for trend: $P < 0.0001$). This relationship did not change after logarithmic transformation of the values. This finding suggests that the data for self-reported drinking habits at the baseline survey were sufficiently valid and accurate.

Table 1 Baseline characteristics by categories of alcohol intake in 17 497 men, Ohsaki NHI Cohort Study, Japan, in 1994.

	Life-long abstainers	*Current drinkers (g/week)*			
		1–149	*150–299*	*300–449*	*450 ≥*
Number of subjects (%)	3352 (19.2)	6749 (38.6)	5086 (29.1)	1823 (10.4)	487 (2.8)
Age (SD[a])	60.6 (10.7)	58.9 (10.7)	57.8 (9.9)	54.3 (9.4)	52.7 (9.4)
Smoking (%)					
Current	47.9	51.5	63.3	72.2	75.8
Ex-smoker	22.8	25.1	22.9	17.9	15.2
Never	29.3	23.4	13.7	9.9	9.0
BMI[b] (%)					
<21.0	21.8	20.0	18.9	20.4	21.5
21.0–24.9	53.5	54.6	55.8	52.8	50.3
≥25.0	24.7	25.4	25.3	26.8	28.2
Walking (%)					
<30 minutes/day	28.0	25.7	24.6	26.4	35.9
30–1 hour	24.1	24.6	23.5	19.6	17.8
≥1 hour/day	47.9	49.8	51.9	54.0	46.3

[a]SD, standard deviation. [b]BMI, body mass index.

Table 2 Liver functions data of the subjects by categories of alcohol intake in 5355 men, Ohsaki NHI Cohort Study, Japan, 1995.

	Life-long abstainers	*Current drinkers (g/week)*				
		1–149	*150–299*	*300–449*	*450 ≥*	*P-value*
Number of subjects(%)	937 (16.2)	2306 (40.0)	1624 (28.2)	411 (7.1)	77 (1.3)	
AST[a] mean (SD[b])	24.7 (9.0)	25.5 (9.4)	28.3 (17.1)	32.3 (21.9)	36.4 (28.4)	<0.001[c,d]
ALT[e] mean (SD[b])	22.6 (13.4)	22.5 (13.2)	24.4 (22.9)	28.1 (21.4)	32.0 (27.8)	<0.001[c,d]
GGT[f] mean (SD[b])	22.9 (18.5)	32.7 (31.9)	50.5 (58.5)	83.7 (97.5)	107.7 (143.8)	<0.001[c,d]

[a]AST, aspartate aminotransferase; [b]SD, standard deviation; [c]tested by analysis of variance (ANOVA); [d]P for trend < 0.0001; [e]ALT, alanine aminotransferase; [f]GGT, serum g-glutamyltransferase.

Drinking habits and medical costs

Per-capita per-month hospital days and in-patient cost showed U-shaped relationships with alcohol consumption, both for crude data and after adjustment for age, smoking status, BMI and walking (Table 3). Hospital days and in-patient cost were highest for subjects consuming more than 450 g/week (0.56 days, 95% CI: 0.40, 0.72; £74.96, 95% CI: 54.39, 95.52) and for life-long abstainers (0.58 days, 95% CI: 0.52, 0.64; £69.16, 95% CI: 62.08, 77.83), and lowest for subjects consuming 150–299 g/week (0.37 days, 95% CI: 0.32, 0.42; £51.69, 95% CI: 45.33, 58.04).

Out-patient care use did not show a U-shaped curve, but an inverse linear relationship with alcohol consumption for both crude data and after adjustment (*P* for trend: $P < 0.0001$). Per-month visits and per-month costs were highest for life-long abstainers (£78.31, 95% CI: 74.04, 82.57), and decreased with higher alcohol consumption.

Table 4 lists in-patient and out-patient use by age specific analysis. Per-capita per-month hospital days and in-patient cost showed a U-shaped relationship with alcohol consumption at all ages, but in-patient cost was lowest for those consuming 1–149 g/week in the less than 49 age group. Number of physician visits and out-patient costs also showed an inverse linear relationship with alcohol consumption among parts of all age groups.

DISCUSSION

This 4-year prospective observation study confirmed a U-shaped relationship between alcohol consumption and in-patient care use. In contrast, there was an inverse linear association between alcohol consumption and out-patient care use.

Our study had several methodological strengths. Under the NHI system, differences in access to medical care due to socio-economic status are unlikely. We followed-up a large number of subjects ($n = 17,497$) for 4 years. Because we collected a variety of life-style

Table 3 Per-capita per-month medical care utilization and its costs by alcohol intake categories in 17 497 men, Ohsaki NHI Cohort Study, Japan, 1995–98.

		Current drinkers (g/week)				
	Life-long abstainers	*1–149*	*150–299*	*300–449*	*450 ≥*	*P-value*
In-patient care						
Number of hospital days (95% CI[a])						
Crude	0.63 (0.56, 0.70)	0.45 (0.40, 0.50)	0.36 (0.30, 0.41)	0.36 (0.26, 0.45)	0.46 (0.28, 0.64)	<0.0001[b]
Adjusted mean[d]	0.58 (0.52, 0.64)	0.44 (0.39, 0.48)	0.37 (0.32, 0.42)	0.44 (0.36, 0.52)	0.56 (0.40, 0.72)	<0.0001[b]
Medical cost (£) (95% CI[a])						
Crude	77.12 (67.79, 86.45)	59.67 (53.09, 66.24)	50.63 (43.06, 58.21)	47.77 (35.12, 60.43)	58.94 (34.45, 83.43)	<0.0001[b]
Adjusted mean[d]	69.16 (62.08, 77.83)	57.97 (52.46, 63.47)	51.69 (45.33, 58.04)	60.03 (49.34, 70.72)	74.96 (54.39, 95.52)	<0.01[b]
Out-patient care						
Number of physician visits (95% CI[a])						
Crude	2.07 (1.99, 2.16)	1.90 (1.84, 1.96)	1.77 (1.70, 1.84)	1.35 (1.24, 1.47)	1.24 (1.02, 1.46)	<0.0001[b,c]
Adjusted mean[d]	1.87 (1.79, 1.94)	1.83 (1.78, 1.88)	1.82 (1.76, 1.88)	1.72 (1.63, 1.82)	1.74 (1.55, 1.93)	0.21[b,c]
Medical cost (£) (95% CI[a])						
Crude	85.97 (80.23, 91.71)	71.81 (67.76, 75.85)	65.10 (60.44, 69.76)	46.83 (39.05, 54.61)	45.58 (30.52, 60.63)	<0.0001[b,c]
Adjusted mean[d]	78.31 (74.04, 82.57)	69.37 (66.39, 72.36)	66.94 (63.49, 70.38)	60.21 (54.42, 66.01)	62.79 (51.65, 73.94)	<0.0001[b,c]

[a]CI, confidence interval; [b]tested by analysis of covariance (ANCOVA); [c]*P* for trend < 0.05; [d]adjusted for age (continuous variable), smoking status (never, ever or current), BMI (<21.0, 21–24.9, = 25.0), walking (<30 minutes, 30 minutes-1 hour or = 1 hour/day).

Table 4 Age-specific analysis of per-capita per-month medical care utilization and its costs by alcohol intake categories in 17 497 men, Ohsaki NHI Cohort Study, Japan, 1995–98.

			Current drinkers (g/week)				
	Age	*Life-long abstainers*	*1–149*	*150–299*	*300–449*	*450 ≥*	*P-value*
In-patient care							
Number of hospital days[a] (95%CI[b])							
	≤49	0.34 (0.23, 0.44)	0.15 (0.09, 0.22)	0.16 (0.09, 0.24)	0.19 (0.09, 0.30)	0.32 (0.14, 0.50)	0.026[c]
	50–59	0.45 (.034, 0.56)	0.27 (0.20, 0.35)	0.25 (0.17, 0.33)	0.28 (0.16, 0.40)	0.33 (0.08, 0.57)	0.045[c]
	≥60	0.78 (0.69, 0.87)	0.66 (0.59, 0.73)	0.52 (0.44, 0.60)	0.61 (0.45, 0.78)	0.82 (0.47, 1.18)	0.0009[c]
Medical cost (£)[a] (95%CI [b])							
	≤49	23.95 (15.19, 32.72)	13.20 (7.73, 18.67)	14.91 (8.66, 21.15)	27.61 (18.93, 36.30)	27.69 (12.46, 42.91)	0.018[c]
	50–59	57.86 (43.09, 72.63)	36.66 (26.63, 46.69)	33.14 (22.20, 44.08)	38.56 (21.97, 55.16)	42.68 (9.81, 75.56)	0.11[c]
	≥60	101.82 (89.33, 114.31)	91.04 (81.74, 100.35)	77.21 (66.15, 88.27)	76.73 (54.21, 99.26)	124.98 (76.64, 173.32)	0.019[c]
Out-patient care							
Number of physician visits[a] (95%CI[b])							
	≤49	0.87 (0.79, 0.96)	0.79 (0.74, 0.85)	0.75 (0.69, 0.82)	0.71 (0.62, 0.79)	0.77 (0.62, 0.92)	0.094[c,a]
	50–59	1.29 (1.16, 1.41)	1.31 (1.22, 1.39)	1.33 (1.24, 1.42)	1.26 (1.12, 1.40)	1.15 (0.88, 1.43)	0.76[c]
	≥60	2.71 (2.60, 2.84)	2.63 (2.54, 2.72)	2.54 (2.43, 2.64)	2.26 (2.05,2.48)	2.19 (1.72, 2.65)	0.0015[c,d]
Medical cost (£)[a] (95%CI[b])							
	≤49	40.80 (32.89, 48.72)	31.86 (26.92, 36.79)	27.59 (21.96, 33.23)	24.57 (16.73, 32.41)	26.07 (12.32, 39.81)	0.039[c,d]
	50–59	57.17 (46.84, 67.49)	53.82 (46.81, 60.83)	49.33 (41.68, 56.98)	43.50 (31.89, 55.10)	44.76 (21.79, 67.74)	0.42[c]
	≥60	109.59 (103.84, 115.35)	96.75 (92.46, 101.04)	93.39 (88.29, 98.49)	78.38 (68.01, 88.77)	80.12 (57.84, 102.39)	0.0001[c,d]

[a]Adjusted for smoking status (never, ever or current), BMI (<21.0, 21–24.9, ≥25.0), walking (<30 minutes, 30 minutes-1 hour or = 1 hour/day); [b]CI, confidence interval; [c]tested by analysis of covariance (ANCOVA); [d]P for trend <0.05.

information at the baseline survey, we were able to analyse the impact of alcohol consumption on medical cost after adjustment for possible confounders. Self-reporting of alcohol consumption was sufficiently valid and accurate, as evidenced by the high correlation with objective data from liver function tests (AST, ALT and GGT). The representativeness of our study was confirmed fully in a previous paper [22].

The association between alcohol consumption and use of in-patient care was inconsistent in previous studies, which is attributable partly to study limitations. First, most previous studies were based on hypothetical [18], cross-sectional [7,13,16] or retrospective [12,14,17] study designs. Secondly, some studies involved small sample sizes [10,20]. Thirdly, socio-economic status might have confounded the association between alcohol consumption and medical care use [30,31]; for example, some excessive drinkers might not have used medical care because they were un- or underinsured. Fourthly, most of the studies did not separate life-long abstainers from ex-drinkers [7,10,13,15,19,20], and a study by Tsubono *et al.* suggests that epidemiological studies of alcohol and total mortality may overestimate the lower risk in moderate drinkers if they do not separate life-long abstainers from ex-drinkers [32]. Some previous studies showed that abstainers had extremely high in-patient care use, but this could be explained by the fact that the abstainer group of ex-drinkers presumably includes people who ceased alcohol consumption because of illness (related or unrelated to drinking) [7,10,13,15,19,20].

Our study is a large-scale population-based cohort study in which every member had equal access to medical care services, and ex-drinkers were excluded as study subjects. This methodological advantage suggests that our finding of a U-shaped curve for in-patient use is more reliable than findings of previous studies. Furthermore, in-patient cost was lowest for individuals consuming 1–149 g/week in the less than 49 age group, followed by those consuming 150–299 g/week with an increase in age. Young people might be expected to show a stronger effect of alcohol consumption in relation to medical care utilization because of the smaller influence of chronic diseases unassociated with alcohol consumption. Moreover, the data for the less than 49-year age group showed the same tendency as the J- or U-shaped mortality curve [1–5].

Because out-patient care use is influenced more by patients' care-seeking behaviour [11], the association between alcohol consumption and in-patient care use may provide an appropriate clue to the question of whether alcohol consumption has beneficial or harmful effects. This 4-year prospective observation study confirmed a U-shaped relationship between alcohol consumption and in-patient care use. Our data support the known substantial health and social risks of consuming large amounts of alcoholic beverages. Armstrong *et al.* demonstrated that light drinkers (<1 drink/month) had a morbidity experience similar to that of life-long abstainers. Thus the suggestion that life-long abstainers might differ from light drinkers in some unknown way with respect to illness risk might not be plausible. Therefore, the higher in-patient cost among life-long abstainers than among light drinkers might indicate a beneficial effect of light drinking. A meta-analysis has demonstrated a beneficial influence of alcohol on coronary heart disease, ischaemic stroke and diabetes mellitus [6]. Furthermore, San José *et al.* have reported a U-shaped relationship between alcohol consumption and psychosocial health parameters such as perceived general health, health complaints, chronic conditions, mobility complaints, pain complaints, sleeping complaints, social isolation, emotional complaints and lack of energy complaints, that may indicate an influence of alcohol intake on health [33]. The U-shaped relationship observed in our study might reflect this association. Although alcohol consumption may have some beneficial effects, alcohol consumption increases the risk for some types of cancer, hypertension, haemorrhagic cancer, cirrhosis of the liver, etc. [6]. Thus, the present U-shaped association might have been the result of a heterogeneous relationship between alcohol consumption and health problems. Given that heterogeneity, we believe that public health recommendations for promotion of alcohol drinking to reduce medical care costs is not a reasonable strategy. Any encouragement of light or moderate drinking should be based on the characteristics of each individual.

In contrast to in-patient care use, out-patient use showed a linear inverse relationship with alcohol consumption. Past studies have also shown that use of out-patient care decreased with alcohol consumption [7–14]. There are several possible explanations for our results. First, alcohol consumption is associated positively with acute conditions such as road injuries, injuries due to falls, fires, excessive cold, drowning, occupational and machine injuries and suicide [6], which would yield more in-patient needs than out-patient needs. These acute conditions might partly explain the inverse linear association. Secondly, alcohol consumption is associated positively with depressive disorders [6]. People with depression are less likely to seek medical care in the early stage of their disease, which would lead to less use of out-patient care. Thirdly, although every individual had equal access to medical care services in our study, their financial status might have influenced their care-seeking behaviour. A person with a poor income, who may tend to be a heavy drinker, would be less likely to visit a physician. Future prospective studies should therefore exercise

care in adopting a wider variety of information at the baseline survey, including financial status.

Our study had another limitation. The 4-year follow-up period was probably not long enough. Consequently, we might have underestimated the health risks of those who were currently consuming a large amount of alcohol. However, we did observe a U-shaped relationship between alcohol consumption and in-patient cost.

The amount of alcohol consumed in Japan has been increasing rapidly since the end of World War II [34], and the current per-capita consumption of 6.6 l is almost the same as that of the United States (6.7 l) and United Kingdom (8.1 l) [35].

In conclusion, this large-scale prospective study, using a health insurance system providing every member with equal access to medical care services, demonstrated that days of hospitalization and in-patient care cost had a U-shaped relationship with alcohol consumption, and that the number of physician visits and out-patient cost had an inverse linear relationship with alcohol consumption.

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C．今後の研究計画

今後は生活習慣のみならず、健診データ等様々な因子と医療費についても研究を行いたい。また、本コホートは高齢者（79 歳まで）を対象に含むことからがん罹患件数が多く、わが国ではまだ相対的に数の少ないがん（例えば、前立腺がん）などを積極的に研究したいとも考えている。本コホートでは、すでに 161 件の前立腺がんを観察している。

ベースライン調査から 10 年経過しているので、対象者の生活習慣が変化している可能性がある。平成 18 年度に生活習慣の再調査を行い、生活習慣の変化を考慮した上で、医療費を含めた様々な outcome との関連を包括的に研究する計画である。

9．富山職域コホートおよび小矢部コホートの概要、成果と今後の計画

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1．コホートの概要

1）富山職域コホート

富山県にあるアルミ製品製造業企業の黒部事業所及び滑川事業所従業員を対象としたコホートである。1980 年以降、研究者が産業医として従業員の健康管理を 25 年にわたり行っている。コホート規模は約 7,000 人で、男女比は約２対１である。

本コホートは職域コホートであるため、従業員全体が毎年 95%以上の受診率で検診を受診しており、各種検査値の高い率での経年追跡が可能である。また現業系従業員では転勤が少なく、また、途中退職も比較的少ないため長期の追跡が可能である。

1980 年以降、折に触れて質問調査および追加検査がなされており、各種の要因とその後の疾患発症との関連についての検討が可能である。これまで実施された調査あるいは追加検査は以下の通りである。

1980年　健康管理開始。基本質問調査実施
1990年　労働に関する質問調査。以後、35 歳未満にも血液検査実施
1993 年　HbA1c、空腹時インスリン、血糖値、HDL コレステロール測定開始。
　　ストレス、食行動質問調査実施
1994年　生活習慣質問調査実施
1996 年　労働省職業要因質問調査実施。フィブリノーゲン、ウエスト／ヒップ測定
2002 年　職業要因質問調査実施。フィブリノーゲン、ウエスト、高感度 CRP 測定
2003 年　JALS 統合研究ベースライン調査実施（フルバージョン栄養調査、身体活動調査）
2004 年　睡眠に関する質問調査実施。血清ピロリ菌抗体測定

本コホート研究グループは本事業所での産業医活動を通して、詳細なエンドポイント発生の把握を実施している。すなわち、在職中の脳卒中、虚血性心疾患、悪性新生物、精神疾患等の発症および死亡の把握、検診データ追跡による在職中の高血圧、糖尿病、高脂血症等の発症の把握である。また、一般に職域コホートでは定年退職後の疾患発症の追跡が困難であるが、本コホートでは退職後も近隣に在住するものがほとんどのため、1990 年以降退職者については郵送による退職後健康調査を毎年実施し、脳血管疾患、心疾患の発症および死亡を追跡している。在職中および退職後の脳心事故発症者については同意を得た上で、医療機関での医療記録調査を実施している。

以上より、本コホートの特色としては、（１）地域ではコホート設定が困難な青壮年期の男性を多く含むコホートであること、（２）青壮年期男性のライフスタイルや危険因子に影響が大きいと考えられる職業面での要因について詳細な情報が収集されていること、（３）各種危険因子の経年推移が高い追跡率で把握されていること、がある。

2）小矢部コホート

富山県小矢部市は富山県の西部に位置し、面積 134km^2、人口約 35,000 人の市である。主な産業は農業および軽工業であり、脳卒中死亡率は全国よりも比較的高めの地域である。富山県旧小矢部保健所管内では、脳卒中発症者への保健および福祉の充実の目的で 1967 年より地域脳卒中登録が開始された。脳卒中発生の情報源は主に医師による届け出であるが、そのほかに保健師の訪問活動、救急車出動記録、死亡診断書が活用された。さらに婦人会や患者友の会などの協力を得て、極めて高い率での患者把握がなされている。ただし、その後、富山県全域での脳卒中登録制度の開始とともに、小矢部保健所管内の脳卒中登録は終了した。

小矢部コホート研究は、1988 年に小矢部市住民検診を受診した 35-79 歳男女 5,074 人（男 1,569 人、女 3,505 人）をコホートに設定して、1998 年末までの約 10 年間、主に脳卒中発症について追跡したものである。コホート対象者は同市の当該年齢人口の約 25%にあたり、おもに農業、自営業者、主婦、退職者が参加している。1988 年ベースライン調査の特色としては、参加者全員の血圧がトレーニングされたスタッフによりランダムゼロ血圧計で測定されたこと、また、当時は測定が一般的でなかった血清 HDL コレステロールが測定されたこと、がある。

コホートにおいては脳卒中発症が脳卒中登録および死亡診断書から把握された。登録は主に医師からの届け出であるが、一過性脳虚血や無症候性病変は含まれない。登録症例のうち少なくとも 85%が X 線 CT を備えた医療機関からの届け出によるものである。

1998 年末までの追跡期間中の新規脳卒中発生は 132 例（男 63 例、女 69 例）であった。また 388 人が死亡した。転出などによる途中脱落者は 92 人であった。脳卒中発症のほぼ全例で病型（脳梗塞、脳出血、くも膜下出血）が判明している。

2．最新の研究成果

1）飲酒量と 7 年間の血圧上昇度との関連に関する研究（富山職域コホート）

（Yoshita K, Miura K, Morikawa Y, Ishizaki M, Kido T, Naruse Y, Soyama Y, Suwazono Y, Nogawa K, Nakagawa H. Relationship of alcohol consumption to 7 year blood pressure change in Japanese men. *J Hypertens* 2005;23:1485-1490.）

【背景と目的】

飲酒と血圧との関連についての従来の疫学研究は多くが横断研究や短期の介入研究であり、長期にわたる縦断研究は少ない。さらに縦断研究の多くは高血圧発症をエンドポイントとしたものであり、正常範囲内を含めた長期の血圧の上昇度を指標とした追跡研究は国際的にもほとんどない。

一方、検診などで毎年継続的に測定される「繰り返し測定データ」の変化とその関連要因について、各種交絡因子や追跡期間中の影響因子を調整して明らかにする多変量解析法である Generalized Estimating Equation (GEE)法が近年開発されて注目されている。そこで本研究は、大規模な成人男性集団を対象として、飲酒量がベースラインの血圧および

その後7年間にわたる長期の血圧の上昇度とどのような関連を示すのかを、年齢、体重増加、生活習慣要因（特に飲酒と関連する食習慣）、職業要因の影響を考慮して明らかにするものである。

【方法】

本コホートにおける20歳から59歳の男性3,900人を対象とし、1994年から2001年までの7年間の血圧値を毎年追跡した。

ベースライン調査においては職業要因、生活習慣要因等についての自記式の質問票にて調査を行った。生活習慣要因については、食習慣、主な食品群の摂取頻度、飲酒・喫煙習慣、日常生活の身体活動量についての詳しい情報を得た。

血圧測定は、全従業員に対し毎年定期検診時に実施された。分析においては、2001年まで7年間の収縮期血圧および拡張期血圧測定値の変化、すなわち年当たり血圧上昇の勾配を目的変量として解析した。この際他の交絡要因の影響を除外して解析するために、GEE法による解析を行った。

【結果】

収縮期血圧おいては、週当たり300g以上の純アルコール摂取者群は非摂取者群に比べ、年齢と体重を調整した場合、ベースライン値で5.21mmHg高値を示し（$p<0.001$）、年当たりの血圧変化においても0.44 mmHg（$p<0.001$）の 有意に大きな上昇を示した。これは7年間では3.08mmHg大きい血圧上昇となる。さらに職業要因および各種食品群摂取量などの生活習慣要因を加えて調整した場合でも、ベースライン値で4.97mmHg高値を示し（$p<0.001$）、年当たりの血圧変化においては 0.33 mmHg（$p=0.022$）の有意に大きな上昇を示した。ベースラインの収縮期血圧は純アルコール摂取量が週 200g 以上でも著しい上昇を示した（$p<0.001$）。

拡張期血圧おいては、週当たり300g以上の純アルコール摂取者群は非摂取者群に比べ、年齢と体重を補正した場合、ベースライン値で4.16mmHg高値と有意差を示し（$p<0.001$）、年当たりの血圧変化においても 0.19 mmHg 大きい上昇傾向を示した（$p=0.067$）。しかし、職業要因・生活習慣要因を加えて補正した場合は、年当たりの血圧変化には有意差は認められなかった。

【考察と結論】

今回得られた成績は、大規模な男性集団において純アルコールで週300g以上の飲酒習慣がベースラインの血圧値はもとより、その後長期にわたる血圧上昇度に対しても強く関与することを明らかにした新しい知見である。また、この関連は追跡中の体重増加や飲酒に伴う様々な食習慣・職業要因を多変量解析にて調整しても認められ、多量のアルコール摂取自体が長期の血圧上昇をもたらしたことが明らかとなった。純アルコール週300g以上の摂取は日本酒換算週13合程度以上の飲酒となる。これまで高血圧と関連する飲酒量は1日2-3合以上（週14-21合以上）とされていたので、それより少ない飲酒量であっても長期の血圧の上昇度が高まることを新たに示したものとも言える。

集団レベルでは、僅か数mmHgの血圧分布の変化によって、虚血性心疾患や脳血管疾患等

の循環器疾患の発症者数が大幅に変動することが指摘されている。したがって、循環器疾患予防の観点からは、正常範囲内を含めた集団全体の血圧平均値を少しでも低い方向に移動させる対策が必要である。このためには若年期からの適正な飲酒量の普及啓発とその実践が重要であり、今回の研究結果は今後の高血圧予防対策の立案において重要なエビデンスになると考えられる。

Relationship of alcohol consumption to 7-year blood pressure change in Japanese men

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Objective To determine the association of alcohol consumption with years-long blood pressure (BP) change, as well as baseline BP, adjusted for potential confounders.

Design A prospective cohort study.

Setting A metal-products factory in Toyama, Japan.

Participants A total of 3900 men aged 20–59 years.

Main outcome measures BP was measured annually for 7 years after the baseline examination. The generalized estimating equation method was used to analyze the relationship of alcohol consumption to baseline BP and average annual BP change, adjusting for age, yearly weight, work-related factors, and lifestyle factors, including the frequency of intake of 22 food groups.

Results The baseline systolic BP after multivariate adjustment was 3.9 and 5.0 mmHg higher in drinkers consuming 200–299 and ≥ 300 g alcohol/week, respectively, than in non-drinkers ($P < 0.001$). The annual increase in systolic BP was 0.44 mmHg greater in drinkers consuming ≥ 300 g/week than in non-drinkers after adjustment for age and weight change ($P < 0.001$), where the increase over 7 years was estimated to be 3.08 mmHg greater. Even after being adjusted for the frequency of intake of 22 food groups, drinkers consuming ≥ 300 g/week showed a 0.33 mmHg greater annual increase in systolic BP than non-drinkers ($P = 0.022$). Baseline diastolic BP was significantly associated with alcohol consumption, but annual BP change was not.

Conclusions An alcohol intake ≥ 300 g/week was associated with significantly greater annual BP increase, and baseline BP was significantly higher in drinkers consuming ≥ 200 g/week. It is necessary to limit alcohol intake to less than 200 g/week to prevent hypertension. *J Hypertens* 23:1485–1490 © 2005 Lippincott Williams & Wilkins.

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Keywords: blood pressure change, alcohol, food intake, prospective population study

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Introduction

Hypertension is one of the most important risk factors for cardiovascular diseases, and its prevention and treatment are of international importance [1–3]. The association between alcohol consumption and blood pressure (BP) is widely recognized, and many cross-sectional epidemiologic studies have reported an association between alcohol intake and BP [4–9]. Short-term interventional studies have shown that BP is decreased by reduction or cessation of alcohol consumption [10–13]. Longitudinal studies have examined the long-term effects of alcohol consumption on BP using the onset of hypertension as the endpoint [14–18]. However, these studies have ignored BP increases within the normal range. Therefore, few previous longitudinal studies have observed years-long BP increases, including those within the normal range, to investigate any association with alcohol consumption.

In order to make a longitudinal investigation on BP change, it is necessary to exclude the effects of confounding variables such as baseline BP level, age, and weight change. Moreover, very few longitudinal studies have included adjustment for the intake of various food groups, the importance of which was pointed out in the Dietary Approaches to Stop Hypertension studies [19,20]. The generalized estimating equation (GEE) method, a multivariate analysis method for detecting

changes in repeated measurement data, was developed [21] and has come into use in epidemiologic studies [22,23].

The objective of the present study was to determine the association of alcohol consumption with BP change over seven consecutive years, as well as baseline BP, in a large adult male population, with adjustment for the effects of baseline BP, age, weight change, and lifestyle-related factors such as the intake of various food groups, using the GEE method.

Methods

The study population consisted of workers at a metal-products factory in a rural area in Toyama Prefecture, located in the center of Japan. The details of this population have been described elsewhere [24,25]. The baseline survey of this 7-year follow-up was conducted in 1994.

Alcohol consumption was assessed by a self-reporting questionnaire [26–28]. Participants reported the presence or absence of an alcohol drinking habit at the time of survey and before the survey, the frequency of alcohol consumption during a typical week, and the amount of alcohol intake on each occasion. They were asked to estimate their alcohol intake based on *gou*, a traditional Japanese drinking unit corresponding to 23 g ethanol. One *gou* is equivalent to 180 ml *sake* (Japanese rice wine), and its ethanol content is roughly equivalent to that of a bottle of beer (633 ml), two single shots of whisky (70 ml), a half-glass of *shochu* (Japanese traditional spirits) (110 ml), or 240 ml wine. Then, the amount of ethanol consumption per week was calculated for each participant, and participants were divided into six groups of alcohol consumption; non-drinkers, ex-drinkers, less than 100 g/week, 100–199 g/week, 200–299 g/week, and 300 g/week or more. Lifestyle-related and work-related factors were also investigated with a self-reporting questionnaire. The questionnaire included items about work-related factors: awareness of physical and mental stress at work; and lifestyle-related factors: the average time of exercise per week, the average time of walking per day, smoking habit, preference for high-salt foods, and preference for fatty foods. Information on the frequency of intake of 33 major food groups was also obtained. Of the 33 food groups, the frequency of intake of 22 food groups that could affect the association between BP and alcohol consumption was used for multivariate adjustments: beef, pork, chicken, egg, milk, yogurt, cheese, fresh fish, spinach, carrot and pumpkin, tomato, cabbage, lettuce, Chinese cabbage, mushroom, potato, pickle, beans, tofu (bean curd), citrus fruit, other fruits, and sweets.

The BP was measured once in the right arm after 5 min of rest in a seated position, by well-trained nurses using a standard mercury sphygmomanometer. Measurements were taken every year until 2001. Time of measurement was between 0900 and 1500 h throughout the study period, and measurement within 30 min after a meal or heavy physical activity was avoided. Standard mercury sphygmomanometers were checked and calibrated every year.

The subjects for the present study were selected as follows. In 1994 (baseline), 7428 employees received a medical examination conducted at this factory, and this included 4479 men aged 20–59 years. From these, we excluded 381 men who received fewer than three of the eight examinations conducted until 2001, and another 198 men with missing data about their baseline alcohol drinking habit, age, height, weight, or BP. Finally, 3900 subjects were enrolled for analysis.

Statistical analyses were performed by the GEE method for longitudinal data [21] to estimate the relationship of baseline alcohol consumption to average yearly change in systolic or diastolic BP, with adjustment for baseline BP and probable confounders. The relationship of each alcohol level to BP change was measured by the coefficient of the cross-product (interaction) term between alcohol level and a time variable, t ($t = 0, 1, \ldots, 7$). The multivariate adjusted relationship of alcohol consumption to baseline BP was also estimated from coefficients in the same GEE models when $t = 0$. Analyses on the relationship of alcohol consumption to baseline BP and BP change were serially adjusted for confounding factors in four GEE models: a model adjusted for baseline age only; Model 1, with adjustment for baseline age and weight at each year; Model 2, with adjustment for baseline age, weight at each year, number of cigarettes consumed, exercise status, physical stress of labor, mental stress of labor, preference for salty taste and fatty foods; and Model 3, with adjustment for Model 2 covariates plus the frequency of intake of 22 food groups. For each potential baseline variable in the model, a cross-product term with time was included to adjust for the relationship of the confounder with BP change. Adjustment for categorical confounders was done by including dummy variables for each variable and the cross-product terms between these dummy variables and time. Only for adjustment of weight, coefficients for baseline BP were adjusted for weight at baseline. Results are expressed as coefficients, which represent the difference in baseline BP or annual BP change between a higher alcohol consumption group and the reference group (non-drinkers); P values are given for coefficients. The sample size of this study was considered to be sufficient to detect a meaningful difference in annual BP change, except for the category of ex-drinkers [29]. The analyses were performed using procedure GENMOD in the SAS program, Release 8e (SAS Institute Inc., Cary, North Carolina, USA).