Table 3 Interaction between smoking and total cholesterol for cause specific mortality. NIPPON DATA80 1980–99

	Never smoker				Current smoker				
	N	*n*	Age-adjusted mortality rate	RH	*N*	*n*	Age-adjusted mortality rate	RH	*P* for interaction[b]
Men									
Coronary heart diseases									
Q1(<4.25 mmol/l[a])	173	4	1.3	1	709	4	0.2	0.48 (0.10–2.22)	
Q2(4.26–4.80 mmol/l[a])	177	2	0.4	1	678	5	0.5	0.38 (0.06–2.27)	
Q3(4.81–5.39 mmol/l[a])	189	3	1.0	1	605	14	1.2	2.07 (0.57–7.57)	
Q4(≥5.40 mmol/l[a])	184	4	1.2	1	531	15	1.5	1.64 (0.52–5.19)	
Total	723	13		0.70 (0.32–1.54)[c]	2523	38		2.00 (1.46–2.74)[c]	0.03
Ischaemic stroke									
Q1(<4.25 mmol/l[a])	173	4	0.6	1	709	17	0.8	1.77 (0.51–6.17)	
Q2(4.26–4.80 mmol/l[a])	177	3	0.4	1	678	22	1.7	3.50 (0.96–12.75)	
Q3(4.81–5.39 mmol/l[a])	189	4	0.6	1	605	11	0.9	1.37 (0.40–4.69)	
Q4(≥5.40 mmol/l[a])	184	1	0.1	1	531	12	1.4	7.99 (0.84–76.14)	
Total	723	12		0.55 (0.21–1.43)[c]	2523	62		1.09 (0.79–1.50)[c]	0.09
Ischaemic cardiovascular diseases									
Q1(<4.25 mmol/l[a])	173	8	1.9	1	709	21	1.0	1.07 (0.42–2.74)	
Q2(4.26–4.80 mmol/l[a])	177	5	0.8	1	678	27	2.1	2.01 (0.72–5.63)	
Q3(4.81–5.39 mmol/l[a])	189	7	1.6	1	605	25	2.1	1.70 (0.71–4.08)	
Q4(≥5.40 mmol/l[a])	184	5	1.3	1	531	27	2.8	2.60 (0.94–7.18)	
Total	723	25		0.65 (0.36–1.19)[c]	2523	100		1.42 (1.13–1.80)[c]	0.01
Women									
Coronary heart diseases									
Q1(<4.25 mmol/l[a])	1074	9	0.9	1	91	2	1.6	2.18 (0.34–14.11)	
Q2(4.26–4.80 mmol/l[a])	1063	8	0.5	1	102	0	0.0	–	
Q3 (4.81–5.39 mmol/l[a])	1089	11	0.5	1	115	3	1.0	2.49 (0.62–10.00)	
Q4(≥5.40 mmol/l[a])	1187	16	0.6	1	125	4	1.4	3.77 (1.21–11.74)	
Total	4413	44		0.88 (0.61–1.28)[c]	433	9		1.12 (0.46–2.73)[c]	0.28
Ischaemic stroke									
Q1(<4.25 mmol/l[a])	1074	8	0.8	1	91	1	0.9	1.50 (0.16–14.33)	
Q2(4.26–4.80 mmol/l[a])	1063	14	0.8	1	102	0	0	–	
Q3(4.81–5.39 mmol/l[a])	1089	13	0.6	1	115	1	0.4	0.55 (0.06–4.97)	
Q4(≥5.40 mmol/l[a])	1187	22	0.8	1	125	6	2.2	4.65 (1.73–12.52)	
Total	4413	57		0.96 (0.70–1.34)[c]	433	8		1.98 (0.45–8.73)[c]	0.71

(continued)

Table 3 *Continued*

	Never smoker				Current smoker				
	N	*n*	Age-adjusted mortality rate	RH	*N*	*n*	Age-adjusted mortality rate	RH	*P* for interaction[b]
Women									
Ischaemic cardiovascular diseases									
Q1(<4.25 mmol/l[a])	1074	17	1.7	1	91	3	2.5	1.86 (0.45–7.62)[d]	
Q2(4.26–4.80 mmol/l[a])	1063	22	1.3	1	102	0	0.0	–	
Q3(4.81–5.39 mmol/l[a])	1089	24	1.2	1	115	4	1.4	1.37 (0.43–4.34)	
Q4(≥5.40 mmol/l[a])	1187	38	1.3	1	125	10	3.6	4.24 (2.02–8.88)	
Total	4413	101		0.92 (0.72–1.18)[c]	433	17		1.28 (0.65–2.50)[c]	0.02

Age-adjusted mortality rate, age-adjusted mortality rate per 1000 person-years.
In multivariate-adjusted model, we adjusted for age, body mass index, systolic BP, use of anti-hypertensive medication, diabetes and drinking category (never, past, occasional, and daily).
[a]<4.25 mmol/l, <164 mg/dl; 4.26–4.80 mmol/l, 165–185 mg/dl, 4.81–5.39 mmol/l, 186–208 mg/dl; ≥5.40 mmol/l, ≥209 mg/dl.
[b]*P* for interactions: interactions between TC (continuous) and smoking status were examined using cross-product terms in the regression model.
[c]Relative hazards of cholesterol increase per 1 mmol/l(continuous) for cause specific deaths.
[d]Because of questionable model fitting, we have excluded diabetes and anti-hypertensive medication from the model.
TC, total cholesterol; *N*, numbers of participants; *n*, numbers of mortality.

The strengths of our study are that we used a representative Japanese population from a national survey, as well as a validated and standardized TC measurement.

Several possibilities could explain the interaction. From a biological viewpoint, the findings that the association of smoking with ischaemic CVD is closer among individuals with higher, than with lower TC, were consistent with those of recent studies indicating that smoking is associated more closely with advanced, than with early, subclinical atherosclerosis.[7,8] In both the Atherosclerosis Risk in Communities (ARIC) study and in the Multiethnic Study of Atherosclerosis, Sharrett *et al.* showed that smoking was more closely associated with severe atherosclerosis (lower extremity artery disease or severe carotid artery intimal medial thickness, IMT) than with moderate IMT, and that low density lipoprotein cholesterol (LDL-C) was a more important determinant than smoking of the earliest ultrasound-detectable stage of atherosclerosis. A study of young adults similarly found that the determinants of carotid IMT were only lifetime LDL-C and (inversely) high density lipoprotein cholesterol (HDL-C), but not smoking pack-years or diabetes.[18] Thus, the impact of smoking could be higher in those with high TC and lower in those with low TC. The second possibility is that higher CVD mortality among those who never smoked with lower TC explains the interaction. Although men with lower TC who had never smoked had a preferable CVD risk factor profile, they had a higher age-adjusted CVD mortality rate. We considered two explanations for this. One is that the risk of haemorrhagic stroke mortality is higher in men who had never smoked with low TC. Haemorrhagic stroke is not atheromatous, and is affected by hypertension but not by serum TC. Furthermore, some epidemiological studies suggested that lower TC is associated with higher haemorrhagic stroke risk[19]. Thus, haemorrhagic stroke might increase the CVD risk. However, the higher CVD mortality rates in men with lower TC who had never smoked persisted even when CHD or ischaemic CVD were the end-points. Another explanation for the higher CVD mortality rate in the subgroup of non-smokers with low TC might be personal characteristics. Most Japanese men, especially the elderly, have smoked cigarettes at some point during their lives. For example, almost 80% (77.5%) of men aged ≥20 years smoked in 1970,[20] and the remainder of those who had never smoked might have some degree of frailty. Although the exclusion of early death that occurred within 5 years did not alter the interaction, some residual confounding might have remained. For example, some might have had respiratory conditions before starting to smoke, such as tuberculosis or childhood asthma. Participants with poor nutrition, irrespective of symptoms, might have a higher CVD risk. Since information on history of respiratory diseases was unavailable, we could not determine the validity of this speculation. Unknown confounding factors might also exist that could explain the higher mortality in never smoked with lower TC. Further studies are required to understand the relationship between TC and CVD among Japanese who have never smoked. Regardless, both biological mechanisms and personal characteristics in men with lower TC who had never smoked might explain the interaction.

Our findings are consistent with recent changes in the relationship between smoking and CVD in Japan.[2,13] In the two

Japanese cohorts (Tanushimaru and Ushibuka) in the Seven Countries Study, which collected baseline data between 1957 and 1964 and followed participants for 25 years, excess CHD or stroke-associated mortality[8] did not significantly differ among smokers and non-smokers. Although most prospective studies have found a significant relationship between smoking and CHD,[10,13,14] older studies did not find a significantly increased multiple-adjusted risk of stroke among smokers.[9–11] However, recent studies, in which TC levels are higher, have established a significant and closer relationship between cigarette smoking and stroke, especially ischaemic stroke.[12–15] Thus, our findings appear to be relevant and are also supported by several other epidemiological studies. The Hisayama study found that the relative risk of smoking for CHD was obviously greater among those with high, than low, TC.[10] However, they did not formally test the effect-modification. A recent finding from the ARIC study also revealed a modest but significant interaction between smoking and LDL-C for CHD incidence.[21] However, two large Korean studies (with shorter follow-ups) and a US study found that lower serum TC levels did not modify the risk relationship between smoking and CVD.[5,22,23]

One of the limitations of this study is the use of mortality data. Lower-quality nutrition might determine early death after CVD events. Thus, the risk of TC might have been under-estimated. Another limitation is the low mortality rate, especially among men who had never smoked and among women who current smoked. Our findings should be substantiated by longer studies of larger cohorts using CVD incidence data.

Mean levels of TC in Japan are rapidly increasing in Japan.[2] The National Nutrition Survey in Japan conducted in 2000 reported that the mean level of TC in Japan is 5.16 mmol/l (199.7 mg/dl) for men and 5.36 mmol/l (207.5 mg/dl) for women.[24] The prevalence of cholesterol values of $\geqslant$6.22 mmol/l ($\geqslant$240 mg/dl) in the 2000 survey (12.0% for men and 17.4% for women) was double that found in an identical national survey in 1980, which was the source of our cohort data (6.1% for men and 8.5% for women).[24] In the same report in 2000, although the prevalence of current cigarette smoking was <50% overall (45.6% for men and 10.5% for women), it was higher among younger populations (56.8% and 55.0% in men aged 30–39 and 40–49 years, respectively; 18.5 and 13.7% in women aged 30–39 and 40–49 years).[22] Thus, the impact and contribution of smoking or TC to CVD mortality, especially ischaemic CVD in Japan could increase.

In conclusion, we found that powerful effect modifications between smoking and TC for CVD mortality among Japanese men. This pattern was also observed for CHD mortality and ischaemic CVD in men and for ischaemic CVD mortality in women. Thus, the weak association of cigarette smoking with CVD mortality in Japan may be partly explained by a lower TC level. Since TC is increasing among Japanese, especially among younger men who often smoke,[25] greater efforts to reduce smoking are warranted in Japan and in other Asian countries.

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Appendix

List of the NIPPON DATA 80 Research Group.

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随時血糖高値と冠動脈疾患、循環器疾患、総死亡との関係

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目的

空腹時血糖（FBG）値高値は冠動脈疾患（CHD）、循環器疾患（CVD）の危険因子である。FBG値や経口ブドウ糖負荷試験（OGTT）は糖尿病の診断に使われている。しかし午後に病院を訪れる患者等では絶食での来院は難しいことがある。また、我が国の循環器疾患のスクリーニングのための健診等では受診率を上げるため、受診者に空腹状態で来ることを要求していない。そのため、最終の食事時間に関わらない随時血糖（CBG）値高値がCHDやCVD死亡を予測するかを明らかにする必要があるが、日本で両者の関係を調べた前向き研究はほとんど無い。我々はCBG値とCHDやCVD死亡との関係を、日本人の代表集団のコホート研究（NIPPON DATA80）を用いて解析した。また、正常範囲内のCBG値とCHDやCVD死亡との関連、CBG高値やCBG境界値のCHD死亡やCVD死亡に対する寄与を調べた。

方法

1980年の循環器疾患基礎調査は調査では国内の300箇所で、30歳以上の住民を無作為に13771人抽出して行い、10546人が参加した。この受診者の追跡調査（NIPPON DATA80)を用い、CVD既往のある者や、最初の段階で情報に欠如のあった者を除いた9444名を解析した。

調査項目にはCBG値、総コレステロール値、血圧、体重、身長、問診による糖尿病既往と最後の食事時間、服薬内容、喫煙・飲酒状況が含まれていた。身長・体重よりBMI(Body Mass Index)を計算した。追跡中に亡くなった受診者については、ICD 9・ICD10を用いて死因を分類した。受診者をCBG値に応じて以下の4群に分けた。CBG高値群：CBG≧200 mg/dlまたは糖尿病（DM）既往あり。CBG境界群：140≦CBG＜200 mg/dl。正常高値群：94≦CBG＜140mg/dl。

正常低値群：CBG<94 mg/dl。正常高値群と低値群の境界値はCBG≦140 mg/dlの群の中央値を用いた。

年齢、性別、総コレステロール値、BMI、高血圧、喫煙、飲酒、居住地の情報を調整し、CHD死亡やCVD死亡、総死亡の多因子調整ハザード比（HR）を計算した。

結果

平均17.3年間追跡し、追跡率は91%であった。追跡期間内の死亡総数は1911人であり、CHD死亡は137人、CVD死亡は692人、CHD粗死亡率は1000人あたり0.84人であった。CBG値が140mg/dl未満の群を基準群とし、140mg/dl以上の群のCHD死亡のHRを求めた。採血までの食後経過時間(1時間、2時間、3-4時間、5時間以上)で分割すると、HRは食後1時間群では有意でなかったものの、それ以外の群では有意に高かった。CBG正常低値群を基準群としたCHD死亡の多因子調整HR（95%信頼区間）は、CBG境界群で2.43（1.29-4.58)、CBG高値群で2.62（1.46-4.67）であり、CBG値の上昇とともにHRも上昇した。CVD死亡や総死亡でも同様であった。CBG値正常範囲群(CBG＜140mg/dl)で1mmol/l（18mg/dl）CBG値が上昇した際のCVD死亡のHRは1.12(1.02-1.22)であった。このCBG値正常範囲群をさらに5群に等分し、最もCBG値の低い群を基準群としたCVD死亡のHRは、CBG値の上昇に従い段階的に上昇した。集団寄与危険割合は、CBG高値群と境界群を合わせると、CHD死亡が12.0%、CVD死亡が4.9%、総死亡が3.5%であった。

結論

CBG高値はCHDやCVD死亡を予測する。CBG高値はたとえ正常範囲であってもCVD死亡と関連する。CBG境界群以上の高CBGは5%のCVD死亡に寄与していると考えられる。

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ARTICLE

Relationship of elevated casual blood glucose level with coronary heart disease, cardiovascular disease and all-cause mortality in a representative sample of the Japanese population. NIPPON DATA80

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Abstract
Aims/hypothesis High fasting blood glucose is one of the well-known risk factors for CHD. However, in certain settings, patients cannot always be expected to fast. For example, community screenings for cardiovascular disease (CVD) risk factors in Japan are performed under non-fasting conditions to achieve high participation rates. Thus, we examined a representative cohort of the Japanese population (n=9,444, follow-up period 17.3 years) to clarify whether high casual blood glucose (CBG) can predict CVD mortality.
Methods We defined CBG groups as follows: high CBG≥ 11.1 mmol/l or participants with a history of diabetes mellitus; borderline high, 7.77≤CBG<11.1 mmol/l; higher normal, 5.22≤CBG<7.77 mmol/l); and lower normal, CBG<5.22 mmol/l. The multivariate-adjusted hazard ratios (HRs) for CHD, CVD and all-cause mortality were calculated.
Results The crude CHD mortality rate was 0.84 per 1,000 person-years. Age- and sex-adjusted HRs for CHD mortality were high among participants with CBG levels ≥7.77 mmol/l, regardless of time since last meal. Multivariate-adjusted HRs (95% CI) of CHD mortality in high and borderline high CBG groups were 2.62 (1.46–4.67) and 2.43 (1.29–4.58), respectively. Similar results were observed for both CVD

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and all-cause mortality. Even within the normal blood glucose range, each 1 mmol/l increase in CBG was associated with a statistically significant increase in the HR for CVD mortality (1.12, 95% CI 1.02–1.22). Population-attributable fractions of the combined groups of high and borderline high CBG for CHD, CVD and all-cause mortality were 12.0, 4.9 and 3.5%, respectively.

Conclusions/interpretation Increases in CBG, even within the normal range, predict CVD mortality.

Keywords Cardiovascular disease · Casual blood glucose · Cohort study · Coronary heart disease · Diabetes mellitus · Japanese · Mortality · Population-attributable fraction

Abbreviations

CBG	casual blood glucose
CVD	cardiovascular disease
HR	hazard ratio
ICD	International Classification of Diseases
NIPPON DATA80	National Integrated Project for Prospective Observation of Non-communicable Diseases and its Trends in the Aged, 1980
PAF	population-attributable fraction

Introduction

Impaired glucose tolerance and diabetes mellitus are well-known risk factors for coronary heart disease (CHD) and cardiovascular disease (CVD) [1–4]. A fasting blood glucose level or a fasting blood glucose level plus 2 h post-glucose load (75 g OGTT) are usually used to diagnose diabetes mellitus [5]. However, in some settings, it is unrealistic to require all participants to fast. It is impractical to require either of these tests from clinic patients, especially those who visit at night or in the afternoon. Furthermore, in Japan, general screenings for CVD risk factors are performed under non-fasting conditions to improve the participation rates. Thus, the question of whether a casual blood glucose (CBG) level, whose value can be obtained at any time of the day regardless of time since last meal, can predict CHD or CVD mortality is of great interest. Only one prospective study has reported this relationship between CBG and CHD [6], though some prospective studies have reported the relationship between CHD and fasting blood glucose or OGTT [7–9]. We investigated the relationship of CBG with CHD, CVD and all-cause mortality in a 17.3-year follow-up study with a representative sample from the Japanese population. We also investigated whether a CBG level predicts CHD or CVD mortality within a normal glucose range and examined what proportion of CHD or CVD deaths was attributable to high CBG or borderline high CBG levels.

Methods

Population The cohort studies of the National Survey on Circulatory Disorders 1980 were called the National Integrated Project for Prospective Observation of Non-communicable Diseases and its Trends in the Aged, 1980 (NIPPON DATA80). Details of these cohorts have been previously reported [10–14]. Briefly, 13,771 participants were randomly selected in 300 districts from the overall population aged 30 years or older in Japan by the Japanese Ministry of Health and Welfare. Among them, 10,546 individuals completed a baseline survey, namely, the National Survey of Circulatory Disorders, in 1980. All participants were assured a right to refuse the participation in this survey. The participation rate in this survey was 76.6% (10,546 of 13,771). They were followed-up until 15 November 1999 by using the national Vital Statistics. Of the 10,546 participants, 1,102 were excluded for the following reasons: past history of CHD (n=45) or stroke (n=108); information missing at the baseline survey (n=41); or lost to further contact due to incomplete residential access information at the first survey (n=908). The remaining 9,444 participants (4,134 men, 5,310 women) were included in the analysis.

Baseline examination Blood was drawn from seated patients into a plain, siliconised glass tube and the serum was separated. The serum was centrifuged soon after blood coagulation at 1,500×g. Fasting was not required prior to blood draw. The blood was gathered and analysed at one specific laboratory (formerly Center for Adult Diseases, Osaka; now named Osaka Medical Center for Health Science and Promotion, Osaka, Japan). Since April 1975, this laboratory has been certified by the CDC-NHLBI Lipid Standardization Program of the Center for Disease Control and Prevention (Atlanta, GA, USA) [15]. Blood glucose levels were measured at this site using the cupric-neocuproine method [16] between 1975 and 1986 [17]. Because blood glucose levels are now widely measured with the hexokinase method, the serum glucose levels were adjusted by using a formula ([0.047×(glucose concentration in mg/dl)]−0.541) previously reported by the same laboratory, which gives levels in mmol/l [17]. Iso et al. [17] reported that this formula was obtained from 60 random samples of blood with the regression line (r^2=0.93). Total cholesterol levels were also measured. BMI was calculated as weight (kg) divided by the square of height (m). Obesity was defined as BMI≥25 kg/m^2 [18]. Public health nurses obtained information about past history of diabetes mellitus, time since last

meal, smoking, drinking and medication histories. The nurses measured baseline blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants after a 5 min rest. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents or any combination of these. Residential districts were classified as urban, suburban, sub-rural and rural based on the population size of the municipality in which the participants lived [19].

Follow-up survey For deceased participants, the underlying cause of death obtained from National Vital Statistics was coded according to the International Classification of Diseases (ICD), using the 9th revision (ICD9) for the period between 1980 and 1994, and the 10th revision (ICD10) for the period between 1995 and 1999. Deaths from CHD (ICD9: 410–414, ICD10: I20–I25), all heart diseases (ICD9: 410–429, ICD10: I20–I25, I30–I52) and CVD (ICD9: 390–459, ICD10: I00–I99) were defined according to ICD9 and ICD10 codes. The details of the classification in the present study have been described elsewhere [20]. Permission to use National Vital Statistics was obtained from the Management and Coordination Agency, Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (number 12–18, 2000).

Statistical analysis Participants were divided into the following three groups according to their CBG levels: (1) less than 7.77 mmol/l (normal); (2) 7.77 to <11.1 mmol/l (borderline high CBG); and (3) ≥11.1 mmol/l or patients with a history of diabetes mellitus (high CBG). In some analyses, the 'normal' CBG group was divided into two groups at their median, i.e. higher normal (CBG 5.22 to <7.77 mmol/l) and lower normal (CBG<5.22 mmol/l). The 'borderline high CBG' and 'high CBG' groups were categorised on the basis of OGTT criteria [21]. According to the OGTT criteria, blood glucose levels from 7.77 to <11.1 mmol/l and ≥11.1 mmol/l at 2 h after glucose intake are defined as impaired glucose tolerance and diabetes mellitus, respectively. In some analyses, we combined higher normal and lower normal into one category.

The risk characteristics of each group at the baseline survey and cause-specific mortality were described as means, standard deviation (SD) for continuous variables and proportions for categorical variables. Analysis of variance was used for comparisons of multiple group means and the χ^2 test was used to compare proportions.

We calculated age- and sex-adjusted hazard ratios (HRs) for CHD deaths for the participants whose CBG levels were ≥7.77 mmol/l by comparing the death rate with that for the group whose CBG levels were <7.77 mmol/l. We divided the participants into four groups by time since last meal to examine the effect of that time on CHD deaths. The four groups were defined as 1, 2, 3–4, and ≥5 h since the last meal. The multivariate-adjusted HRs of all four blood glucose categories for CHD, CVD, all-heart or all-cause morality were calculated using a Cox proportional hazard model adjusted for age, total cholesterol, BMI, hypertension, smoking categories (never smokers, past smokers, smoking ≤20 cigarettes per day or smoking ≥21 cigarettes per day), drinking categories (never drinkers, past drinkers, occasional drinkers or everyday drinkers) and residential districts. We applied dummy variables to the smoking and drinking categories. We defined the lower normal group (i.e. CBG≤5.22 mmol/l) as the reference group. We included sex in the model when analysing the combined dataset of men and women. The trend tests were performed by allocating scores 1, 2, 3 and 4 for all participants in lower normal, higher normal, borderline high CBG and high CBG, respectively. To assess whether the positive relationship between CBG and CHD or CVD mortality was observed in participants within the normal blood glucose range, we analysed the relationship between CBG (continuous levels) and CHD or CVD mortality in participants whose blood glucose levels were <7.77 mmol/l. Additionally, we divided the participants whose blood glucose levels were <7.77 mmol/l into quintiles and calculated multivariate adjusted HRs of CVD mortality to check for a threshold within normal and higher normal CBG. We used a Cox proportional hazard model adjusted for age, total cholesterol, BMI, hypertension, smoking categories, drinking categories and residential districts.

Population-attributable fractions (PAFs) for CHD, all heart disease, CVD and all-cause mortality were calculated as pd×(HR−1)/HR [22], where pd is the proportion of death cases in the groups exposed to the risk, i.e. the borderline high CBG groups and the high CBG groups, and the multiple-adjusted HRs were used for the calculations. When calculating the PAF of the borderline high CBG group alone, the results for the high CBG group were not included. We calculated all PAFs using the combined dataset of men and women.

All confidence intervals were estimated at the 95% level. A p value of <0.05 was considered significant. The Statistical Package for the Social Science (version 11.0J; SPSS Japan, Tokyo, Japan) was used for the analysis.

Results

The age (mean±SD) at the baseline survey for all participants was 50.4±13.2 for men and 50.8±13.3 for women. The mean level of adjusted serum glucose with the hexokinase method was 5.67±1.82 mmol/l for men and 5.59±1.60 mmol/l for women. Table 1 shows baseline

Table 1 Prevalence characteristics stratified by CBG levels at the baseline survey in 1980, NIPPON DATA80

	CBG levels at baseline (mmol/l)				
	Lower normal (<5.22)	Higher normal (5.22≤CBG<7.77)	Borderline high (7.77≤CBG<11.1)	High[a] (≥11.1)	*p* value
Men					
n	1,915	1,814	187	218	<0.01
Age (years)	48.3±12.2	51.3±13.7	54.8±14.0	57.0±11.1	<0.01
S glucose (mmol/l)	4.64±0.50	6.02±0.64	8.83±0.90	9.14±5.03	<0.01
S total chol (mmol/l)	4.80±0.81	4.80±0.86	4.80±0.94	5.06±0.92	<0.01
Current smoker (%)	64.1	61.8	65.3	66.0	0.66
Current drinker (%)	77.0	73.2	66.3	73.0	<0.01
Hypertension (%)	43.1	54.3	61.5	67.0	<0.01
Obesity (%)	18.3	19.8	17.6	24.8	0.11
Residential districts					
Urban (%)	31.7	31.0	28.9	35.3	0.19
Suburban (%)	24.8	22.9	21.9	23.9	
Sub-rural (%)	15.7	15.0	15.5	15.6	
Rural (%)	25.0	28.9	29.9	21.1	
Women					
n	2526	2467	175	142	<0.01
Age (years)	47.4±12.5	53.5±13.3	56.7±11.6	60.3±11.5	<0.01
S glucose (mmol/l)	4.67±0.44	6.00±0.60	8.95±0.88	10.7±5.22	<0.01
S total chol (mmol/l)	4.83±0.84	5.02±0.91	5.12±0.86	5.32±0.86	<0.01
Current smoker (%)	9.0	8.6	9.7	9.1	0.54
Current drinker (%)	21.4	19.0	16.0	15.5	0.19
Hypertension (%)	32.1	48.3	61.1	69.0	<0.01
Obesity (%)	19.6	25.2	25.7	36.6	<0.01
Residential districts					
Urban (%)	31.7	32.3	31.4	32.4	<0.01
Suburban (%)	26.4	21.4	26.3	26.8	
Sub-rural (%)	16.0	15.0	15.4	15.5	
Rural (%)	23.4	28.6	25.7	23.2	

Unless indicated otherwise, values are means (±SD)
ANOVA was used for comparisons of multiple group means and the χ^2 test was used to compare frequencies
Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic pressure ≥90 mmHg, the use of antihypertensive agents or any combination of these. Obesity was defined as BMI≥25 kg/m^2
[a] Participants with a history of diabetes mellitus were placed in the high CBG group
S glucose, serum glucose; S total chol, serum total cholesterol

characteristics of the participants according to the serum glucose category. The higher glucose groups for both sexes had a higher age and higher prevalence of hypertension than lower glucose groups. Serum total cholesterol mean values for women were higher in the higher glucose groups. The prevalence of current smoking for men was higher in the higher glucose groups, but this difference was not statistically significant. The prevalence of obesity was highest in the high CBG groups in both sexes. The prevalence of current drinking and the residential districts for both sexes was not associated with glucose categories.

Diabetes prevalence in our data per 10 year age groups was 1.0% for those in their 30s and 2.4, 5.0, 7.2, 7.3 and 4.8% for those in their 40s, 50s, 60s, 70s and 80s, respectively. When borderline high CBG was included, the prevalence was 3.1, 5.4, 9.7, 13.0, 12.8 and 11.6% for the age groups above. Total person-years were 163,044 (69,946 for men, 93,098 for women) and the mean follow-up period was 17.3 years. During follow-up, we observed 1,911 all-cause deaths (1,025 for men, 886 for women), 137 CHD deaths (68 men, 69 women), 336 all heart diseases (164 men, 172 women) and 692 CVD deaths (345 men, 347 women).

Figure 1 shows age- and sex-adjusted HRs for CHD mortality of participants whose blood glucose levels for given time categories since last meal were ≥7.77 mmol/l compared with those whose CBG levels were <7.77 mmol/l. All HRs were positive regardless of the time since the last meal, though the HR was not statistically significant in the 1 h since last meal category.

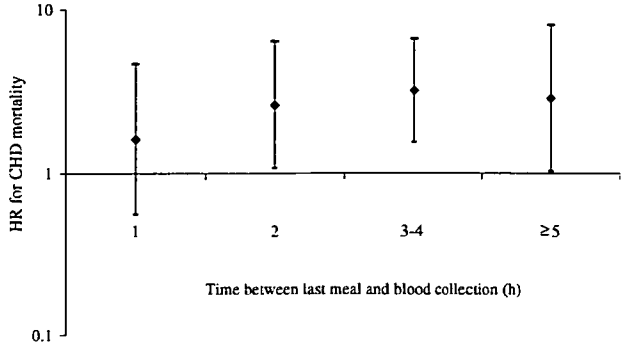

Fig. 1 Age- and sex-adjusted HRs with 95% CIs for CHD deaths in participants whose CBG levels were ≥7.77 mmol/l or who self-reported diabetes mellitus compared with those whose CBG levels were <7.77 mmol/l. Results are grouped according to time in hours between last meal and blood collection time, and a log scale was used. Participants per time category: n=1,164, 1,148, 2,822 and 4,310 for 1, 2, 3–4 and ≥5 h, respectively. HRs per time category: HR=1.62, 2.62, 3.22 and 2.89 for 1, 2, 3–4 and ≥5 h, respectively

Table 2 shows the number of deaths and multivariate adjusted HRs for CHD, all heart diseases, CVD and all-cause mortality. The crude CHD mortality rate was 0.84 per 1,000 person-years in men and women combined (0.97 for men, 0.74 for women). HRs for any cause-specific CVD mortality suggested a graded relationship with glucose categories. HR values for CHD mortality were consistently higher in the high CBG and the borderline high CBG groups than in the reference groups. The HRs for CHD mortality were also higher in the higher normal blood glucose groups than in the reference groups. HRs for CVD and all heart diseases mortality showed similar tendencies. Because no interaction between sex and CBG was observed for CVD (p=0.91), we combined men and women in the following analyses. When we combined lower normal and higher normal into one category as the reference group (i.e. CBG≤7.77 mmol/l), the HRs for CHD mortality were 2.12 (95% CI 1.19–3.79) for borderline high CBG and 2.29 (95% CI 1.36–3.86) for high CBG. Similar findings were observed in both sexes (data not shown). Even when we restricted the analysis to participants with values within the normal blood glucose range (CBG≤7.77 mmol/l), each 1 mmol/l increase in CBG was associated with a significant increase in the HR for CVD mortality (HR 1.12, 95% CI 1.02–1.22). The HR for CHD mortality per 1 mmol/l increase in CBG was similar to that for CVD, but this increase was not significant (HR 1.09, 95% CI 0.89–1.34). When we divided participants within the normal blood glucose range (CBG≤7.77 mmol/l) into quintiles, HRs for CVD mortality

Table 2 The number of deaths and multivariate-adjusted HRs for CHD, all heart diseases, CVD and all-cause mortality according to CBG levels

	Baseline serum CBG, men and women combined			
	Lower normal	Higher normal	Borderline high	High
Glucose (mmol/l)	<5.22	5.22≤CBG<7.77	7.77≤CBG<11.1	≥11.10
n	4,441	4,281	362	360
Person-years	78,635	73,005	5,939	5,465
Cause of death				
CHD				
Deaths (n)	38	69	13	17
Mortality rate[a]	0.5	0.9	2.2	3.1
HR (95% CI)[b]	1	1.24 (0.83–1.86)	2.43 (1.29–4.58)	2.62 (1.46–4.67)
All heart diseases				
Deaths (n)	105	167	29	35
Mortality rate[a]	1.3	2.3	4.9	6.4
HR (95% CI)[b]	1	1.06 (0.83–1.36)	1.78 (1.17–2.70)	2.07 (1.41–3.06)
CVD				
Deaths (n)	205	379	47	61
Mortality rate[a]	2.6	5.2	7.9	11.2
HR (95% CI)[b]	1	1.22 (1.03–1.45)	1.46 (1.06–2.01)	1.82 (1.37–2.43)
All causes				
Deaths (n)	665	976	107	163
Mortality rate[a]	8.5	13.4	18.0	29.8
HR (95% CI)[b]	1	1.07 (0.96–1.18)	1.13 (0.92–1.38)	1.63 (1.37–1.93)

Sex was included in the model, as the combined dataset of men and women was analysed

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents or any combination of these

[a] The mortality rate is the crude mortality rate per 1,000 person-years

[b] The HRs were adjusted for age, serum total cholesterol levels, BMI, hypertension, cigarette smoking categories, drinking categories and residential districts. p<0.001 for all trends

increased gradually in the high CBG groups ($p<0.01$ for trend; Table 3). PAFs of high CBG and borderline high CBG for CHD, all heart diseases, CVD and all-cause mortality were 12.0, 8.8, 4.9 and 3.5%, respectively, compared with normal CBG groups (CBG<7.77 mmol/l). PAFs of high CBG alone for CHD, all heart diseases, CVD and all-cause mortality were 7.0, 5.2, 3.3 and 3.1%, respectively. PAFs of the borderline high CBG alone for CHD, all heart diseases, CVD and all-cause mortality were 5.0, 3.6, 1.5 and 0.4%, respectively.

Discussion

In this study, we found that CBG levels predicted CHD mortality. The risk for CHD mortality increases with CBG levels, regardless of time since last meal. We also found that participants with borderline high CBG or high CBG had higher mortality due to CHD. Furthermore, the data showed that lower blood glucose levels led to lower HRs for CVD mortality, even within the normal blood glucose range.

Our cohort study was conducted with a representative sample from the Japanese population with a long-term follow-up period. The participants were randomly selected from across Japan. The participation rate and follow-up rate were high: more than 75 and 90%, respectively. Thus our data should be applicable to the general Japanese population. Due to our study's representative nature, we were able to assess the PAF of high CBG and borderline high CBG groups for CHD mortality.

Table 3 The number of deaths and multivariate-adjusted HRs for CVD according to CBG levels <7.77 mmol/l divided into five classes, for men and women combined

Cardiovascular diseases					
Baseline CBG (mmol/l)	*n*	Person-years	Deaths (*n*)	Mortality rate[a]	HR (95% CI)[b]
1.40–4.63	1,710	31,552	71	2.3	1
4.68–5.01	1,766	32,905	84	2.6	1.07 (0.78–1.47)
5.06–5.44	1,632	30,485	117	3.8	1.30 (0.97–1.75)
5.48–6.01	1,579	29,826	141	4.7	1.33 (1.00–1.78)
6.05–7.76	1,603	29,655	193	6.5	1.39 (1.06–1.83)

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents or any combination of these

The HRs were adjusted for age, sex, serum total cholesterol levels, BMI, hypertension, cigarette smoking categories, drinking categories and residential districts

[a] The mortality rate is the crude mortality rate per 1,000 person-years

[b] p for trend <0.01

The prevalence of diabetes mellitus in our data at baseline was comparable with that reported in other studies. Sairenchi et al. [23] reported that the diabetes prevalence in men aged 40–59 at baseline was 6.2% in those who survived, 8.4% in participants who died of CVD and 12.4% in those who died of non-CVD causes during a follow-up period of 9 years. The prevalence for women was 2.6, 11.4 and 5.4%, respectively. The corresponding prevalence in those aged 60–79 at baseline was 7.8, 11.4 and 10.7% for men and 5.2, 12.2 and 7.4% for women. The investigators collected non-fasting samples and defined diabetes mellitus as a plasma glucose level ≥7.0 mmol/l (fasting), ≥11.1 mmol/l (non-fasting) or treatment for diabetes mellitus. We believe that these results are consistent with ours. As expected, CHD mortality rates from our data were very low compared with those of other developed countries. Other papers have also pointed out the low CHD mortality in Japan [24, 25]. Although the reason is unclear, various hypotheses have been proposed, e.g. low serum cholesterol levels in Japanese in 1980 compared with westernised countries [11], as well as levels of fish [26] or green tea intake [27] among the Japanese.

In the present study, we were able to show that CBG potentially predicts future CVD mortality. Thus, in some settings, such as community screenings for CVD risk factors, where high participation rates are desired, as well as in clinics normally not visited in a fasting state, CBG could be a viable alternative to OGTT or fasting blood glucose. Our finding on prediction of CVD mortality was also consistent with previous reports. Based on the NIPPON DATA80, the probability of death over a 10 year period from CHD, stroke and CVD was calculated and displayed as colour charts [10]. These charts showed that participants with diabetes mellitus defined as CBG levels ≥11.1 mmol/l had higher CHD, stroke and CVD mortality risks than those without diabetes mellitus. Our results expanded on those results. Irie et al. [6] reported the relationship between CBG obtained in general health check-ups and CHD, CVD and all-cause mortality in a Japanese population. Their study had a large sample with a shorter follow-up period of 5 years. Similarly to our results, they found that the HRs for CHD, CVD and all-cause mortality were higher than the reference groups, even among participants in the borderline high CBG group.

It should, however, be emphasised that although CBG is a feasible way of assessing CVD risk factors in community screenings, it cannot be used for a definitive diagnosis of diabetes because of the difficulty in standardisation. Recently, diabetes risk scores incorporating age, sex, BMI, steroid or antihypertensive medication, family history,

smoking history and other factors have been accepted as the most appropriate tool for initial diabetes mellitus screening [28–30]. The use of such a risk score might also be feasible for initial screening, although its value has yet to be established in the Japanese population.

In our study, HRs for CVD mortality were higher in participants in the higher normal blood glucose group than in those in the lower normal group. Furthermore, a statistically significant positive linear relationship was observed within normal glucose levels. The HRs for CVD mortality seemed to increase linearly when we divided normal CBG (<7.77 mmol/l) into quintiles. We considered the relationship between CBG and CVD risk as continuous, rather than being determined by a threshold. Thus, similarly to blood pressure [31–33], lower CBG may yield lower CVD mortality rates, as some epidemiological studies have shown in meta-analyses with fasting blood glucose [34] or in other studies with OGTT [9, 35].

From a public health perspective, these results suggest that there is a certain impact on excess risk of CVD death, even when serum blood glucose increases mildly, without reaching the borderline high CBG level. In our study, the number of participants with higher normal glucose was much greater than that for those with borderline high CBG and high CBG. As a population strategy, lifestyle modifications such as body weight reduction, smoking cessation and an increase in physical activity may be effective, less intensive ways to improve a higher normal glucose level [36]. Other strategies such as adequate medication and/or intensive lifestyle modifications might reduce the risk of CVD mortality for individuals with borderline high CBG or high CBG.

The present study has a number of limitations. First, since it was based on blood glucose level measurement on one occasion only, the results might include a regression dilution bias, possibly attenuating the association between CBG and long-term mortality [37]. Second, since we used death as an endpoint, we only estimated fatal CVD and did not include non-fatal cases. Third, since we had no information on fasting blood glucose levels or post load glucose obtained by OGTT results, we were unable to compare the predictive power of the different methods for assessing blood glucose levels. Finally, socioeconomic status might have affected our results, but we were unable to adjust for this factor owing to a lack of relevant information. In conclusion, CBG predicted CHD and CVD mortality in a Japanese population regardless of time since last meal. Even within the normal range, raised CBG levels were related to an elevated risk of CHD and CVD mortality in Japanese. Thus, CBG could be an alternative to fasting blood glucose or OGTT, in situations where it is unrealistic to ask all patients to fast, as in population screening for CVD risk factors, which requires higher participation rates.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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Aspartate aminotransferase (AST) 値の肝疾患および肝疾患以外の死亡に与える影響

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【要旨】1990 年の循環器基礎疾患調査受診者の内、年齢、性、収縮期及び拡張期血圧、喫煙習慣、Body Mass Index（以後、BMI)、Aspartate aminotransferase （以後、AST）などについて情報が得られ、追跡開始後 1 年未満の死亡または追跡不可能に該当しなかった 7681 人について COX の比例ハザードモデルを用いて AST 値が死亡に与えるハザード比を男女別に算出した。

年齢のみを調整したモデル、年齢、糖尿病の有無、高血圧の有無、BMI、飲酒及び喫煙習慣、コレステロール値を調整したモデルの 2 通りとも、肝疾患による死亡、肝疾患以外の死亡、総死亡の 3 種類のいずれも有意に AST が 20IU/L 増加する毎にハザード比が増加する傾向を男女ともに認めた。肝疾患以外の死亡について男では 80IU/L 以上、女では 60.0IU/L 以上の者でハザード比が上昇していた。日本人全体を代表するコホートについて、AST の異常は 10 年間追跡後の生命予後を予測可能な因子の一つと考えられる。

【目的】健康診断における肝機能検査の項目として一般的に aspartate aminotransferase（以後 AST）及び alanine aminotransferase（以後 ALT）及び gammaglutamyl transpeptidase（以後γ-GTP）が幅広く用いられている。しかし、ウイルス肝炎や脂肪肝の検出についての有効性はこれまでに検討されているが、死亡原因を考慮した上で肝機能異常を有する者の長期予後が検討されたことはほとんど無い。今回、1990 年の循環器基礎疾患調査受診者を対象として、AST 異常が肝疾患および肝疾患以外による死亡に与える影響について検討した。

【対象と方法】対象者は 1990 年の循環器基礎疾患調査受診者のうち、2000 年の時点で追跡可能であった 8339 名である。死因は WHO が勧告した国際疾病分類第 10 回修正死因統計分類（International Statistical Classification of Diseases and Related Health Problems 10th Revision 、以後 ICD-10）に基づいて分類した。ICD-10 における、B15-B19（ウイルス肝炎）、C22（肝及び肝内胆管の悪性新生物）、K72（肝不全，他に分類されないもの）、K73（慢性肝炎，他に分類されないもの）、K74（肝線維症及び肝硬変）による死亡を肝疾患による死亡とし、それ以外の死亡を肝疾患以外の死亡とした。分析にあたっては、肝疾患による死亡、肝疾患以外の死亡、総死亡の 3 種類のエンドポイントについて、AST が 20IU/l 未満の者を基準とし、AST が 20IU/L 増加する毎のハザード比を年齢（10 歳階級）のみを調整したモデルと、年齢、糖尿病、高血圧、BMI、飲酒及び喫煙、コレステロール値を調整したモデルの 2 通りの解析を男女別に実施した。なお、解析に必要な

情報に欠損値が認められる場合と追跡開始後1年未満の死亡または追跡不可能の場合は解析から除外した。

「高血圧あり」の判定は、A:収縮期血圧 140mmHg 以上、B:拡張期血圧 90mmHg 以上、C:血圧降下薬を服用している者の条件の内、少なくとも一つを満たす者とした。「糖尿病あり」の判定は、A:HbA1c 6.5 以上の者、B:随時血糖 200mg/dl 以上の者、C:食後 2 時間以上で血糖値が 140mg/dl 以上 200mg/dl 未満の者、D:糖尿病の薬物治療を受けている者の条件の内、少なくとも一つを満たす者とした。Body Mass Index（以後、BMI)、は「やせ」（20 未満）「正常範囲」（20 以上 25 未満)、「肥満」（25 以上）の3階級に区分し、「正常範囲」を reference としたダミー変数にて調整した。飲酒及び喫煙の有無は、現在飲酒又は喫煙習慣を有する者を「あり」とした。コレステロール値は「低値」（160mg/dl 未満）「正常範囲」(160mg/dl 以上 240mg/dl 未満)「高値」(240mg/dl 以上）の3階級に区分し、「正常範囲」を reference としたダミー変数にて調整した。統計学的解析にはパッケージソフトＰＣ－ＳＡＳ（Ver.9.1.3）を用いた。

【結果】最終的に 7681 人（男 3198 人（41.6%)、女 4483 人（58.4%））が解析対象となった。Table 1 に追跡開始時点における解析対象者の属性を示す。AST の分布については、男は 20.0-39.9IU/L の者が最も多く全体の 65.9%を占めていた。女では 20.0IU/L 未満の者が 47.9%、20.0-39.9IU/L の者が 47.7%とほぼ同じ値であった。40.0IU/L 以上の者は男で 8.7%、女で 4.5%であった。男女とも 40.0IU/L 未満の者が 90%以上を占めていた。

男では、AST 値の上昇に伴って、年齢、BMI、収縮期血圧、拡張期血圧、血糖値の平均値が増加する傾向が認められた。コレステロール値は 40.0-59.9IU/L の階級が最も高くなっており、100IU/L 以上の階級は 20IU/L の階級よりも低い値となっていた。また、喫煙習慣、飲酒習慣、高血圧、糖尿病を有する者の割合も AST 値の上昇に伴って増加する傾向が認められた。女では、コレステロール値のピークが 20.0-39.9IU/L の階級に認められたことの他は、ほぼ男と同様の傾向であった。

Table2 に肝疾患による死亡、肝疾患以外の死亡、総死亡の3種類のエンドポイントについて、AST が 20IU/L 未満の者を基準とし、AST が 20IU/L 増加する毎のハザード比を男女別に年齢のみを調整して算出した結果を示す。

男では、370 人の総死亡の内、13 人（3.5%）が肝疾患による死亡であった。女では、309 人の総死亡の内、9 人（2.9%）が肝疾患による死亡であった。

肝疾患による死亡、肝疾患以外の死亡、総死亡の3種類のいずれも有意に AST が 20IU/L 増加する毎にハザード比が増加する傾向を男女ともに認めた。肝疾患による死亡については、男の 40.0-59.9IU/L では肝疾患による死亡が認められなかったが、60IU/L 以上での肝疾患による死亡に対するハザード比はいずれも有意に上昇していた。女では 100IU/L 以上の階級では肝疾患による死亡が認められなかったが、60～99.9IU/L の範囲では肝疾患による死亡に対するハザード比はいずれも有意に上昇していた。肝疾患以外の死亡について

は、男では80-99.9IU/L及び100IU/Lの階級では有意にハザード比が上昇していた。女では80-99.9IU/Lの階級では肝疾患以外の死亡が認められなかったが、60.0-79.9IU/L及び100IU/Lの階級では有意にハザード比が上昇していた。総死亡については、男女ともに60.0IU/Lの者では有意にハザード比が上昇していた。

Table3に肝疾患による死亡、肝疾患以外の死亡、総死亡の3種類のエンドポイントについて、ASTが20IU/L未満の者を基準とし、ASTが20IU/L増加する毎のハザード比を男女別に年齢、糖尿病の有無、高血圧の有無、飲酒習慣及び喫煙習慣の有無、BMI、コレステロール値を調整して算出した結果を示す。

女の肝疾患以外の死亡を除き、肝疾患による死亡、肝疾患以外の死亡、総死亡の3種類のいずれも有意にASTが20IU/L増加する毎にハザード比が増加する傾向が年齢のみを聴視したときと同様に認めた。肝疾患以外の死亡について、男では80-99.9IU/L及び100IU/Lの階級では有意にハザード比が上昇していたことや、女では80-99.9IU/Lの階級では肝疾患以外の死亡が認められなかったが60.0-79.9IU/L及び100IU/Lの階級では有意にハザード比が上昇していたことなど、年齢のみを調整したモデルとほぼ同様の結果であった。

【考察】今回の分析では、肝疾患による死亡、肝疾患以外の死亡、総死亡の3種類のいずれも有意にASTが20IU/L増加する毎にハザード比が増加する傾向が認められた。ASTの分布を男女別に検討したところ、分布のピークがやや男女で異なっており、男の方が女よりやや高い側にシフトするような分布系であった。男は女よりも飲酒習慣を有する者の割合が高いことなど、他の交絡因子の影響とも考えられたため、男女別に解析を実施した。また、AST値によって血圧やBMIなどの交絡因子の分布が異なるため、年齢のみを調整したモデルと多変量解析にて複数の交絡因子を調整したモデルの2通りの解析を実施した。死亡数の低下による検出力の低下という問題は存在するが、男女ともASTが20IU/L増加するにつれて死亡のハザード比が上昇するという結果が得られた。また、年齢のみを調整したモデルと多変量解析にて複数の交絡因子を調整したモデルの双方の結果に大きな差異は認められなかった。　日本人全体を代表するコホートについて、ASTの異常は10年間追跡後の生命予後を予測可能な因子の一つと考えられる。

今回の分析では慢性ウイルス肝炎の存在については検討されていない。しかし、死亡小票により、死亡原因別に検討した結果、肝疾患以外の死亡についても男では80IU/L以上、女では60.0IU/L以上の者でハザード比が上昇していた。慢性ウイルス肝炎の存在が肝疾患以外の死亡と独立しているかどうかについての検討が別途必要である。

今回は、肝機能異常の評価指標としてASTのみを用いた。γ-GTPと死亡との関連は既にNIPPON DATA90で検討されている。また、ALTについては十分検討されていない。AST、ALT、γ-GTPというスクリーニング検査で一般的に用いられる肝機能検査の指標が独立しているのか、相互に関連しているのかを検討することは今後の課題である。

Table 1 Baseline characteristics by category of aspartate aminotransferase (AST) of 7681 Japanese men and women aged 30 years and over in 1990, NIPPON DATA90

	Base line AST level (IU/L)					
	<20	20.0-39.9	40.0-59.9	60.0-79.9	80-99.9	≥100
Men						
Number of subjects	810	2109	186	47	23	23
Age	51.6±13.9	53.7±13.4	53.1±14.0	53.9±11.5	56.2±12.2	56.3±10.4
Body mass index (kg/m^2)	22.2±2.7	23.2±3.0	23.9±3.8	23.8±3.9	23.9±4.6	23.4±3.0
Systolic blood pressure (mmHg)	133.5±20.0	138.8±19.7	141.6±19.7	148.7±28.5	148.2±24.6	147.8±23.0
Diastolic blood pressure(mmHg)	81.0±11.4	84.5±11.5	85.4±11.0	90.1±14.2	88.8±13.6	88.1±11.5
Serum total cholesterol(mg/dl)	194.4±34.4	200.9±36.3	202.1±43.2	182.9±37.0	182.7±54.6	178.0±55.8
Serum glucose (mg/dl)	106.8±43.5	101.1±28.9	105.2±35.4	115.3±45.5	113.3±32.8	111.7±70.0
Hemoglobin A1c (%)	5.1±0.9	5.0±0.7	5.1±0.8	5.0±1.0	4.9±0.8	5.1±1.3
Current smoker (%)	482(59.5%)	1121(53.2%)	109(58.6%)	27(57.4%)	16(69.6%)	17(73.9%)
Current drinker (%)	47.4%	61.5%	64.0%	63.8%	69.6%	69.6%
Hypertension (%)	8.5%	12.9%	12.4%	19.1%	8.7%	13.0%
Diabetes mellitus (%)	9.5%	8.1%	12.4%	17.0%	26.1%	21.7%
Hypercholesterolemia (%)	10.0%	13.6%	17.7%	8.5%	13.0%	13.0%
Women						
Number of subjects	2146	2137	137	33	10	20
Age	47.3±13.0	56.8±13.1	60.7±12.4	56.1±14.0	60.1±14.1	58.6±9.1
Body mass index (kg/m^2)	22.5±3.0	23.0±3.4	24.6±4.2	24.8±3.5	24.5±5.5	24.5±4.7
Systolic blood pressure (mmHg)	128.7±19.2	137.5±21.0	142.9±21.6	142.9±27.1	146.4±22.5	146.9±21.2
Diastolic blood pressure(mmHg)	77.7±11.3	81.0±11.9	84.2±12.5	85.0±13.3	84.4±10.2	84.7±12.5
Serum total cholesterol(mg/dl)	199.9±36.8	213.9±38.8	210.8±42.1	210.8±55.6	192.4±44.2	193.9±63.1
Serum glucose (mg/dl)	101.1±30.2	103.5±30.2	110.1±33.1	116.0±48.2	110.8±15.1	119.0±50.4
Hemoglobin A1c (%)	4.8±0.7	4.9±0.6	5.1±1.0	5.1±1.1	5.0±0.9	4.9±1.2
Current smoker (%)	10.3%	8.0%	13.1%	21.2%	20.0%	15.0%
Current drinker (%)	5.9%	7.3%	6.6%	6.1%	10.0%	10.0%
Hypertension (%)	8.3%	16.5%	19.7%	24.2%	40.0%	40.0%
Diabetes mellitus (%)	5.9%	7.3%	12.4%	18.2%	10.0%	25.0%
Hypercholesterolemia (%)	14.2%	23.6%	27.0%	30.3%	10.0%	20.0%

Table 2 The number of deaths and age-adjusted HRs(95%CIs) for liver disease, Non-liver disease and all-cause mortality; according to serum aspartate aminotransferase (AST) level at the baseline survey in 1990, NIPPON DATA 90

Baseline AST level, IU/L	Number of persons	Person-years	Liver disease		Non-liver disease		All-cause	
			No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
Men								
<20	810	7738	1	1.00(reference)	80	1.00(reference)	81	1.00(reference)
20.0-39.9	2109	20115	3	1.04 (0.11 - 10.02)	228	0.90 (0.70 - 1.16)	231	0.90 (0.70 - 1.17)
40.0-59.9	186	1751	0		26	1.10 (0.71 - 1.72)	26	1.10 (0.70 - 1.71)
60.0-79.9	47	414	3	53.97 (5.61 - 519.04)	7	1.73 (0.80 - 3.75)	10	2.44 (1.26 - 4.70)
80-99.9	23	181	1	38.24 (2.39 - 612.29)	10	5.61 (2.91 -10.83)	11	6.06 (3.22 -11.38)
≥100	23	178	5	184.69 (21.51 -1585.90)	6	3.63 (1.58 - 8.34)	11	6.50 (3.46 -12.23)
				(p for trend =<0.0001)		(p for trend =<0.0001)		(p for trend =<0.0001)
Women								
<20	2146	21083	1	1.00(reference)	93	1.00(reference)	94	1.00(reference)
20.0-39.9	2137	20631	3	2.48 (0.35 - 17.64)	180	0.94 (0.73 - 1.21)	183	0.95 (0.74 - 1.22)
40.0-59.9	137	1317	1	23.59 (3.94 -141.20)	12	0.78 (0.43 - 1.42)	13	0.84 (0.47 - 1.50)
60.0-79.9	33	282	2	28.54 (2.59 -314.82)	9	4.55 (2.30 - 9.03)	11	5.51 (2.95 -10.29)
80-99.9	10	87	2	55.39 (5.02 -611.39)	0		2	2.14 (0.53 - 8.67)
≥100	20	180	0		6	5.03 (2.20 - 11.49)	6	4.95 (2.17 -11.30)
				(p for trend =<0.0001)		(p for trend =0.0184)		(p for trend =0.0006)

Table 3 The number of deaths and multivariable-adjusted HRs(95%CIs) for liver disease, Non-liver disease and all-cause mortality; according to serum aspartate aminotransferase (AST) level at the baseline survey in 1990, NIPPON DATA 90

Baseline AST level, IU/L	Number of persons	Person-years	Liver disease		Non-liver disease		All-cause	
			No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
Men								
<20	810	7738	1	1.00 (reference)	80	1.00 (reference)	81	1. 00 (reference)
20.0-39.9	2109	20115	3	1.02 (0.10 - 9.89)	228	0.96 (0.74 -1.24)	231	0.96 (0.74 - 1.24)
40.0-59.9	186	1751	0		26	1.15 (0.73 -1.80)	26	1.15 (0.74 - 1.80)
60.0-79.9	47	414	3	78.72 (7.41 - 835.82)	7	1.54 (0.71 -3.38)	10	2.24 (1.15 - 4.38)
80-99.9	23	181	1	60.92 (3.49 -1064.62)	10	5.19 (2.65 -10.15)	11	5.75 (3.02 -10.95)
≥100	23	178	5	362.39 (36.61 -3587.30)	6	3.29 (1.41 -7.64)	11	6.10 (3.19 -11.66)
				(p for trend =<0.0001)		(p for trend =0.0002)		(p for trend =<0.0001)
Women								
<20	2146	21083	1	1.00 (reference)	93	1.00 (reference)	94	1.00 (reference)
20.0-39.9	2137	20631	3	2.60 (0.26 - 26.61)	180	0.98 (0.76 -1.27)	183	1.00 (0.78 -1.29)
40.0-59.9	137	1317	1	7.58 (0.41 - 139.02)	12	0.71 (0.39 - 1.31)	13	0.76 (0.42 -1.38)
60.0-79.9	33	282	2	53.53 (4.08 - 703.05)	9	3.76 (1.85 - 7.66)	11	4.46 (2.32 -8.56)
80-99.9	10	87	2	132.11 (10.89 -1602.62)	0		2	1.66 (0.41 -6.75)
≥100	20	180	0		6	4.37 (1.88 -10.17)	6	4.21 (1.81 -9.78)
				(p for trend =<0.0001)		(p for trend =0.0522)		(p for trend =0.004)