Table 3 Hazard ratios and 95% CIs of hepatocellular carcinoma according to metabolic factors by hepatitis viral infection status[a]

	HCV-antibody positive subjects					HCV-antibody and HBsAg negative subjects				
	Number of subjects	Number of cases	Person-years	HR	(CI)	Number of subjects	Number of cases	Person-years	HR	(CI)
Components of metabolic factors										
High blood pressure										
Absent	346	26	4,113.2	1.00		6,650	7	84,548.0	1.00	
Present	612	47	7,142.0	0.98	(0.56–1.72)	9,563	11	121,691.1	0.60	(0.21–1.70)
High glucose										
Absent	730	48	8,678.0	1.00		12,889	10	164,622.3	1.00	
Present	228	25	2,577.2	1.49	(0.85–2.61)	3,324	8	41,616.8	2.48	(0.93–6.60)
Low HDL-cholesterol										
Absent	705	48	8,346.6	1.00		12,445	14	158,055.8	1.00	
Present	253	25	2,908.6	1.18	(0.65–2.16)	3,768	4	48,183.3	0.63	(0.18–2.17)
High triglycerides										
Absent	779	63	9,117.6	1.00		12,307	13	156,661.8	1.00	
Present	179	10	2,137.6	0.64	(0.30–1.39)	3,906	5	49,577.3	2.14	(0.64–7.18)
Overweight										
Absent	706	44	8,335.5	1.00		141,479	11	11,883.0	1.00	
Present	252	29	2,919.7	2.66	(1.54–4.62)	64,760	7	4,678.5	1.81	(0.64–5.07)
Metabolic factors in the aggregate										
≥3 factors										
Absent	753	51	8,850.8	1.00		12,596	12	160,133.1	1.00	
Present	205	22	2,404.4	1.83	(1.05–3.18)	3,617	6	46,106.0	1.80	(0.65–4.98)
≥2 factors in addition to being overweight										
Absent	826	57	9,710.2	1.00		13,556	14	172,296.2	1.00	
Present	132	16	1,545.0	2.57	(1.37–4.80)	2,647	4	33,942.9	1.79	(0.57–5.63)

[a] Model includes gender (stratified, men and women combined only), age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150–<300 g per week, ≥300 g per week), coffee intake (never, 1–2 days/week, 3–4 days/week, everyday (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous) and HCV infection status (anti-HCV antibody negative, positive) and HBV infection status (HbsAg negative, positive) and individual components of metabolic syndrome, namely, high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and overweight (yes, no)

Table 4 Hazard ratios and 95% CIs of hepatocellular carcinoma according to body mass index and glucose level status[a]

		Total subjects					HCV-antibody positive subjects					HCV-antibody and HBsAg negative subjects				
		Number of subjects	Number of cases	Person-years	HR	(CI)	Number of subjects	Number of cases	Person-years	HR[a]	(CI)	Number of subjects	Number of cases	Person-years	HR	(CI)
Body mass index																
<25		12,180	64	153,362.4	1.00		704	44	8,335.5	1.00		11,193	11	141,479.4	1.00	
25 to <27		2,903	21	37,183.2	2.07	(1.22–3.52)	150	16	1,690.6	2.55	(1.34–4.85)	2,684	4	34,619.2	1.91	(0.59–6.14)
≥27		2,507	17	32,255.0	2.72	(1.51–4.89)	102	13	1,229.1	3.08	(1.51–6.30)	2,336	3	30,140.5	1.84	(0.48–7.04)
p for trend					*0.019*					*0.017*					0.414	
Overweight	High glucose															
Absent	Absent	9,874	43	124,802.5	1.00		550	29	6,549.6	1.00		9,101	8	115,441.0	1.00	
Absent	Present	2,306	21	52,690.9	1.57	(0.88–2.79)	156	15	1,785.9	1.75	(0.86–3.58)	2,092	3	26,038.4	1.14	(0.28–4.62)
Present	Absent	4,076	22	28,559.9	2.01	(1.16–3.49)	180	19	2,128.4	3.06	(1.59–5.88)	3,788	2	49,181.3	0.77	(0.16–3.69)
Present	Present	1,334	16	16,747.3	4.10	(2.19–7.69)	72	10	791.3	3.36	(1.47–7.68)	1,232	5	15,578.4	5.14	(1.60–16.55)
p for interaction between high glucose and overweight					*0.620*					*0.369*					*0.121*	

[a] Adjusted for age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150 to <300 g per week, ≥300 g per week), coffee intake (never, 1–2 days/week, 3-4 days/week, everyday (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous), and HCV infection status (anti-HCV antibody-negative, -positive) and HBV infection status (HBsAg-negative, -positive)

mass. In the liver, FFAs produce an increased production of glucose, triglycerides, and secretion of very low density lipoproteins (VLDL), with lipid/lipoprotein abnormalities such as reductions in HDL-cholesterol and an increased density of low density lipoprotein (LDL) [8]. This VLDL secretion and fatty acid β-oxidation, may in turn, result in increased triglyceride synthesis in the liver [41, 42]. A similar mechanism may also be involved in the association between metabolic factors and HCC. In this study, however, the positive association between low HDL-cholesterol and risk of HCC was not significant.

Based on this study, we speculate that metabolic factors may affect the risk of HCC not only in those with hepatitis virus infection but also without hepatitis virus infection, via a common or different pathway. More specifically, metabolic factors may play a role in those without hepatitis virus infection through NASH/NAFLD and related conditions, and in promoting carcinogenesis after infection. Nevertheless, our analyses among both HCV- and HBV infection-negative subjects were based on a small number of cases, meaning no definite conclusions can be drawn, and any interpretation requires caution. In addition, clinical investigations have shown that most HCC in this population originates from HCV- or HBV infection [7], and that the proportion of non-B/non-C HCC in all HCC has been reported to be around 10–12% since 1999 [43]. In addition, a small proportion of NAFLD/NASH patients develop HCC [44]. Together, these findings imply that the contribution of factors other than hepatitis virus infection such as NASH/NAFLD in this population may not be large, at the present time at least. However, given the increasing trend in the incidence of HCC unrelated to hepatitis virus infection, the contribution of metabolic factors among the overall etiology, if any, will soon likely increase. The small number of cases prevented us from restricting analysis to HBV-positive subjects, and is a limitation of this study. Whether the effect of metabolic factors on HCC differs between those positive and negative for hepatitis virus infection, and between those positive for HCV and for HBV, is not conclusive for lack of consistency between studies.

The major strength of this study is its prospective design, in which information was collected before the subsequent diagnosis of HCC, thereby avoiding the exposure recall bias inherent with case–control studies. Other strengths include: study subjects were selected from the general population; the proportion of loss to follow-up (0.3%) was negligible; the quality of our cancer registry system was satisfactory over the study period; and potential confounding factors could be adjusted to minimize their influence on risk values, in spite of the possible influence of residual confounding.

Against this, several obvious limitations can be identified. First, waist circumference was not available to assess exposure. However, given previous studies that a BMI of 25.0 kg/m^2 was equal to 100 cm^2 of visceral fat area as central obesity [32], misclassification by the use of BMI instead of waist circumference, if any, might be small. Likewise, we used non-fasting data, in particular non-fasting triglycerides $\geq$1.69 mmol/l (150 mg/dl), as a component of the metabolic factors, although justification for the use of the same cut-off point as for fasting status is presently under debate. In this study, nevertheless, analyses limited to fasting subjects yielded closely similar results.

Second, evaluation by single measurement of components of metabolic factors at baseline might have produced misclassification, even though this would likely have been non-differential and might lead to an underestimation of results. Further, the subjects of this study were restricted to 26% of the total study subjects with complete questionnaire responses and health checkup data. More women than men tend to participate in health checkup surveys provided by local governments. Further, participants often differ from nonparticipants in socioeconomic status and have a more favorable lifestyle profile, such as lower smoking rates, greater participation in physical exercise, and higher intake of green vegetables and fruits, particularly women [45, 46]. Differences in these factors may have influenced the association between metabolic factors and HCC. In addition, the incidence of HCC in this study population during the follow-up period was 45.7 per 100,000 person-years versus 67.5 in the whole JPHC Study, suggesting that subjects who were already under care for hepatitis virus infection or any of the components of metabolic factors may have been less willing to attend a health checkup. Together, these considerations mandate the need for caution in interpreting or generalizing these results.

Allowing for these methodological issues, metabolic factors in the aggregate may have been associated with an increased risk of HCC in the study population. The effects of overweight and high glucose state appear to have been the main contributors to this association, even under the condition of HCV infection. Our results imply the need to include obesity and diabetes as a crucial target in preventing progression to HCC, even among those already infected with HCV.

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Appendix

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