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Impact of Lifestyle and Psychosocial Factors on the Incidence of Hepatobiliary Enzyme Abnormalities After the Great East Japan Earthquake: Seven-Year Follow-up of the Fukushima Health Management Survey

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Abstract

Objective: Residents who lived near the Fukushima Power Plant accident were forced to change their lifestyle after the 2011 accident. This study aimed to elucidate the association of resident lifestyle and psychological factors with onset of hepatobiliary enzyme abnormalities (HEA) after the accident.

Methods: This longitudinal study included 15705 residents who underwent a comprehensive health check, as well as a mental health and lifestyle survey between June 2011 and March 2012. Follow-up surveys were conducted between June, 2012 and March 2018. Risk factors for new HEA onset were evaluated using the Cox proportional hazards model, moreover, population attributable risks for new HEA onset were calculated.

Results: HEA developed in 29.7% of subjects. In addition to metabolic factors such as overweight, hyperglycemia, and hyperlipidemia; there were differences in alcohol intake, evacuation, unemployment, educational background, and psychological distress between subjects with and without HEA onset. After we adjusted for potential confounding factors, an association of being overweight, hypertension, and dyslipidemia, as well as alcohol consumption, evacuation, and psychological distress with increased risk of HEA onset was realized. Among these identified risk factors, evacuation accounted for the greatest share.

Conclusions: Metabolic characteristics and disaster-related lifestyle aspects, including mental status, were risk factors for HAE onset after the Fukushima Power Plant accident.

Introduction

The prognosis of liver disease has changed dramatically following the establishment of hepatitis C virus treatment. In contrast, metabolic factors and alcohol consumption are deeply associated with lifestyle and have recently attracted special attention as causes of liver disease.

The Great East Japan Earthquake that occurred in March 2011, and the associated tsunami and accident at the Fukushima Daiichi nuclear power plant, dramatically changed the lifestyle of residents in evacuation-designated areas near the plant in Fukushima Prefecture.[1] Since the accident, residents who lived near the plant have been monitored by the Fukushima Health

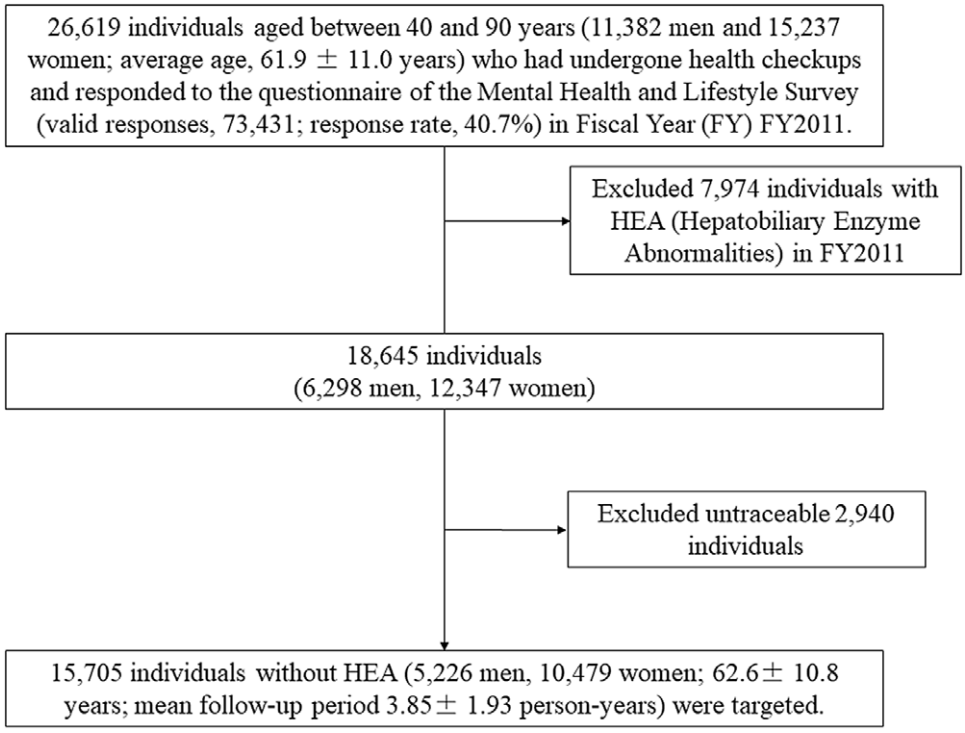

Figure 1. Flow chart of participant selection for this study.

Management Survey (FHMS).[2] Based on the FHMS, we have previously reported an association of evacuation- and disaster- related factors with hepatobiliary enzyme abnormalities (HEA) after the disaster by cross-sectional study.[3,4] Moreover, we showed significant association between increases in daily physical activity and improved HEA using a longitudinal study.[5]

We have reported about various backgrounds of residents with HEA at start of FHMS during June 2011 through March 2012.[3,4] On the other hand, many residents of evacuation-designated areas were forced to shift out of their homes after the accident. This lifestyle change may cause HEA in residents who were without HEA at the start of FHMS, but no studies have reported the long-term association between psychosocial factors and the development of HEA in residents of the evacuation areas. The aim of this study was to evaluate the effect of changed lifestyle and psychological factors due to the accident on new onset of HEA in residents who were initially without HEA.

Methods

Study population

The subjects were residents who lived in evacuation-designated areas near the Fukushima Daiichi nuclear power plant at the time of the disaster. From June 2011 through March 2012, 26619 people aged 40 – 90 years participated in both the comprehensive health check and the mental health and lifestyle survey of the FHMS.[2–6] We conducted follow up on both surveys between June 2012 and March – end 2018, with a mean follow up of 3.9 years. We excluded 10914 participants who had HEA in 2011 – 2012 or were missing follow-up data between 2012 and 2017. Ultimately, 15705 participants (5226 men and 10479 women) were eligible for analysis (Figure 1). This study protocol was approved by the ethics committee of Fukushima Medical University (#29064) and conducted in accordance with the Helsinki Declaration, as revised in 2004. Informed consent was obtained from all subjects.

Data collection and definition

Trained technicians measured each subject's height, weight, and blood pressure. Body mass index (BMI) was calculated as body weight (kg)/ height (m).[2] The following laboratory data were obtained under overnight fasting conditions: aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), gamma-glutamyl transferase (γ-GTP, U/L), and high-density lipoprotein cholesterol (mg/dL), as well as low-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), fasting plasma glucose (FPG, mg/dL), and hemoglobin A1c (HbA1c, % of total hemoglobin). HEA was defined as AST ≥ 31U/L, ALT ≥ 31U/L or γ-GTP ≥ 51U/L, based on the definition of the Ministry of Health, Labor, and Welfare. Overweight was defined as BMI ≥ 25 kg/m^2. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive agents.[7] Diabetes and dyslipidemia were defined as previously reported.[8,9] The status of participants' mental health was evaluated by the Japanese versions of the Kessler 6-item scale (K6),[10] and Post-traumatic Stress Disorder Checklist (PCL-S).[11] Psychological distress was defined as corresponding to a K6 score of ≥ 13.[12] In addition, we classified participants as having probable PTSD if their overall PCL-S score was ≥ 44.[11] Asides from K6 and PCL-S, the questionnaires also included educational background and disaster-related experiences, anxiety about radiation, and other various lifestyle factors such as sleep dissatisfaction, cigarette smoking, alcohol intake, and employment status.[13,14]

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Table 1. Clinical and biochemical characteristics of 15705 participants at baseline

	Non-HEA group	Incident HEA group	*P* value
Participants	11047	4658	
Age (y)	62.6 (11.1)	62.8 (10.1)	0.267
Body weight (kg)	56.1 (9.4)	59.1 (10.4)	< 0.001
BMI (kg/m^2)	23.2 (3.2)	23.8 (3.3)	< 0.001
SBP (mmHg)	130.0 (16.3)	131.9 (15.9)	< 0.001
DBP (mmHg)	77.4 (10.1)	78.7 (10.1)	< 0.001
Triglycerides (mg/dL)	101.2 (54.6)	112.3 (64.6)	< 0.001
HDL-C (mg/dL)	62.0 (15.1)	59.5 (15.3)	< 0.001
LDL-C (mg/dL)	127.0 (31.4)	126.4 (31.6)	0.233
FPG (mg/dL)	99.5 (18.9)	101.0 (18.6)	< 0.001
HbA1c	5.5 (0.6)	5.5 (0.7)	0.001
AST (U/L)	20.4 (3.9)	22.4 (4.1)	< 0.001
ALT (U/L)	15.6 (5.0)	18.7 (5.4)	< 0.001
γ-GTP (U/L)	19.5 (8.2)	25.9 (10.8)	< 0.001
Overweight (BMI ≥25) (%)	2838 (25.7)	1533 (32.9)	< 0.001
Hypertension (%)	5313 (48.5)	2519 (54.5)	< 0.001
Dyslipidemia (%)	5967 (57.7)	2705 (61.6)	< 0.001
Diabetes (%)	1014 (9.3)	481 (10.4)	0.026

Values are expressed as the mean (standard deviation) or number (percentage).
Abbreviations: HEA, hepatobiliary enzyme abnormality; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density-lipoprotein-cholesterol; LDL-C, low-density-lipoprotein-cholesterol; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c, AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase.

Statistical analysis

The characteristics of subjects were compared between those who developed HEA during the follow-up period (HEA group) and those who did not (non-HEA group) using unpaired-t test for continuous variables and Chi-square test for categorical data. The hazard ratios (HRs) and 95% confidence intervals (CIs) for HEA onset after the accident were calculated with potential confounding factors using the Cox proportional hazards model. The potential confounding factors were age, sex, BMI and hypertension, as well as dyslipidemia, educational background, alcohol intake, and experience of tsunami. Other cofounding factors were: experience of hearing the explosion, evacuation, unemployment, and psychological distress. Population attributable risks for identified risk factors of new HEA onset were calculated according to previous reports.[15] SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for analyses. All probability values for statistical tests were 2-tailed and P - values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Overall, 4658 (29.7%) of 15705 participants without HEA in 2011 – 2012 developed HEA during the follow-up period. HEA developed more frequently in men than in women. BMI was significantly higher in the HEA group than in the non-HEA group, and the prevalence of hypertension, diabetes, and dyslipidemia was also significantly higher in the HEA group than in the non-HEA group. In addition, there were significant differences in laboratory data, including AST, ALT, γ-GTP, FPG, HbA1c and triglycerides between the HEA and non-HEA groups (Table 1).

Lifestyle characteristics and accident-related factors

Table 2 shows the comparison of lifestyle characteristics and accident-related factors between the groups. The prevalence of exercise habit, smoking, and alcohol consumption were significantly higher in the HEA group than in the non-HEA group. Educational background was significantly lower in the HEA group than in the non-HEA group. Experience of the tsunami, experience of hearing the explosion, evacuation, and unemployment were significantly higher in the HEA group than in the non-HEA group. The prevalence of psychological distress was found to be significantly higher in the HEA group than in the non-HEA group.

Risk factors for HEA

Table 3 shows age-, sex-, and multivariable- adjusted HRs and 95% CIs of HEA onset. There was no multicollinearity in disaster related factors such as evacuation, tsunami experience, experience of hearing and unemployment. Men (HR 1.85, 95% CI 1.74 - 1.89), overweight (HR 1.33, 95% CI 1.25 - 1.41), hypertension (HR 1.27, 95% CI 1.19 - 1.35), suffering from dyslipidemia (HR 1.21, 95% CI 1.14 - 1.28), alcohol consumption ≥ 44 g/day (HR 1.44, 95% CI 1.28 - 1.64), evacuation (HR 1.24, 95% CI 1.17 - 1.32), with the experience of hearing the explosion (HR 1.11, 95% CI 1.04 - 1.17), experience of hearing the explosion (HR 1.18, 95% CI 1.10 - 1.26), and psychological distress (HR 1.19, 95% CI 1.09 - 1.29), were associated with an increased risk of HEA onset. After adjustment for these factors, overweight, hypertension, dyslipidemia, alcohol consumption, evacuation, and psychological distress were associated with increased risk of HEA onset in both men and women. In men, unemployment (HR 1.10, 95% CI 1.04 - 1.29), educational background (high school) (HR 0.90, 95% CI 0.82 - 1.00), and educational background (university/ graduate school) (HR 0.84, 95% CI 0.71 - 0.99) were associated with increased and decreased risk, respectively, of HEA development. We also confirmed that increase of BMI, alcohol consumption, and psychological distress were associated with increased risk of HEA onset in both men and women (data not shown). The population attributable risk (PAR) for risk factors of new HEA onset in both men and women were evacuation (PAR 0.12, 95% CI 0.10 - 0.14), hypertension (PAR 0.09, 95% CI 0.07 - 0.10), overweight (PAR 0.07, 95% CI 0.05 - 0.08), as well as dyslipidemia (PAR 0.07, 95% CI 0.05 - 0.09), alcohol consumption ≥ 44 g/day (PAR 0.06, 95% CI 0.05 - 0.07), and psychological distress (PAR 0.01, 95% CI 0.01 - 0.02).

Sensitivity analysis

In this study, a multivariate Cox regression analysis was conducted for sensitivity analysis of the relationship between mental distress and HEA onset, separately for age (under 60 and over 60), obesity status, and drinking habits (data not shown). The results showed that the HR (95% CI) for psychological distress for HEA was 1.15 (1.00 - 1.31) for those under 60, 1.13 (1.02 - 1.26) for those over 60, 1.11 (1.01 - 1.23) for those without obesity, 1.23 (1.06 - 1.43) for those with obesity, 1.11 (0.99 - 1.24) for those without drinking habits, and 1.20 (1.05 - 1.36) for those with drinking habits, thus indicating the robustness of the results of this study.

Discussion

The FHMS was initiated after the Fukushima Daiichi nuclear power plant accident to monitor the long-term health of residents who lived in evacuation-designated areas,[2] and has been used to

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Table 2. Lifestyle and disaster-related characteristics of 15705 participants at baseline

		Non-HEA group	Incident HEA group	*P* value
Education	Elementary school and junior high school	2941 (27.7)	1290 (28.7)	< 0.001
	High school	5352 (50.4)	2347 (52.3)	
	Junior or vocational college	1713 (16.1)	579 (12.9)	
	University/ graduate school	611 (5.8)	273 (6.1)	
Exercise habit	Every day	1952 (18.2)	916 (20.1)	0.002
	2 – 4 times / week	2733 (25.4)	1202 (26.4)	
	Once per week	1629 (15.2)	693 (15.2)	
	Never	4430 (41.2)	1740 (38.2)	
Smoking status	Current smoker	1136 (10.7)	571 (12.7)	< 0.001
	Ex-smoker	1944 (18.3)	1109 (24.6)	
	Non-smoker	7548 (71.0)	2823 (62.7)	
Alcohol consumption	Non-drinker	6397 (59.4)	2334 (51.2)	< 0.001
	Ex-drinker	278 (2.6)	136 (3.0)	
	< 44 g/day	3697 (34.3)	1733 (38.0)	
	≥ 44 g/day	397 (3.7)	357 (7.8)	
Sleep status	Satisfied	2968 (33.1)	1293 (34.1)	0.564
	Somewhat dissatisfied	4122 (46.0)	1709 (45.1)	
	Quite dissatisfied	1468 (16.4)	603 (15.9)	
	Dissatisfied or insomnia	411 (4.6)	184 (4.9)	
Earthquake experience	No	474 (4.3)	196 (4.2)	0.814
	Yes	10573 (95.7)	4462 (95.8)	
Tsunami experience	No	8913 (80.7)	3683 (79.1)	0.020
	Yes	2134 (19.3)	975 (20.9)	
Heard the explosion	No	5064 (45.8)	1971 (42.3)	< 0.001
	Yes	5983 (54.2)	2687 (57.7)	
Evacuation	No	5315 (48.3)	1866 (40.2)	< 0.001
	Yes	5680 (51.7)	2775 (59.8)	
Change of job	No	10774 (97.5)	4544 (97.6)	0.930
	Yes	273 (2.5)	114 (2.4)	
Unemployment	No	8750 (78.8)	3503(75.2)	< 0.001
	Yes	2342 (21.2)	1155 (24.8)	
Psychological distress	K6 < 13	8701 (85.2)	3627 (83.9)	0.045
	K6 ≥ 13	1515 (14.8)	698 (16.1)	
Post-traumatic stress disorder symptoms	PCL-S < 44	8017 (77.2)	3352 (75.9)	0.093
	PCL-S ≥ 44	2368 (22.8)	1063 (24.1)	

K6, Kessler 6-item scale; PCL-S, Post-traumatic Stress Disorder Checklist.

elucidate the association of change in lifestyle with many diseases, including HEA and mental health.[4,7,8,16,17] The present longitudinal study is the first to identify the lifestyle- and disaster-related social psychological risk factors for HEA onset after the accident.

Various disasters or accidents in the world are associated with increase in post-traumatic stress and alcohol consumption.[18–20] On the other hand, chronic diseases, including liver disease, increased in Puerto Rico after Hurricane Maria.[21] We have previously shown that the evacuation after the accident was associated with an increase in HEA.[3] However, the frequency of HEA gradually decreased between June 2013 and March 2014. This was due to reasons of increased daily activity and more frequent consumption of breakfast.[5] Despite this, the incidence of new HEA onset after the accident has not been assessed. The results of the present study revealed that subjects with new-onset HEA had a greater number of metabolic factors such as overweight, hypertension, hyperglycemia, and dyslipidemia in baseline when compared with those who did not develop HEA. This result is reasonable because of the strong association of obesity and metabolic syndrome with fatty liver.

Residents who lived near the power plant had to change their lifestyle after the disaster. Although we reported in our cross-sectional analysis that physical activity was associated with HEA,[4] the present study found that exercise habit was not associated with new onset of HEA. On the contrary, the prevalence of exercise as a habit was significantly higher in the HEA group than in the non-HEA group. As baseline metabolic factors were significant in the HEA group, these residents may have been encouraged to exercise. Evaluation of exercise continuity might be necessary to elucidate the true effects of exercise on new HEA onset.

Like our previous cross-sectional study,[4] the results of the present study showed that lifestyle and accident-related factors such as evacuation, alcohol intake, and unemployment were associated with new HEA onset after the accident. Among these risk factors, evacuation had the greatest impact for new HEA onset. Moreover, this study has newly identified an association of psychological distress with new HEA onset after the accident. FHMS has previously shown the effects of psychological distress on lifestyle factors such as physical activity, alcohol intake and diet.[22–24] Excess alcohol intake causes liver injury, while low physical activity and overnutrition are major causes of non-alcoholic liver disease (NAFLD).[25] Also, stress itself has been associated with NAFLD through the production of catecholamines and cortisol.[26] As a result of these, taking care to avoid psychological distress after such an accident may be essential for avoiding new HEA onset. A high level of education was also associated with new HEA onset in men. Education level has been reported to be associated with health-conscious behavior and quality of life.[27] Sex differences regarding the effect of education level on HEA were unclear; however, the difference may be due to alcohol intake, as the frequency of quitting drinking after the accident was significantly higher in men than in women (9.6% vs. 4.3%, $P < 0.001$).

A strength of this study is that it is the first longitudinal analysis regarding new HEA onset after the accident. There are several limitations of this study, including the lack of information about the causes of HEA. The results of this study may suggest fatty liver disease as a cause of HEA. However, HEA due to drug induced liver injury cannot be denied because subjects with HEA have

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Table 3. Risk factors influencing HEA onset after the disaster among 15750 participants from 2011 to 2017

	All participants (15750)				Men (5226)		Women (10479)	
	Sex - and age - adjusted		Multivariable[1]		Multivariable[2]			
	HRs (95% CI)	*P*	HRs (95% CI)	*P*	HRs (95% CI)	*P*	HRs (95% CI)	*P*
Age (1 - year increase)	1.00 (1.00 – 1.00)	0.405	0.99 (0.99 – 1.00)	0.001	0.99 (0.98 – 0.99)	< 0.001	1.06 (1.05 – 1.07)	0.941
Men (ref: women)	1.85 (1.74 – 1.96)	< 0.001	1.77 (1.65 – 1.90)	< 0.001				
Overweight (ref: 18.5 ≤ BMI < 25)	1.33 (1.25 –1.41)	< 0.001	1.25 (1.17 – 1.33)	< 0.001	1.19 (1.08 – 1.31)	< 0.001	1.31 (1.2 – 1.43)	< 0.001
Hypertension	1.27 (1.19 – 1.35)	< 0.001	1.18 (1.11 – 1.26)	< 0.001	1.19 (1.08 – 1.31)	< 0.001	1.16 (1.07 – 1.27)	0.001
Dyslipidemia	1.21 (1.14 – 1.28)	< 0.001	1.17 (1.10 – 1.25)	< 0.001	1.15 (1.05 – 1.26)	0.003	1.17 (1.08 – 1.28)	< 0.001
Diabetes	1.06 (0.97 – 1.17)	0.205						
Education status (ref: elementary school and junior high school)								
High school	0.98 (0.91 – 1.05)	0.528	0.98 (0.91 – 1.05)	0.576	0.90 (0.82 – 1.00)	0.045	1.07 (0.97 – 1.19)	0.157
Junior or vocational college	0.84 (0.76 – 0.93)	0.001	0.86 (0.78 – 0.96)	0.005	0.85 (0.71 – 1.02)	0.072	0.92 (0.81 – 1.05)	0.228
University/graduate school	0.83 (0.73 – 0.95)	0.006	0.87 (0.76 – 0.99)	0.037	0.84 (0.71 – 0.98)	0.031	0.88 (0.68 – 1.13)	0.304
Exercise habit (ref: every day)								
2 – 4 times/week	0.98 (0.90 – 1.07)	0.711						
Once per week	0.97 (0.88 – 1.07)	0.525						
Never	0.92 (0.85 – 1.01)	0.066						
Alcohol consumption (ref: non - drinker)								
Ex - drinker	0.99 (0.83 – 1.18)	0.875	0.99 (0.83 – 1.18)	0.877	0.99 (0.81 – 1.22)	0.958	0.96 (0.65 – 1.43)	0.845
< 44 g/day	1.01 (0.95 – 1.08)	0.708	1.04 (0.97 – 1.11)	0.301	1.01 (0.91 – 1.13)	0.797	1.07 (0.98 – 1.18)	0.127
≥ 44 g/day	1.44 (1.28 – 1.64)	< 0.001	1.42 (1.25 – 1.60)	< 0.001	1.35 (1.17 – 1.56)	< 0.001	1.44 (1.03 – 2.02)	0.035
Smoking								
Current smoker	0.97 (0.88 – 1.07)	0.536						
Ex - smoker	0.99 (0.91 – 1.08)	0.794						
Evacuation (ref: non - evacuation)	1.24 (1.17 – 1.32)	< 0.001	1.19 (1.12 – 1.27)	< 0.001	1.23 (1.12 – 1.35)	< 0.001	1.16 (1.07 – 1.26)	0.001
Tsunami experience (ref: no)	1.06 (0.99 – 1.14)	0.117						
Heard the explosion (ref: no)	1.11(1.04 – 1.17)	0.001	1.04 (0.98 – 1.11)	0.167	1.06 (0.96 – 1.16)	0.248	1.03 (0.95 – 1.11)	0.525
Unemployment (ref: no)	1.18 (1.10 – 1.26)	< 0.001	1.09 (1.01 – 1.17)	0.022	1.10 (1.04 – 1.29)	0.007	1.06 (0.96 – 1.16)	0.261
Psychological distress (ref: K6 < 13)	1.19 (1.09 – 1.29)	< 0.001	1.14 (1.05 – 1.24)	0.002	1.18 (1.03 – 1.35)	0.020	1.11 (1.00 – 1.23)	0.046

[1]Adjusted for age, sex, BMI, and hypertension, as well as dyslipidemia, educational background, drinking habit, and experience of nuclear accident (heard the explosion). Also adjusted for experience of evacuation, unemployment, and psychological distress.
[2]Adjusted for age, BMI, hypertension, and dyslipidemia, as well as educational background, drinking habit, experience of nuclear accident (heard the explosion), and experience of evacuation. Also adjusted for unemployment and psychological distress.
CI, confidence interval; K6, Kessler 6-item scale.

comorbidities including psychologic distress. Identifying the causes of HEA onset may help to avoid severe liver disease such as cirrhosis and hepatocellular carcinoma. In addition, we could not evaluate changes of lifestyle in this study. As our findings suggest that a detailed lifestyle analysis might reveal methods for preventing new HEA onset, it becomes pertinent that lifestyle changes after the accident must be evaluated in the future.

In conclusion, the results of this study showed that baseline metabolic characteristics, lifestyle, and mental health after the accident were risk factors for new HEA onset in residents who lived in evacuation-designated areas. In addition to health-checkups and lifestyle recommendations, attention to mental health after a major accident is important to prevent future HEA.

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Authors' contributions. All authors participated in study conception and design. A Takahashi, T Ohira, and K Hayashi performed statistical analysis of the data and wrote the manuscript. All authors participated in interpretation of the results and drafting of the manuscript and approved the final version.

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Competing interest. None declared.

Abbreviations. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, Body Mass Index; CIs, Confidence Intervals; FHMS, Fukushima Health Management Survey; FPG, Fasting Plasma Glucose; HbA1c, hemoglobin A1c; HEA, hepatobiliary enzyme abnormality; HRs, hazard ratios; K6, Kessler 6-item scale; PAR, Population Attributable Risk; PCL-S, Post-traumatic Stress Disorder Checklist; PTSD, Post-Traumatic Stress Disorder.

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