論　文　内　容　要　旨

Modeling the natural history of fatty liver using lifestyle–related risk factors: Effects of body mass index (BMI) on the incidence of fatty liver

（生活習慣に関連したリスクファクターを用いた脂肪肝の自然史モデリング：脂肪肝の発症に対するボディマス指数（BMI）の影響）

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Fatty liver is an adaptation to lipid loading in the liver, which increases the risk of non–alcoholic fatty liver disease (NAFLD). It is currently the most common form of chronic liver disease with a steady increase correlating with the rise in obesity worldwide. NAFLD may slowly progress to end–stage liver diseases such as liver cirrhosis and hepatocellular carcinoma. In addition, NAFLD is an independent risk factor for cardiovascular disease and is closely associated with type 2 diabetes. Its potential to progress to such diseases makes the prevention of fatty liver important. To prevent fatty liver, lifestyle modification is highly recommended. This study aimed to model the natural history of incident fatty liver using lifestyle–related risk factors for Japanese men and investigated which factors most strongly affected the prevalence of fatty liver.

The study population consisted of Japanese men aged 20–69 years who participated in health examinations and completed questionnaires on their lifestyle behaviors annually from 2012 to 2016 (n = 1891, 1949, 2036, 2063 and 2240 for the years 2012–2016, respectively). The following variables (V) were used for analysis: diagnosis of fatty liver, age, body mass index (BMI), low–density lipoprotein cholesterol (LDL–C), high–density lipoprotein cholesterol (HDL–C), LDL–C / HDL–C ratio, triglyceride (TG), systolic blood pressure (SBP), hemoglobin A1c (HbA1c), smoking, alcohol drinking, regular exercise and shift work. Model predictors and their predictive algorithms were determined by prospective regression analyses between Vi(t) and Vj(t+1) using the 5–year data of the study population. The prevalence of fatty liver was simulated based on such population data using Monte Carlo simulation methods. After the model calibration, internal/external consistency of the projected fatty liver prevalence among those in their 30s to 70s was evaluated. Sensitivity analysis was performed by varying the initial characteristics of the simulated population and varying the predictive algorithms of the predictor variables for fatty liver.

The BMI and LDL– C/HDL–C ratio were significant predictor variables for incident fatty liver. The transition probabilities for the onset of fatty liver were 0.072 (if BMI≥25 kg/m^2), 0.074 (if LDL/HDL ratio ≥2), 0.164 (if BMI≥25 kg/m^2 and LDL/HDL ratio ≥2) and 0.031 (at no risk). The model was well–calibrated for 2013–2016 projections based on the initial 2012 population. When the prevalence of fatty liver was projected using the data of participants aged 30–39 years, the prevalence increased from 19.8% to 31.5% at 40–59 years of age before decreasing to 24.9% at 70–79 years of age. The uncertainty interval around the projection estimates was ±2.0%, which was calculated as 2SD of Monte Carlo variations. The projected prevalence was comparable with prevalence observed in an internal population (which was used for model construction) and was in the range of reported prevalence in external populations (which were not used for model construction). When the initial proportion of those with a BMI ≥25 kg/m^2 varied by ±40% (from 27.0% to 16.2%/37.8%), the initial prevalence of fatty liver changed by −6.9~5.7 percentage points. When the proportion of those with an LDL–C/HDL–C ratio ≥2 varied by ±40% (from 56.9% to 34.1%/79.7%), the initial prevalence of fatty liver changed by −6.0~6.2 percentage points. However, those changes in the fatty liver prevalence decreased as future projections of the fatty liver prevalence continued. By contrast, when annual estimates of BMI and LDL–C/HDL–C ratio varied from the baseline estimates, projected changes in the prevalence of fatty liver increased as projection year steps increased. Furthermore, the sensitivity of annual estimates of BMI to the projected prevalence of fatty liver was greater than that of annual estimates of LDL–C/HDL–C ratio. For instance, when annual estimates of BMI varied by ±1% from the baseline estimates, the peak prevalence of fatty liver (31.5%) changed by −8.0~10.7 percentage points. On the other hand, when annual estimates of LDL–C/HDL–C ratio varied by ±1% from the baseline estimates, the change was −1.6~1.4 percentage points.

We modeled the natural history of fatty liver for adult Japanese men. The model includes BMI and LDL–C/HDL–C ratio, which played a significant role in predicting the prevalence of fatty liver. Specifically, annual changes in BMI of individuals more strongly affected the prevalence of fatty liver than those in the LDL–C/HDL–C ratio. Sustainable BMI control for individuals may be the most effective option for reducing the fatty liver prevalence among Japanese men.