Modeling the Natural History of Non-Alcoholic Fatty Liver Disease: Impact of Reduction in Body Mass Index and/or Cholesterol on the Prevalence of NAFLD

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a manifestation of metabolic syndrome which may lead to liver cancer. As there has been a recent increase in obesity, NAFLD is a growing public health concern. In this study, we constructed the microsimulation model for NAFLD which allows us to estimate the effectiveness of reduction in elevated body mass index (BMI) and/or cholesterol on the prevalence of NAFLD. The study population was approximately 2,000 Japanese males who were aged 18-69 years and observed from 2012 to 2016. NAFLD was presented in individuals if the presence of fatty liver was accompanied by the absence or a little alcohol consumption. The predictor variables and their transition probabilities manipulating the model for NAFLD were determined by longitudinal multivariate regression analysis. Forty-year projection for NAFLD in the initial cohort comprised of subjects aged 20-29 years and they provided the baseline trajectory of the prevalence of NAFLD. Similar projections were carried out under the various prevention scenarios, followed by the comparison with the baseline trajectory. The magnitude of the effectiveness was strongly dependent on the types of measures. If all the population had normal BMIs and/or cholesterol profiles, the prevalence of NAFLD simply decreased to 3% (aged 60-69 years) while the

baseline prevalence peaked at 20% (aged 35-44 years) before decreasing to 12% (aged 60-69 years). In contrast, the prevalence of fatty liver including NAFLD simply decreased to reach a plateau of 8% (aged 30 years or over) while the baseline prevalence peaked at 32% (aged 45-54 years) before decreasing to 29% (aged 60-69 years) in the projection period. Reduction in the risks of elevated BMI and/or LDL/HDL was predicted to significantly decrease the prevalence of NAFLD; however, its effectiveness was shown to be insufficient to eliminate NAFLD. The details on the limitations affecting the prediction of NAFLD outcome were also presented.

KEYWORDS: Microsimulation, Non-Alcoholic Fatty Liver Disease, Metabolic Syndrome, Body Mass index, Cholesterol,

JEL classification: C15, C63, I19

1. INTRODUCTION

Non-alcoholic liver disease (NAFLD) is a hepatic manifestation of the metabolic syndrome [1], which can lead to end stage liver diseases including liver cancer [2,3]. Due to pandemic of obesity and metabolic syndrome, NAFLD is widespread with steadily rising trends in many countries [4-7]. In Japan as well, NAFLD is becoming the most common form of chronic liver disease and is a growing public health concern [8-10], when compared with alcoholic liver disease or virus-induced hepatitis. Due to the absence of subjective symptoms neither no effective pharmacological therapy is available [11,12], and prevention of NAFLD by improving lifestyle factors are important [13-15]. Meanwhile, to prevent metabolic syndrome nationwide in Japan, metabolic screening and health education has been implemented since 2008 [16]. However, little is known about the quantitative effectiveness of the measures on the outcome of the prevalence of NAFLD.

Recently, health-related microsimulation models have been developed and are being used focusing on health insurance, medical care expenditure and population disease burden [17-19]. The models, for example, provide information to guide health policy decisions by predicting trends in disease incidence under alternative health policy scenarios, and comparing the effectiveness and cost-effectiveness of measures [20,21]. For these purposes, various models have been developed for the following non-communicable diseases, coronary heart disease, stroke, type 2 diabetes, obesity, cancer, respiratory diseases, and vascular dementia [22-28]. Simulation models can predict long-term disease outcomes and assess experimentally the effectiveness of alternative measures. Therefore, simulation studies on chronic diseases are increasing when compared with cost and time demanding long-term cohort studies on chronic

diseases. However, no model for NAFLD has been developed to predict the outcome of the prevalence of NAFLD in association with lifestyle-related risk factors including obesity.

In this study, we have constructed a microsimulation model that predicts the outcome of the prevalence of NAFLD for Japanese adult males. This model estimates the effectiveness of reduction in the risks, elevated BMI and/or cholesterol, on the incidence of NAFLD. Our model was developed using the following scheme: Modelling procedures included specifying both a model structure and parameters. They were specified by the possible predictor variables for NAFLD and their update rules. Variable selection and identification of update rules were performed by longitudinal multivariate regression analysis utilizing the sample source data. NAFLD projection was carried out utilizing real population data to describe the baseline or counterfactual trajectory. The obtained trajectories were subsequently compared to estimate quantitative effectiveness of the measures on the outcome of the prevalence of NAFLD.

We developed an unprecedented model for NAFLD associated with lifestyle related risks, elevated BMI and/or cholesterol profile. However, to distinguish NAFLD from ALD by alcohol consumption at each time may not be consistent with histologically confirmed NAFLD. This problem will be addressed in the discussion section.

2. METHODS

2.1 Study Population

The study population consisted of Japanese adult males aged 18-69 who participated in annual health examinations, and completed questionnaires regarding their health and lifestyle, which were observed from 2012 to 2016 (n=1908, 1958, 2046, 2079 and 2269). The entire study population consisted of employees of Fujikura Ltd., one of the representative manufacturers in the power & telecommunication industry of Japan.

2.2 Characteristics of the Data

Sample source, a set of all the data from the study population, included the following variables: demographic variables (age and presence or absence of shift-working), health status variables (diagnosis of fatty liver, blood pressure, body mass index (BMI) and laboratory variables (triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), hemoglobin A1c (HbA1c)), presence or absence of medication for hypertension, dyslipidemia or insulin resistance and lifestyle variables (presence or absence of regular exercise and amount and frequency of alcohol consumption). We describe LDL/HDL, the ratio of LDL-C to HDL-C, hereafter.

The diagnosis of fatty liver was carried out by physicians on ultrasonography [29]. Blood

pressure, BMI and laboratory data were measured by standard procedures. Medication, regular exercise and amount and frequency of alcohol consumption were self-reported. For example, if the alcoholic beverage was other than Japanese sake, the gross alcohol consumption was converted to the amount of Japanese sake with equal alcohol content.

Alcohol consumption was measured as the mean ethanol consumption per day, given by the following equation (1):

$$\text{Alcohol consumption (g/day)} = 180 * m * 0.15 * n/7 \quad (1)$$

where m=1, 1.5, 2.5 and 3 if the consumption of Japanese sake (ml/day) is “less than 180”, “180-less than 360”, “360-less than 540” or “540 or over”, respectively, and n=7, 3.5 and 0 if the frequency of drinking alcohol is “every day”, “often” or “seldom or never”, respectively.

2.3 Diagnosis of NAFLD

According to the guidelines for the diagnosis of NAFLD [30], the NAFLD cases were identified as fatty liver with a history of absence or a little amount of alcohol consumption (less than 30 g/day). The cases of fatty liver with elevated alcohol consumption (30g/day or over) was included in alcoholic liver disease (ALD) cases [30]. Patients who had viral infection-induced liver disease, “hepatitis B or hepatitis C”, and/or history of pancreatectomy were also excluded [30].

Projection for NAFLD required initial values including presence or absence of fatty liver, however, no diagnosis of fatty liver was available for individuals of the initial cohort aged 20-29 years as they did not participate in the fatty liver screening. Prior to projection, we predicted the presence or absence of fatty liver in individuals in the initial cohort by applying criteria obtained in the population aged 30-69 years.

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2.4 Construction of the model

2.4.1 Identification of Predictor Variables and their Update Rules

Our longitudinal study revealed that BMI, LDL/HDL, age, presence or absence of fatty liver and alcohol consumption were the potential predictor variables for NAFLD model (Figure 1). The equations to update each predictor variable for NAFLD model were also provided. (Figure 2). (These methods are similar to our previous study which is now under review)

2.4.2 Model Structures

Annual updates of the presence or absence of NAFLD were conducted in the following two

steps, the presence or absence of fatty liver and alcohol consumption was annually updated separately, which was followed by judging if the presence of fatty liver was accompanied by the absence or a little alcohol consumption (less than 30 g/day). Therefore, the predictive model for NAFLD comprised of the predictive model for fatty liver and the predictive model for alcohol consumption because NAFLD is determined by the combination of presence or absence of fatty liver and alcohol consumption [7]. Furthermore, the predictive model for fatty liver included sub-models for the risk factors, BMI or LDL/HDL (Figure 2). Those obtained were closed models where no demographic ins and outs were allowed.

2.4.3 Cohort Setting and Projection

Two types of theoretical cohorts, a validation cohort and an initial cohort, were established. The validation cohort (n=932) comprised of Japanese adult males aged 30-69 years from the sample source. Using the data in 2012 from the validation cohort, the prevalence of NAFLD was predicted in each year from 2013 to 2016, which was followed by comparison with observed prevalence. At the same time, the predictor variables, BMI (kg/m^2) (=0 if < 25, =1 if ≧25), LDL/HDL (=0 if < 2.0, =1 if ≧2.0) and alcohol consumption (g/day) (=0 if < 30, =1 if ≧30), were also projected and described. This description included the proportion of obesity, dyslipidemia and alcohol drinkers, respectively. These obtained trajectories were subsequently compared with the observed ones. The trajectory of the calculated prevalence was given by the means which were generated in the 10-times Monte Carlo simulations for all the individuals at every year step. The obtained means were described with error bars indicating the mean ± 2SDs.

The initial cohort (n=1000) comprised of Japanese adult males randomly selected from the study population aged 20-29 from 2012 to 2016. The prevalence of NAFLD was projected for 40 years to describe the life-course pattern (from 20 to 69 years old) of the baseline prevalence of NAFLD. Furthermore, NAFLD projection for the initial cohort was conducted under various prevention scenarios, which were followed by a comparison with the baseline prevalence of NAFLD to estimate quantitative effectiveness of the measures against NAFLD. Five types of prevention scenarios were assumed:

(a) intervention performed for all the population, 100% of future obesity and dyslipidemia incidents prevented completely
(b) intervention performed for only the population at risk, 100% of future obesity and dyslipidemia incidents prevented
(c) intervention performed for only the population at risk, 50% of future obesity and dyslipidemia incidents prevented
(d) intervention performed for only the population at risk, 10% of future obesity and

dyslipidemia incidents prevented

(e) intervention performed for all obese population, stochastic reduction in BMIs of individuals by -1.1±2.6 (kg/m^2) in the next year step

For each scenario, simulation was conducted in the following rules.

(a) If updated BMI and/or LDL/HDL were the cut-off values or over in individuals, 100% of them were supposed to have 24.9 of BMI and/or 1.9 of LDL/HDL

(b) If the subjects at risk of elevated BMI and/or LDL/HDL, all of them were supposed to have 24.9 of BMI and/or 1.9 of LDL/HDL in the next year step

(c) If the subjects at risk of elevated BMI and/or LDL/HDL, 50% of them were randomly supposed to have 24.9 of BMI and/or 1.9 of LDL/HDL in the next year step

(d) If the subjects at risk of elevated BMI and/or LDL/HDL, 10% of them were randomly supposed to have 24.9 of BMI and/or 1.9 of LDL/HDL in the next year step

(e) If the subjects at risk of elevated BMI, 100% of them were supposed to have reduced BMI by random real number with N (-1.1, 2.6^2) in the next year step.

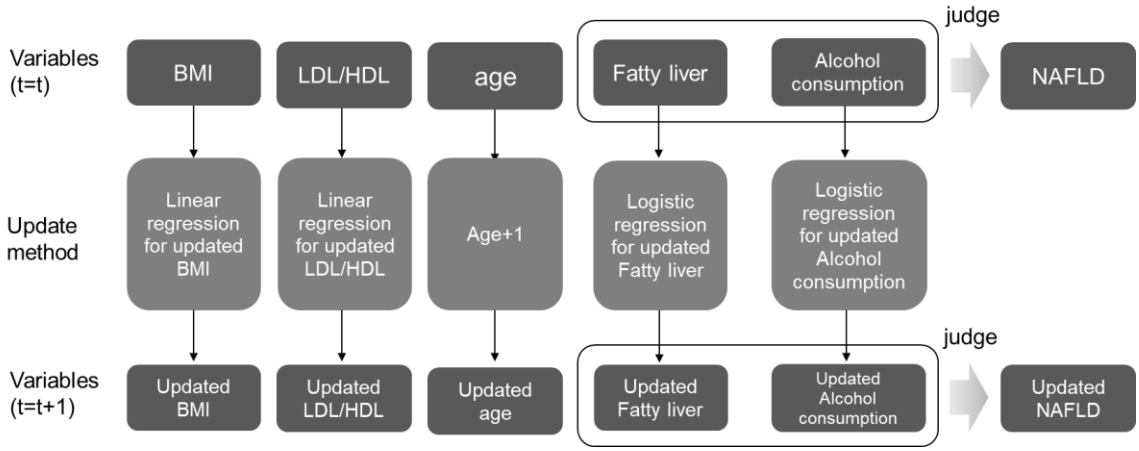

Figure1: The required variables to predict presence or absence of NAFLD for individuals and their updates

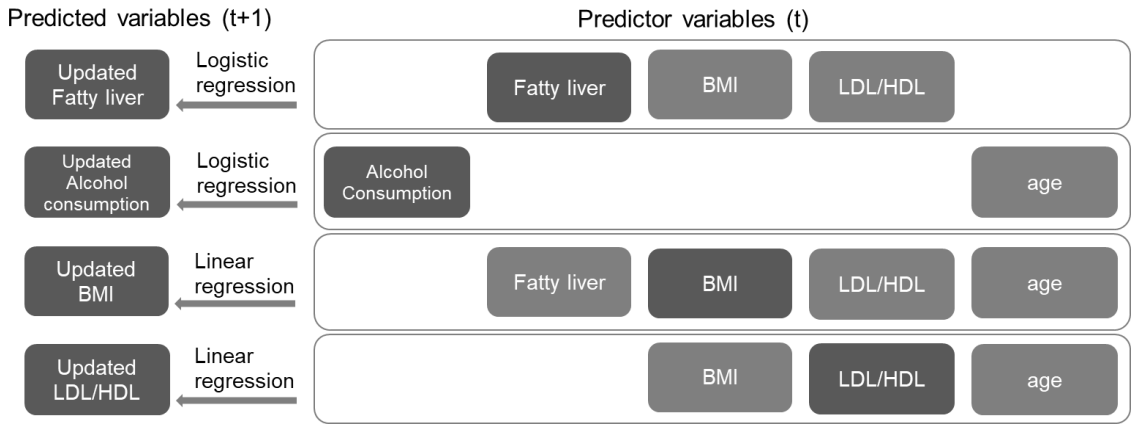

Figure2: Regression equations for updated variables required to predict presence or absence of NAFLD for individuals

2.4.4 Performing Monte Carlo Simulations

All the simulation was performed using mathematical software, "Mathematica 11.0". The outcome of the presence of fatty liver was predicted by Bernoulli trial P(X=1) = p where X=1 if the individuals have fatty liver, and the expectation value (p) was given by the following equations (2) and (3). Alcohol consumption (g/day) (=0 if < 30, =1 if ≧30) was also predicted in the same manner using the equations (2) and (4).

$$p(V_{(t+1)}) = 1/(1+\exp(-Sc)) \quad (2)$$

$$\text{If V=FL (fatty liver), } Sc = C_{0f} + C_{1f}[FL_{(t)}] + C_{2f}[BMI_{(t)}] + C_{3f}[LDL/HDL_{(t)}] \quad (3)$$

$$\text{If V=ALC (alcohol consumption), } Sc = C_{0a} + C_{1a}[ALC_{(t)}] + C_{2a}[age_{(t)}] \quad (4)$$

Updates of BMI and LDL/HDL were conducted by the following equations (5) and (6).

$$[BMI_{(t+1)}] = C_{0f}+C_{1f}[FL_{(t)}] +C_{2f}[BMI_{(t)}] +C_{3f}[LDL/HDL_{(t)}] +\varepsilon_b \quad (5)$$

$$[LDL/HDL_{(t+1)}] = C_{0f}+C_{1f}[FL_{(t)}] +C_{2f}[BMI_{(t)}] +C_{3f}[LDL/HDL_{(t)}] +\varepsilon_l \quad (6)$$

where ε is the real number with N (0, SD^2), SD: the standard deviation of the residuals

ε was incorporated in the equation to predict BMI or LDL/HDL in the next year step.

2.5 Statistical Analysis

All statistical analyses were performed using the software, "IBM SPSS Statistics 24". Quantitative data were expressed as mean values (± standard deviation). The normality of distribution of continuous variables was tested using the Shapiro-Wilk test. Multivariate logistic (or linear) regressions were conducted depending on the properties of predicted variables, binary or numerical. A two-tailed P value < 0.05 was regarded to be statistically significant.

2.6 Ethics Statement

The study protocol was approved by the Ethics Committee of Hiroshima University, Japan. The data utilized in this analysis were obtained from Fujikura Ltd. through opt-out procedure.

3. RESULTS

3.1 Predictor variables and their update rules

The possible predictor variables for NAFLD and their update rules were identified by longitudinal multivariate regression analysis utilizing the data from the sample source. The characteristics are shown in Table 1. The summary of the predictor variables for NAFLD and their predictive equations are presented in Table 2.

3.2 Projection and Validation

Projection was carried out for the validation cohort from 2012 to 2016 to describe the trajectory of the prevalence of NAFLD as well as obesity, dyslipidemia and alcohol drinkers. Each observed value virtually fell in the variance (±2SDs) of calculated value in the same year step (Figure 3).

Table 1 Baseline Characteristics of Sample Source in 2012

	Mean	SD
Age	40.4	9.5
BMI (kg/m^2)*	23.6	3.5
LDL-C (mg/dl)	122.3	29.6
HDL-C (mg/dl)	56.4	13.7
Triglyceride (mg/dl)	128.1	94.9
Hemoglobin A1c (%)	5.4	0.50
Systolic blood pressure (mmHg)	122.2	15.6
Diastolic blood pressure (mmHg)	56.4	13.7

	Positive (%)
Age	
less than 20	0.9
20-30	15.8
30-40	30.3
40-50	35.7
50-60	16.2
60 and over	1.1
Diagnosis of fatty liver	27.9
Medication	
Hypertension	9.0
Insulin Resistance	2.0
hyperlipidemia	4.4
Smoking	33.8
Alcohol consumption (≥30g/day)	34.2
Regular exercise	20.8
Shift-workers	43.3

Table 2 The Characteristics of regression models for predicted variables including coefficients* of predictor variables

	Predictor Variables (t)								
Predicted Variables (t+1)	FL	ALC	BMI	LDL/HDL	age	const.	Regression	H/L test P value	R squared
FL	4.084	——	0.912	0.951	——	-3.489	Logistic	0.04	——
ALC	——	3.652	——	——	0.022	-3.074	Logistic	0.75	——
BMI	-0.068	——	0.968	-0.036	-0.005	1.097	Linear	——	0.93
LDL/HDL	——	——	0.004	0.858	-0.001	0.264	Linear	——	0.75

* Non-standardized coefficient (B) of the predictor variables in the regression models
FL: Fatty liver, ALC: Alcohol consumption

3.3 Baseline and Counterfactual Projections

The baseline characteristics of the initial cohort are shown in Table 3. NAFLD/fatty liver BMI and LDL/HDL were projected for 40 years to describe the trajectory of the baseline prevalence of NAFLD/fatty liver. Similarly, projections were conducted under the scenarios (a)-(e) to give counterfactual prevalence of NAFLD/fatty liver. The comparison among the trajectories given

by the simulations revealed that the magnitude of the effectiveness was remarkably dependent of the types of prevention measures. If all the population had normal BMIs and/or cholesterol profiles, the prevalence of NAFLD simply decreased to 3% (aged 60-69 years) while the baseline prevalence peaked at 20% (aged 35-44 years) before decreasing to 12% (aged 60-69 years). In contrast, the prevalence of fatty liver including NAFLD simply decreased to reach a plateau of 8% (aged 30 years or over) while the baseline prevalence peaked at 32% (aged 45-54 years) before decreasing to 29% (aged 60-69 years) in the projection period. (Figure 4).

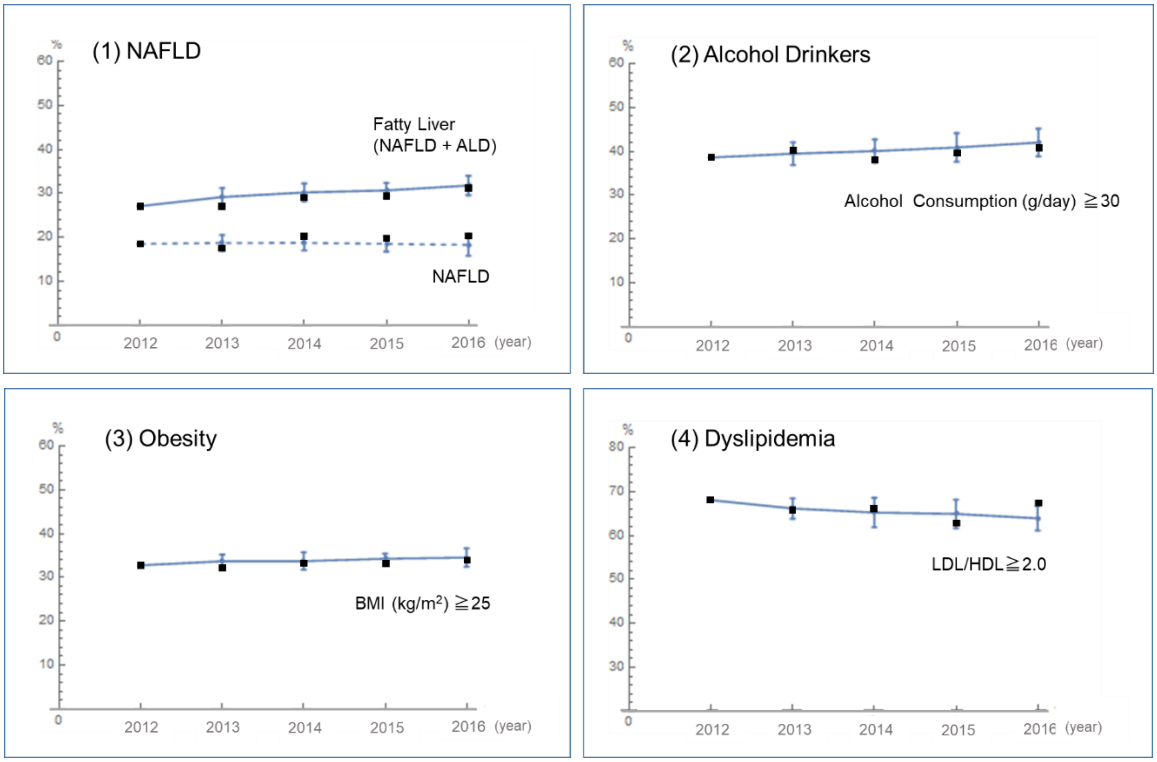

Figure 3: Projected Prevalence of the Validation Cohort:
(1) Fatty liver and NAFLD, (2) Alcohol drinkers, (3) Obesity and (4) Dyslipidemia

Table 3 Baseline Characteristics of the Initial cohort

	Positive (%)
Diagnosis of fatty liver	12.3 *
Medication	
Hypertension	0.4
Insulin Resistance	0.0
hyperlipidemia	0.4
Smoking	21.3
Alcohol consumption (≥30g/day)	24.0
Regular exercise	23.4
Shift-workers	29.3

	Mean	SD
Age	26.8	2.3
BMI (kg/m2)*	22.4	3.4
LDL-C (mg/dl)	107.4	27.6
HDL-C (mg/dl)	57.2	11.8
Triglyceride (mg/dl)	89.6	61.8
Hemoglobin A1c (%)	5.1	0.3
Systolic blood pressure (mmHg)	116.3	12.7
Diastolic blood pressure (mmHg)	70.0	9.3

* estimated value

* BMI (kg/m^2) = (weight (kg)) / (height (m)) ^ 2

4. DISCUSSION

We constructed the microsimulation model in order to predict the outcome of the prevalence of NAFLD for Japanese adult males. The model estimated the quantitative effectiveness of reduction in the risks, elevated BMI and/or cholesterol, on incidence of NAFLD. Our model conducted baseline and counterfactual projections for the prevalence of NAFLD and showed a reduction in the risks of elevated BMI and/or LDL/HDL decreased the prevalence of NAFLD.

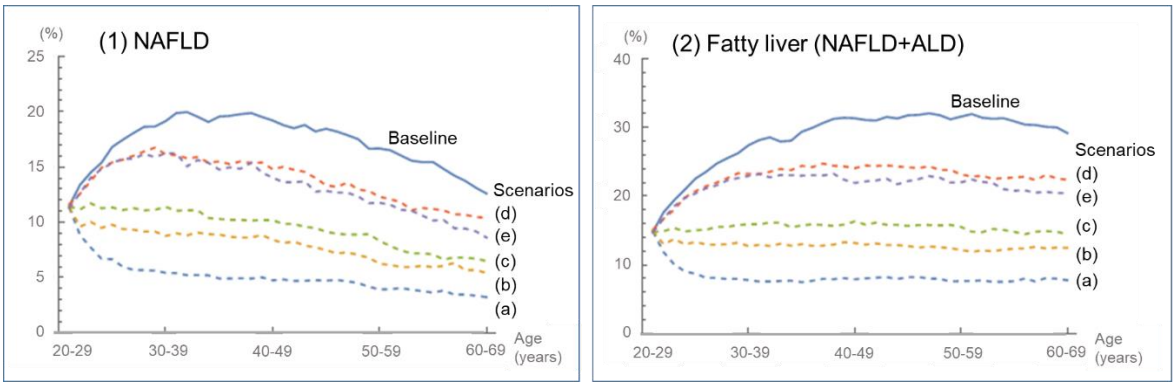

Figure 4: Projected Prevalence of Initial Cohort: (1) NAFLD, (2) Fatty liver (NAFLD + ALD)

The NAFLD risk factors were classified by level of exposure. The cut-off value of BMI was assumed to be 25kg/m^2 as is common in Japan [31]. That of alcohol consumption was 30g/day for adult male [30]. Since it has been recognized that the onset of NAFLD was associated with LDL and inversely associated with HDL [32,33], LDL/HDL was produced as one of the NAFLD/fatty liver risk factors in our model. The cut-off value of LDL/HDL (=2.0) was set because a previous study reported that the exposure of LDL/HDL equals to 2.0 or over significantly leads to sclerosis in association with metabolic syndrome [34-36].

Longitudinal regression analysis clearly showed that BMI and LDL/HDL were significant predictor variables. The evidence for this was consistent with the facts that elevated BMI and/or cholesterol were the possible risk factors for NAFLD [32,33]. HbA1c was also reported to be a possible risk factor for NAFLD [37], however, the results showed it had no additional predictive power in our regressions and was dropped during model selection.

Since limited epidemiological findings were available to validate the prevalence of NAFLD/ fatty liver, all we could conduct was internal validation where simulated values were compared with observed values of the data from the study population in 2012-2016.

The subjects with metabolic syndrome have received 6-month intervention of health education under the current measures. It was reported that the intervention reduced BMIs of subjects

with metabolic syndrome by -1.1±2.6 (kg/m^2) and no significant increase in BMI was observed for 6 months after the intervention [38]. Projection under scenario (e) showed the prevalence of NAFLD and it peaked at 16% (aged 30-39 years) before decreasing to 9% (aged 60-69 years), while the baseline prevalence peaked at 20% (aged 35-44 years) before decreasing to 12% (aged 60-69 years). These results can be used to estimate the effectiveness of current measures against metabolic syndrome in all Japanese adult males. Metabolic screening has been conducted only 50% of the people aged 40 years or over, neither health education has been conducted only 17% of the metabolic subjects as of 2016 [16]. Therefore, the effectiveness of the current measures on prevention of NAFLD is probably very small.

Our simulation indicated that complete reduction in the risks of elevated BMI and/or LDL/HDL decreased the prevalence of NAFLD and fatty liver to 3% and 8%, respectively in 40-year projection for the initial population aged 20-29 years. However, its effectiveness was shown to be insignificant to eliminate NAFLD.

This result may partly be associated with the existence of lean NAFLD found in some of the population, who had no risk of elevated BMI [39-41]. Further prevention strategies other than obesity and/or dyslipidemia may be required. Moreover, further studies are required including those focusing on medical care expenditure and population disease burden in order to maximize total benefits.

5. LIMITATIONS

The NAFLD model was a closed model where no demographic ins and outs were allowed.

The diagnosis of fatty liver was available only for the population aged 30-69 years although we need NAFLD information of the population aged 20-29 years to carry out further simulations. Accordingly, presence or absence of fatty liver in the initial cohort aged 20-29 years was estimated by applying criteria obtained in the population aged 30-69 years. Projection of NAFLD for the population aged 20-29 years might reduce accuracy. In contrast, projection for NAFLD was not carried out after 70 years because it was suspected that extrapolation cannot be applicable.

Our model was constructed using Japanese full-time workers data. The population comprised of full-time workers may be slightly different in the epidemiology of NAFLD/fatty liver compared with other populations comprised of those who work part-time or who are unemployed. This is because the employment condition variations may cause the difference in the prevalence of obesity and dyslipidemia [42]; further study is required comparing BMIs

and cholesterol profiles of the study population with those of whole Japanese adult male. Moreover, gender may also affect the cut-off values of alcohol consumption, BMI and/or LDL/HDL as well as their predictive equations when this model is applied to other populations [43-45]. In this case, external validation and modification of the model will be required.

Distinguishing NAFLD from ALD by alcohol consumption may be accompanied by a certain inaccuracy due to the following reasons; (1) alcohol consumption was self-reported, (2) validity of the cutoff value remains controversial [46,47], and (3) alcohol consumption in individuals may possibly change in their course of life. For the last reason, elevated alcohol consumption in the subjects with NAFLD may change the diagnosis of NAFLD into FLD and vice versa. Therefore, the diagnosis of NAFLD by alcohol consumption is not always assured to be consistent with the histological diagnosis

We admit that the method to distinguish NAFLD from ALD by alcohol consumption includes some uncertainty. However, since cost-effective and noninvasive methods to accurately distinguish NAFLD have not yet been established [48], the classification based on alcohol consumption is a cost-effective and noninvasive method to determine NAFLD with a certain level of significance. The emergence of innovative methods to provide accurate diagnosis of NAFLD is expected in the future.

6. CONCLUSION

We have constructed a microsimulation model that predicts the outcome of the prevalence of NAFLD for Japanese adult males and estimated the effectiveness of reduction in the risks, elevated BMI and/or LDL/HDL, on incidence of NAFLD. Our model showed that a reduction in the risks for NAFLD, elevated BMI and/or LDL/HDL, significantly decreased the prevalence of NAFLD, however, its effectiveness was shown to be insufficient to eliminate NAFLD. Further studies are required including those focusing on medical care expenditure and population disease burden in order to maximize total benefits.

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