

Supplementary Information

Relationship between the dynamics of non-alcoholic fatty liver disease and incident diabetes mellitus

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Supplementary Table S1. Baseline characteristics in BMI group

	All patients (n=3,047)							<i>P</i> -value*
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	
No. of patients	3,047	1,407	805	151	164	170	127	
Age, yr	51.2±8.5	51.9±8.0	51.3±7.5	51.0±7.9	53.3±8.4	50.5±8.2	51.2±8.3	0.0376
Male sex	1.6±0.5	1.7±0.5	1.7±0.5	1.7±0.4	1.7±0.5	1.6±0.5	1.7±0.5	0.0087
BMI, kg/m ²	22.1±1.7	28.1±2.1	23.8±1.0	26.4±1.1	26.1±1.1	24.0±0.8	25.1±1.1	<0.0001
Waist circumference (>80 cm for women, >90 cm for men)	76.6±6.8	89.6±7.4	80.6±6.2	85.1±6.3	85.6±6.2	81.0±6.8	83.3±6.2	<0.0001
SBP, mmHg	119.4±17.2	126.2±17.6	122.0±17.3	124.3±18.1	127.3±19.0	118.1±16.6	123.0±17.5	<0.0001
DBP, mmHg	79.3±10.6	84.4±11.3	80.5±11.3	82.6±10.8	84.0±11.5	78.8±10.2	81.5±10.3	<0.0001
Glucose, mg/dL	81.2±7.8	82.3±8.2	81.9±9.3	82.3±8.3	84.5±9.2	80.1±7.7	82.1±8.6	<0.0001
Creatinine, mg/dl	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.2±0.2	0.3029
Platelet, × mm ⁹	259.8±61.9	275.6±59.8	269.7±65.0	270.6±69.7	274.6±59.3	261.5±62.2	270.3±63.5	<0.0001
Albumin , g/dL	4.2±0.3	4.2±0.3	4.2±0.3	4.2±0.3	4.2±0.3	4.2±0.3	4.2±0.3	0.3029
GGT, U/L	26.8±13.7	28.5±13.1	26.3±7.1	26.6±6.9	28.0±10.3	26.6±9.0	27.9±10.0	0.0387
AST, U/L	22.6±19.2	28.9±20.5	22.7±10.7	25.2±11.2	27.2±16.0	23.8±13.6	25.9±18.5	<0.0001
ALT, U/L	185.5±32.7	193.3±33.2	189.0±33.4	191.1±31.2	196.0±33.8	190.5±38.0	190.0 ±33.1	<0.0001

Total cholesterol, mg/dL	46.1±10.2	42.4±8.6	45.2±9.8	43.6±8.5	42.7±9.9	44.9±10.0	43.5±10.2	<0.0001
HDL, mg/dL	131.7±70.2	166.1±90.7	157.8±97.2	153.5±82.2	174.7±106.4	147.5±70.9	152.7±78.3	<0.0001
TG, mg/dL	3.7±2.9	3.6±2.5	3.3±2.2	3.5±2.2	4.0±2.8	3.4±2.2	3.8±2.9	0.3155
TG/HDL	115.5±31.3	115.2±29.4	120.8±33.1	113.5±31.4	112.2±29.7	115.1±31.0	114.7±28.9	0.2915
LDL, mg/dL	5.5±0.3	5.6±0.3	5.5±0.3	5.6±0.4	5.6±0.3	5.5±0.3	5.6±0.3	<0.0001
HbA1c	1.4±0.9	1.9±1.3	1.4±0.7	1.7±0.8	1.9±1.3	1.3±0.9	1.5±0.8	<0.0001
HOMA-IR	51.2±8.5	51.9±8.0	51.3±7.5	51.0±7.9	53.3±8.4	50.5±8.2	51.2±8.3	0.0376
HSI	30.4±2.8	37.6±3.2	32.4±2.2	35.6±2.4	35.4±2.7	32.6±2.1	34.0±2.5	<0.0001

Data are presented as number (%) or mean±SD.

**P*-value using Scheffe as the post hoc analysis for comparing the groups divided by change pattern of NAFLD status over time.

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *GGT* gamma-glutamyl transferase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HDL* high-density lipoprotein, *TG* triglyceride, *LDL* low-density lipoprotein, *HbA1c* hemoglobin A1c, *HOMA-IR* homeostatic model assessment for insulin resistance, *HSI* hepatic steatosis index, *NAFLD* non-alcoholic fatty liver disease.

Supplementary Table S2. Baseline characteristics in HOMA-IR group

	All patients (n=3,047)							P-value*
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	
No. of patients	1,473	31	606	93	67	280	497	
Age, yr	51.2±8.4	51.3±8.2	51.2±8.1	51.6±9.1	52.9±8.4	52.4±8.4	51.9±8.1	0.1888
Male sex	1.6±0.5	1.6±0.5	1.6±0.5	1.8±0.4	1.7±0.5	1.7±0.5	1.7±0.5	0.0324
BMI, kg/m ²	23.4±2.7	27.4±2.9	24.8±2.7	27.5±3.4	25.3±3.1	25.8±2.9	26.0±2.8	<0.0001
Waist circumference (>80 cm for women, >90 cm for men)	78.7±7.9	89.4±8.7	82.7±8.3	89.4±8.4	84.6±8.6	85.6±7.8	85.9±8.4	<0.0001
SBP, mmHg	119.2±16.9	128.2±16.9	122.9±17.8	128.8±20.1	125.3±19.2	125.3±17.6	126.6±17.9	<0.0001
DBP, mmHg	79.3±10.6	84.0±9.2	82.0±11.3	85.3±11.8	83.0±10.7	83.3±11.0	83.8±11.1	<0.0001
Glucose, mg/dL	80.4±7.4	88.2±9.3	82.3±8.4	88.9±10.4	85.6±8.0	82.0±7.4	84.0±8.7	<0.0001
Creatinine, mg/dL	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8552
Platelet, × mm ⁹	260.6±61.4	265.7±53.3	268.4±61.1	282.9±62.7	255.7±69.1	270.6±58.0	279.3±65.4	<0.0001
Albumin, g/dL	4.2±0.3	4.2±0.3	4.2±0.3	4.2±0.3	4.1±0.3	4.2±0.3	4.3±0.3	0.0036
GGT, U/L	26.8±10.9	34.1±13.5	28.1±17.5	26.6±6.8	24.9±8.0	28.5±13.5	27.5±9.3	0.0028
AST, U/L	22.5±15.7	40.1±23.8	25.9±23.8	29.5±15.8	23.9±16.0	28.9±21.4	27.5±17.1	<0.0001

ALT, U/L	186.3±32.8	202.8±40.4	191.6±33.9	194.0±33.5	187.6±35.1	191.6±32.7	193.5±32.9	<0.0001
Total cholesterol, mg/dL	46.3±10.1	40.0±7.4	43.9±9.5	41.2±7.8	44.4±9.1	42.2±10.2	42.2±8.8	<0.0001
HDL, mg/dL	129.2±67.2	210.5±101.6	150.3±75.9	184.2±87.3	145.9±68.1	176.3±99.1	173.7±102.7	<0.0001
TG, mg/dL	3.7±2.8	3.6±1.9	3.6±2.5	3.5±2.6	3.9±2.6	3.4±2.1	3.7±2.7	0.570
TG/HDL	115.5±31.2	108.9±28.7	115.4±28.8	115.1±33.1	122.4±31.2	116.4±33.0	113.5±29.1	0.3138
LDL, mg/dL	5.5±0.3	5.8±0.4	5.6±0.4	5.7±0.4	5.5±0.3	5.6±0.3	5.6±0.3	<0.0001
HbA1c	1.3±0.5	3.6±1.6	1.4±0.5	3.4±1.7	3.7±2.8	1.5±0.5	2.0±1.2	<0.0001
HOMA-IR	51.2±8.4	51.3±8.2	51.2±8.1	51.6±9.1	52.9±8.4	52.4±8.4	51.9±8.1	0.1888
HSI	31.6±3.6	38.1±1.0	33.7±3.7	37.9±4.6	34.4±4.2	35.3±4.1	35.4±3.9	<0.0001

Data are presented as number (%) or mean±SD.

**P*-value using Scheffe as the post hoc analysis for comparing the groups divided by change pattern of NAFLD status over time.

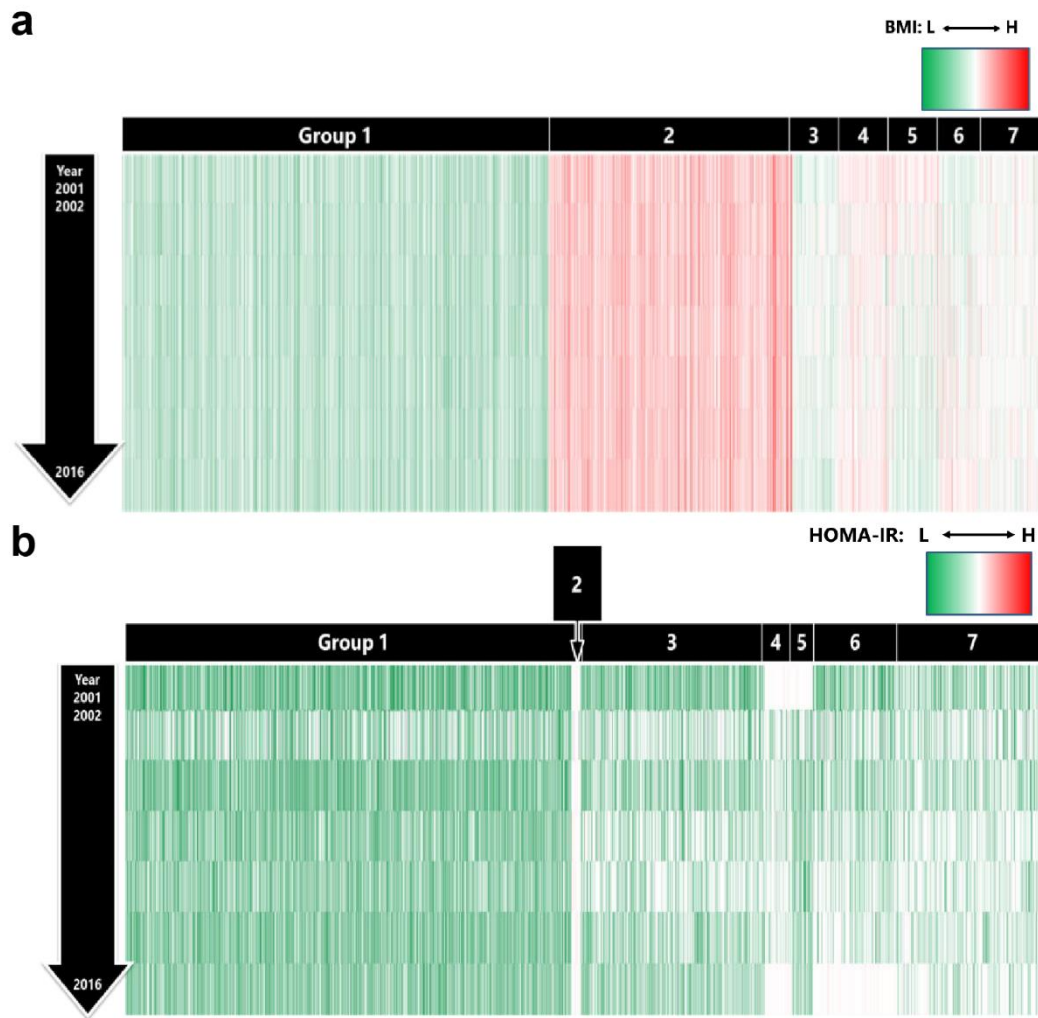
HOMA-IR homeostatic model assessment for insulin resistance, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *GGT* gamma-glutamyl transferase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HDL* high-density lipoprotein, *TG* triglyceride, *LDL* low-density lipoprotein, *HbA1c* hemoglobin A1c, *HSI* hepatic steatosis index, *NAFLD* non-alcoholic fatty liver disease.

Supplementary Table S3. Comparing incident DM risk between BMI groups

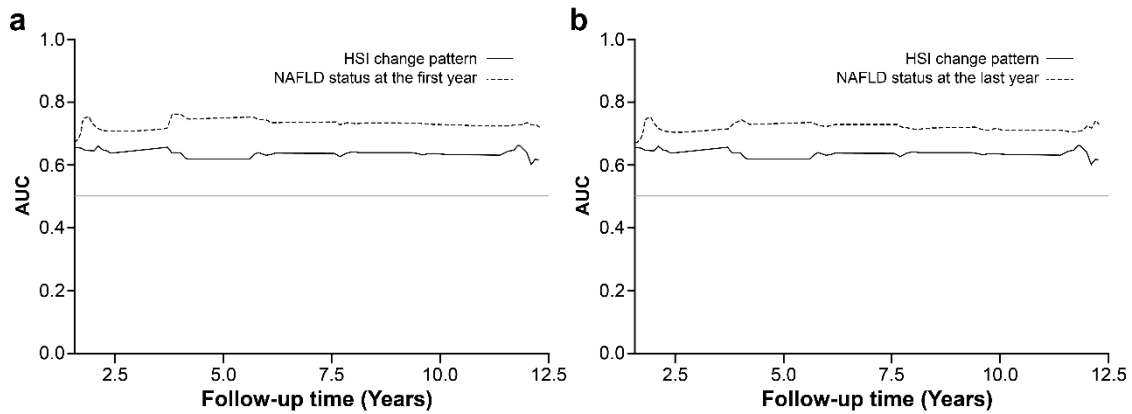
	Univariate analysis		Multivariate analysis (model 1)		Multivariate analysis (model 2)	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Group 1	Ref					
Group 2	3.306 (2.576–4.244)	<0.0001	0.787 (0.492–1.260)	0.3183	0.656 (0.439–0.980)	0.0394
Group 3	2.115 (1.319–3.389)	0.0019	1.072 (0.647–1.778)	0.7890	0.962 (0.586–1.578)	0.8768
Group 4	1.629 (0.985–2.693)	0.0573	0.624 (0.346–1.128)	0.1187	0.561 (0.320–0.984)	0.0439
Group 5	2.896 (1.933–4.340)	<0.0001	1.179 (0.717–1.941)	0.5164	0.975 (0.613–1.551)	0.9160
Group 6	1.274 (0.683–2.378)	0.4459	0.684 (0.353–1.328)	0.2620	0.620 (0.321–1.199)	0.1557
Group 7	2.340 (1.583–3.458)	<0.0001	1.091 (0.696–1.708)	0.7046	1.046 (0.679–1.611)	0.8399

Model 1 was adjusted for age, blood glucose level, ALT, AST, gamma GTP, total cholesterol, HDL, TG, HbA1C, platelet, waist circumference, SBP, DBP, BMI, HOMA-IR, and HSI, including changes in HSI, HOMA-IR, and BMI. Model 2 was adjusted for HbA1c, blood glucose level, HSI, TG/HDL ratio, GGT, and DBP (stepwise selection), including changes in HSI, HOMA-IR, and BMI.

DM diabetes mellitus, *BMI* body mass index, *HR* hazard ratio, *CI* confidence interval, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GTP* glutamyl transpeptidase, *HDL* high-density lipoprotein, *TG* triglyceride, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HOMA-IR* homeostatic model assessment for insulin resistance, *HSI* hepatic steatosis index, *GGT* gamma-glutamyl transferase.



Supplementary Figure S1. Heatmaps according to BMI, HOMA-IR clustering. **(A)** Heatmaps according to BMI clustering. **(B)** Heatmaps according to HOMA-IR clustering. The y-axis represents the observed year during follow-up period and the x-axis represents the group classification. As the value for each year goes from lower to higher value, it is highlighted with green to red color in the heatmap. *BMI* body mass index, *HOMA-IR* homeostatic model assessment for insulin resistance.



Supplementary Figure S2. Comparison of discriminatory ability for predicting the incident diabetes mellitus (DM) between HSI change pattern over time and NAFLD development at specific time point. **(A)** Integrated area under the receiver operating characteristic curve (IAUC) plot based on HSI change pattern and NAFLD status at the first year of follow-up period in predicting incident DM, respectively. **(B)** IAUC plots based on HSI change pattern and NAFLD status at the last year of follow-up period in predicting incident DM, respectively. *HSI* hepatic steatosis index, *NAFLD* non-alcoholic fatty liver disease, *AUC* area under the receiver operating characteristic curve.