Resolution of Fatty Liver and Risk of Incident Diabetes

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Context: Fatty liver is associated with an increased risk of type 2 diabetes, but whether an increased risk remains in people in whom fatty liver resolves over time is not known.

Objective: The objective of the study was to assess the risk of incident diabetes at a 5-year follow-up in people in whom: 1) new fatty liver developed; 2) existing fatty liver resolved, and 3) fatty liver severity worsened over 5 years.

Design and Methods: A total of 13 218 people without diabetes at baseline from a Korean occupational cohort were examined at baseline and after 5 years, using a retrospective study design. Fatty liver status was assessed at baseline and follow-up as absent, mild, or moderate/severe using standard ultrasound criteria. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for incident diabetes at follow-up were estimated after controlling for multiple potential confounders.

Results: Two hundred thirty-four people developed incident diabetes. Over 5 years, fatty liver resolved in 828, developed in 1640, and progressed from mild to moderate/severe in 324 people. Resolution of fatty liver was not associated with a risk of incident diabetes [aOR 0.95 (95% CIs 0.46, 1.96), $P = .89$]. Development of new fatty liver was associated with incident diabetes [aOR 2.49 (95% CI 1.49, 4.14), $P < .001$]. In individuals in whom severity of fatty liver worsened over 5 years (from mild to moderate/severe), there was a marked increase in the risk of incident diabetes [aOR 6.13 (2.56, 95% CI 14.68) $P < .001$ (compared with the risk in people with resolution of fatty liver)].

Conclusion: Change in fatty liver status over time is associated with markedly variable risks of incident diabetes. (***J Clin Endocrinol Metab*** **98: 3637–3643, 2013)**

An aging global population, increasing urbanization, and obesity will all contribute to the doubling of diabetes prevalence that is predicted between 2000 and 2030 (1). Nonalcoholic fatty liver disease (NAFLD) often occurs with obesity, and NAFLD has become one of the most common causes of chronic liver disease worldwide, causing considerable liver morbidity and mortality (2–4). Fatty liver is associated with metabolic syndrome and type 2 diabetes (5–8) and NAFLD is also associated with cardiovascular disease (9). However, despite evidence of an association between NAFLD and type 2 diabetes, the mechanisms by which NAFLD is associated with type 2 diabetes and cardiovascular disease need to be better elucidated to inform approaches to prevention and treatment.

Recent evidence suggests that factors affecting liver fat accumulation are important contributors to the increase in the risk of type 2 diabetes observed in people with NAFLD (10–12), and the more severe forms of NAFLD are associated with a high risk of diabetes (13). However, because

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransaminase; BMI, body mass index; BP, blood pressure; CI, confidence interval; GGT, γ-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

liver fat accumulation occurs early in the NAFLD disease process, a better insight into the nature of the relationship between liver fat development (or resolution) and development of type 2 diabetes will help inform understanding of whether future treatments targeting liver fat resolution per se might also be useful adjuncts for decreasing risk of type 2 diabetes.

Ultrasound is commonly used in a clinical practice setting and can easily be applied to large-scale studies performed in the community. A recent meta-analysis of 4720 participants showed that, compared with histological examination of liver fat as the gold standard, the overall sensitivity and specificity of liver ultrasound was 84.8% and 93.6%, respectively, and importantly, the sensitivity and specificity of ultrasound was similar to that of other imaging techniques [ie, computed tomography or magnetic resonance imaging (14)]. Although it is established that fatty liver is associated with type 2 diabetes, it is not known whether risk of type 2 diabetes remains increased if fatty liver resolves over time. Therefore, the aim of our study was to assess risk of incident diabetes at 5 years of follow-up in people in whom there had been a change in fatty liver status between baseline and follow-up ultrasound examination (both examinations were separated in time by 5 y). Specifically, our aim was to assess the risk of incident diabetes at 5 years of follow-up in the following: 1) in people in whom there was resolution of fatty liver over 5 years, ie, fatty liver that had been present at baseline was not present at follow-up examination; 2) in people in whom there was a development of new fatty liver between baseline and the follow-up examinations; and 3) in people in whom there was an increase in severity of fatty liver status, from mild fatty liver noted at baseline to moderate/severe fatty liver, identified at follow-up examination.

Materials and Methods

Study subjects

The study population consisted of individuals who had a comprehensive health examination at baseline (in 2003) and were reexamined 5 years later (in 2008) at Kangbuk Samsung Hospital (College of Medicine, Sungkyunkwan University, South Korea). In South Korea, employees are required to participate in annual or biennial health examinations by the Industrial Safety and Health Law. Health checks include blood tests, anthropometry, and abdominal ultrasound examination without any selection of high-risk individuals for differential testing. The Institutional Review Board at Kangbuk Samsung Hospital has approved the secondary analysis of anonymized data from the cohort for this study. Informed consent was not required because personal identifying information was not used.

Initially 15 638 participants were identified and 416 were excluded for having type 2 diabetes at baseline (based on any one or more of self-report, medical history, and fasting plasma glucose $\geq$ 7 mmol/L). Individuals with data missing at baseline for the following variables were also excluded: plasma glucose (n = 1), serum insulin (n = 1346), body mass index (BMI; n = 26), alcohol consumption (n = 399), smoking (n = 361), and exercise (n = 309). After all exclusions, 13 218 participants were eligible for this analysis, among which 234 participants had been diagnosed with diabetes mellitus by the follow-up examination in 2008.

Measurements and calculations

The health examination included full medical histories, physical examinations, and blood samples. BMI was calculated as weight in kilograms divided by height in meters squared. Questionnaires were used to ascertain information regarding alcohol consumption (grams per day), smoking (never, ex, current), and frequency of exercise (none, less than once a week, at least once a week).

Blood samples for laboratory examinations were collected after an overnight fast. Fasting plasma glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) concentrations were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 autoanalyzer; Bayer Diagnostics). Low-density lipoprotein cholesterol concentration was calculated using a direct measurement. Insulin concentration was measured with an immunoradiometric assay (Biosource) with an intra- and interassay coefficient of variation of 2.1%–4.5% and 4.7%–12.2%, respectively.

Abdominal ultrasonography (Logic Q700 MR; GE) using a 3.5-MHz probe was performed in all subjects at baseline and at 5-year follow-up by experienced clinical radiologists, and fatty liver was diagnosed or excluded at both time points, based on standard criteria, including hepatorenal echo contrast, liver brightness, and vascular blurring. Mild fatty infiltration was classified as a minimal increase in echogenicity of the liver compared with that of the renal cortex in which the diaphragm and intrahepatic vessels appeared normal. Moderate to severe fatty infiltration was classified by a moderate increase in echogenicity of the liver and a slightly impaired appearance of the diaphragm and intrahepatic vessels; or a marked increase in liver echogenicity with poor penetration of the deep parenchyma and impaired visualization of the intrahepatic vessels and diaphragm (15). Incident diabetes at 5-year follow-up was defined as one or more of self-report, medical history, and fasting plasma glucose results during follow-up.

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD for normally distributed variables or median (interquartile range) if not normally distributed. Continuous variables were compared using independent *t* tests, nonnormally distributed variables were compared using Mann Whitney *U* tests, and categorical variables were expressed as percentages and compared between groups using the χ^2 test. Characteristics for individuals who did and who did not develop diabetes at follow-up were compared, both at baseline and at follow-up. We used logistic regression to determine odds ratios (ORs) for developing incident diabetes at follow-up in the following: 1) in people in whom there was resolution of fatty liver over 5 years, ie, fatty liver that had been present at baseline but was not present at follow-up examination; 2) in people in whom there was development of new fatty

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Table 1. Characteristics of Cohort at Baseline and at Follow-Up Stratified by Presence of Incident Diabetes at Follow-Up

	Baseline Characteristics			Follow Up Characteristics		
	No Incident Diabetes	Incident Diabetes	*P* Value	No Incident Diabetes	Incident Diabetes	*P* Value
n	12 984	234		12984	234	
Men, n, %	9276, 71.4%	208, 88.9%	<.001			
Age, y	41.0 ± 6.0	42.9 ± 5.9	<.001			
Glucose, mg/dl	92.9 ± 8.3	109.0 ± 8.7	<.001	95.1 ± 9.1	149.9 ± 33.1	<.001
AST, IU/L	26.2 ± 23.9	33.4 ± 13.5	<.001	25.1 ± 10.8	33.5 ± 21.0	<.001
ALT, IU/liter	29.6 ± 34.9	49.4 ± 31.1	<.001	26.7 ± 19.5	46.1 ± 33.4	<.001
GGT, IU/L	29.8 ± 30.7	56.7 ± 52.0	<.001	35.1 ± 41.9	70.1 ± 71.3	<.001
Triglycerides, mg/dL	137.5 ± 82.9	204.8 ± 140.5	<.001	134.1 ± 83.9	222.1 ± 162.0	<.001
Median (interquartile)	117.0 (83.0, 167.0)	183.0 (122.3, 248.5)		113 (80.0, 165.0)	195.0 (129.8, 248.5)	
HDL-C, mg/dL	54.4 ± 11.4	50.6 ± 9.6	<.001	54.2 ± 12.3	48.5 ± 9.9	<.001
LDL-C, mg/dL	118.3 ± 29.5	125.6 ± 28.3	<.001	113.9 ± 28.8	120.9 ± 31.7	<.001
Insulin, IU/mL	7.2 ± 2.7	9.8 ± 4.4	<.001	7.9 ± 3.7	11.7 ± 5.1	<.001
BMI, kg/m^2	23.8 ± 2.8	26.71 ± 3.3	<.001	24.0 ± 2.8	26.7 ± 3.4	<.001
SBP, mm Hg	115 ± 13	123 ± 15	<.001	115 ± 14	124.±14	<.001
DBP, mm Hg	74.6 ± 9.9	80.1 ± 10.5	<.001	74.9 ± 9.7	81.3 ± 10.0	<.001
Alcohol, g/d	10.8 ± 15.0	15.2 ± 19.4	<.001			
Smoking (ex or current), n, %	6442, 49.6%	161, 68.8%	<.001			
Exercise ≥ once per week, n, %	4579, 35.3%	79, 33.8%	.34			
Fatty liver status, n, %						
No	9484, 73.0%	74, 31.6%	<.001	8695, 67.0%	51, 21.8%	<.001
Mild	3164, 24.4%	113, 48.3%	<.001	3842, 29.6%	131, 56.0%	<.001
Moderate to severe	336, 2.6%	47, 20.1%	<.001	447, 3.4%	52, 22.2%	<.001

Abbreviations: DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

liver between baseline and follow-up examinations; and 3) in people in whom there was an increase in severity of fatty liver status; ie, from mild fatty liver noted at baseline to moderate/severe fatty liver identified at follow-up examination.

Analyses were undertaken with adjustment adjusted for baseline age, sex, BMI, glucose, insulin, triglycerides, HDL-C, systolic blood pressure (BP), change in BMI between baseline and follow-up, smoking status (never, ex, current), exercise frequency (less than once a week or at least once a week), alcohol consumption (grams per day) and alanine aminotransferase (ALT), aspartate aminotransaminases (AST) and γ-glutamyltransferase (GGT). All data analysis was performed using SPSS, version 15.0 (SPSS). The statistical significance of *P* values in this report was set at $P < .05$.

Results

There were 234 incident cases of diabetes at follow-up, and of these subjects 14 were identified by medical history or self-report. The characteristics of the cohort, stratified by incident diabetes at follow-up, were compared at baseline and at follow-up (Table 1). Table 2 shows the proportions of people without fatty liver and with mild or moderate to severe fatty liver at baseline and at follow-up. Over 5 years, fatty liver resolved in 828, developed in 1640, and progressed from mild to moderate/severe in 324 people. Table 3 shows the numbers and percentage of peo-

Table 2. Fatty Liver Status and Severity at Baseline and at Follow-Up

	Follow-Up Fatty Liver Status		
	No	Mild	Moderate/Severe
Baseline fatty liver status			
No fatty liver (n = 9588)	7918/9558 (82.8%)	1585/9558 (16.6%)[a]	55/9558 (0.6%)[a]
Mild fatty liver (n = 3277)	798/3277 (24.4%)[b]	2155/3277 (65.8%)	324/3277 (9.9%)[c]
Moderate/severe fatty liver (n = 383)	30/383 (7.8%)[b]	233/383 (60.8%)	120/383 (31.3%)

[a] Represents new (incident) cases of fatty liver at follow-up.

[b] Represents cases of resolution of fatty liver at follow-up.

[c] Represents cases of mild fatty liver at baseline with progression to moderate/severe fatty liver at follow-up.

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Table 3. Numbers and Percentage of People With Incident Diabetes According to Baseline and Follow-Up Fatty Liver Status

	Follow-Up Fatty Liver Status			
	No	**Mild**	**Moderate/Severe**	***P* Value**
Baseline fatty liver status				
No fatty liver (n = 9588)	39/7918 (0.5%)	33/1585 (2.1%)	2/55 (3.6%)	<0.001
Mild fatty liver (n = 3277)	11/798 (1.4%)	75/2155 (3.5%)	27/324 (8.3%)	<0.001
Moderate/severe fatty liver (n = 383)	1/30 (3.3%)	23/233 (9.9%)	23/120 (19.2%)	0.012

ple with incident diabetes according to baseline and follow-up fatty liver status.

We examined the proportion of incident cases of diabetes at follow-up, according to fatty liver status at baseline and at follow-up. Of the 828 subjects with fatty liver at baseline, who did not have fatty liver at follow-up, only 12 of 828 people developed incident diabetes. We tested whether the OR for incident diabetes was affected by whether new fatty liver developed between baseline and at follow-up; or whether existing fatty liver that was present at baseline resolved (or was not present) at follow-up examination (Table 4). Table 4 shows the ORs for incident diabetes at follow-up, according to fatty liver status at baseline and at follow-up. After adjustment for age, sex, glucose, insulin, BMI, triglycerides, HDL-C, systolic BP, alcohol, physical activity, change in BMI between baseline and follow-up, and ALT, AST, and GGT, development of new fatty liver between baseline and follow-up examination (OR 2.49 (95% confidence intervals [CIs] 1.49, 4.14), $P < .001$) was associated with incident diabetes. Resolution of fatty liver (that was present at baseline) during follow-up was not associated with incident diabetes [OR 0.95 (95% CIs 0.46, 1.60) $P = .89$]. Progression of fatty liver over time was associated with incident diabetes and in the group of people with fatty liver at baseline in whom fatty liver severity worsened over time [OR 7.38 (95% CI 3.36, 16.22), $P < .001$].

Next, we estimated the risk of developing incident diabetes at follow-up in people in whom fatty liver progressed over time. To undertake this analysis, we assessed the ORs for incident diabetes at follow-up in people in whom fatty liver progressed from mild fatty liver at baseline to moderate/severe fatty liver detected at 5-year follow-up examination (Table 5). After adjustment for age, sex, glucose, insulin, BMI, triglycerides, HDL-C, systolic BP, alcohol use, physical activity, change in BMI between baseline and follow-up, and ALT, AST, and GGT, the OR for incident diabetes at 5-year follow-up was 6.13 [95% CIs 2.56, 14.68 ($P > .001$)]. (The reference group for this analysis was the group of people in whom fatty liver resolved over 5 y, ie, mild fatty liver at baseline, and no fatty liver detected at follow-up examination.)

Table 4. Odds Ratios for Incident Diabetes at Follow-Up According to Fatty Liver Status at Baseline and at Follow-Up

	Incident DM, n (%)	**Model 1 Odds Ratio 95% CIs *P* Value**	**Model 2 Odds Ratio 95% CIs *P* Value**	**Model 3 Odds Ratio 95% CIs *P* Value**	**Model 4 Odds Ratio 95% CIs *P* Value**
Reference					
No fatty liver at both baseline and at follow-up, no fatty liver (n = 7918)	39 (0.5%)	1	1	1	1
Fatty liver at baseline but not follow-up (n = 828)	12 (1.5%)	2.63 (1.36, 5.07) .004	0.89 (0.44, 1.82) .75	0.98 (0.48, 2.02) .97	0.95 (0.46, 1.6) .89
No fatty liver at baseline, but fatty liver at follow-up (n = 1640)	35 (2.1%)	4.06 (2.55, 6.47) <.001	2.86 (1.73, 4.71) <.001	2.59 (1.56, 4.30) <.001	2.49 (1.49, 4.14) <.001
Fatty liver at baseline and at follow-up (n = 2832)	148 (5.2%)	9.93 (6.88, 14.35) <.001	3.27 (2.14, 5.02) <.001	3.13 (2.04, 4.81) <.001	2.95 (1.91, 4.54) <.001
Fatty liver at baseline and remaining static at follow-up (n = 2275)	98 (4.3%)	8.22 (5.55, 12.17) <.001	2.97 (1.83, 4.81) <.001	2.92 (1.80, 4.75) <.001	2.78 (1.70, 4.53) <.001
Fatty liver at baseline and worsening in severity at follow up (n = 324)	27 (8.3%)	15.6 (9.23, 26.18) <.001	9.28 (4.42, 19.46) <.001	7.82 (3.63, 16.86) <.001	7.38 (3.36, 16.22) <.001

Abbreviation: DM, diabetes mellitus. Model 1 was adjusted for baseline age and sex. Model 2 was adjusted for baseline age, sex, BMI, glucose, insulin, baseline triglycerides, HDL-C, systolic BP, alcohol, smoking, and physical activity. Model 3 was adjusted for baseline age, sex, BMI, glucose, insulin, baseline triglycerides, HDL-C, systolic BP, alcohol, smoking, physical activity, and change in BMI between baseline and follow-up. Model 4 was adjusted for baseline age; sex; BMI; glucose; insulin; baseline triglycerides; HDL-C; systolic BP; alcohol use; smoking; physical activity; change in BMI between baseline and follow-up; and ALT, AST, and GGT.

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Table 5. Odds Ratios for Incident Diabetes at Follow-Up According to Change of Severity of Fatty Liver in People With Mild Fatty Liver at Baseline

	Baseline	5-Year Follow-Up Odds Ratio 95% CIs *P* Value	Incident DM, n, % Odds Ratio 95% CIs *P* Value	Model 1 Odds Ratio 95% CIs *P* Value	Model 2 Odds Ratio 95% CIs *P* Value	Model 3 Odds Ratio 95% CIs *P* Value	Model 4 Odds Ratio 95% CIs *P* Value
Reference group n = 798	Mild fatty liver	No fatty liver	11 1.4%	1	1	1	1
n = 2155	Mild fatty liver	Mild fatty liver	75 3.5%	2.62 (1.38, 4.96) .003	2.21 (0.62, 7.89) .22	2.35 (0.61, 9.07) .21	2.28 (1.11, 4.70) .025
n = 324	Mild fatty liver	Moderate to severe fatty liver	27 8.3%	6.87 (3.36, 14.07) <.001	5.96 (1.29, 27.48) .022	6.48 (1.21, 34.7) .029	6.13 (2.56, 14.68) <.001

Abbreviation: DM, diabetes mellitus. Model 1 was adjusted for baseline age and sex. Model 2 was adjusted for baseline age, sex, BMI, glucose, insulin, baseline triglycerides, HDL-C, systolic BP, alcohol, smoking, and physical activity. Model 3 was adjusted for baseline age, sex, BMI, glucose, insulin, baseline triglycerides, HDL-C, systolic BP, alcohol, smoking, physical activity, and change in BMI between baseline and follow-up. Model 4 was adjusted for baseline age; sex; BMI; glucose; insulin; baseline triglycerides; HDL-C; systolic BP; alcohol use; smoking; physical activity; ALT, AST, and GGT; and change in BMI between baseline and follow-up.

Discussion

Our novel data show that changing fatty liver status over a 5-year period is associated with markedly different risks of incident diabetes. For example, over 5 years, in 828 people, fatty liver that had been present at baseline was not present (or had resolved) at follow-up examination. In these individuals there was no increase in risk of incident diabetes over that period, and the risk of incident diabetes was similar to that observed in people who did not have fatty liver (at either baseline or follow-up examination). In contrast, there were 1640 new cases of fatty liver that developed during the 5-year follow-up, and in these individuals the OR for incident diabetes was 2.49 (95% CI 1.49, 4.14) (after full adjustment for potential confounders). Similarly and in support of this finding, in the 324 people in whom fatty liver progressed between baseline and follow-up examination, there was also an increase in the OR for incident diabetes at follow-up [OR 7.38 (95% CIs 3.36, 16.22), $P < .001$ (Table 4)]. With the caveat that this study design cannot address causal relationships, these data strongly suggest that NAFLD severity is associated with a greater risk of diabetes, and attenuation of fatty liver status decreases the risk of developing diabetes.

Why might change in fatty liver status over a 5-year period have a variable effect on the risk of developing diabetes? NAFLD is strongly associated with insulin resistance but not all individuals with fatty liver have insulin resistance (16–18). However, the term insulin resistance embraces a variety of insulin actions, eg, resistance to insulin's effect to prevent the liver from producing excessive glucose from glycogenolysis or gluconeogenesis, and homeostasis model assessment insulin resistance index measurement may not correctly reflect insulin resistance in these pathways. Although our results show that a change in the fatty liver status over time was associated with variable risks of incident diabetes, independently of change in BMI over 5 years, it is plausible that a change in the risk of incident diabetes could be mediated, at least in part, by coexisting changes in visceral adiposity, lifestyle (physical activity, alcohol, smoking), insulin sensitivity, or lipids over the same period of time.

Change in fatty liver status over time might modify the risk of diabetes via a liver-specific effect. Such a liver-specific effect could be mediated by the secretion of hepatokines (19) or inflammatory cytokines that influences the risk of diabetes. In NAFLD, secretion of hepatokines, such as retinol binding protein 4, fetuin A, fibroblast growth factor 21, or inflammatory biomarkers such as C-reactive protein, TNF-α, and IL-6 (20) may directly affect the risk of incident diabetes by adversely affecting hepatic gluconeogenesis, glycogen synthesis (21, 22), and insulin signaling (23). Although we cannot prove it in this cohort, it is plausible from the above evidence that resolution of fatty liver over time may result in normalization of these bioactive molecules and a return to more normal insulin signaling and glucose homeostasis (and consequently to no increase in risk of incident diabetes).

NAFLD is not a single disease entity but describes a spectrum of liver fat-associated hepatic conditions, with differing degrees of liver fat (steatosis), inflammation (nonalcoholic steatohepatitis), and fibrosis. This spectrum of disorders can be assessed using the Kleiner histopathological scoring system (24), but despite this obvious benefit, liver biopsy is associated with a significant morbidity and even mortality, even in the best of centers. Consequently, these unacceptable complications mean that liver biopsy cannot be used to assess NAFLD severity in population studies. Magnetic resonance can be used to assess quantitatively the amount of liver fat, either using magnetic resonance spectroscopy or in- and out-of-phase magnetic resonance imaging. However, both techniques require hardware that is currently not available for large-

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scale, community-based cohort studies. On the other hand, ultrasound can be used effectively in large cohort studies to assess the presence of liver fat and importantly can be used semiquantitatively to assess the severity of liver fat infiltration.

Physical inactivity is associated with hepatic insulin resistance (25), and modest increases in physical activity have recently been shown to be very effective in improving liver enzymes (26) and decreasing liver fat (27–31). It is plausible that more severe NAFLD is a marker of physical inactivity, which increases the risk of type 2 diabetes. In this cohort, information about lifetime physical activity energy expenditure was not available. We had only basic self-reported information on physical activity levels in this cohort, and consequently, it is likely that the estimates are highly likely to be subject to measurement error and there is scope for residual confounding. However, with the information available, we have shown that the association between incident diabetes and the change in fatty liver status was independent of the levels of baseline physical activity (although we do not know whether any change in the fatty liver status may have been associated with a change in physical activity levels).

Our study has some limitations. We have used routine clinical data from a retrospective occupational cohort. Ultrasound has limited sensitivity to detect low levels of fatty liver and to detect fatty liver in very obese subjects. However, in this Asian cohort, there were very few subjects with a BMI greater than 30 kg/m^2 (230 men and 42 women). Oral glucose tolerance tests and glycosylated hemoglobin measurement were not performed in this cohort, and the date of developing diabetes is not known. Data were not available on family history of diabetes, participants' lifetime exposure to alcohol, or use of drugs known to be associated with increased risk of diabetes (although heavy alcohol consumption and use of drugs of interest is likely to be present only in a small percentage of people in this middle-aged occupational cohort). Data on waist circumference and inflammatory markers were incomplete (only available on ~18% of the cohort). The study is limited to one ethnic group, and the distribution of risk factors and their association with diabetes may differ by ethnic group. Our study was not large enough to investigate whether change in fatty liver status provides a valuable addition to diabetes risk scores to improve risk prediction of diabetes, and further research is required to address this important issue. In this cohort it was not possible to assess agreement between radiologists in the reporting of liver ultrasound hepatic steatosis. Although some nondifferential misclassification bias of fatty liver status may have therefore occurred on the basis that several different radiologists reported the results; this limitation would serve to attenuate the magnitude of our effect measures toward the null. Thus, we reason that our results can probably be considered a conservative estimate of the relationship between change in fatty liver status over time and incident diabetes.

In conclusion, in a middle-aged occupational cohort study, we have shown that a change in fatty liver status over time (development of new fatty liver, resolution of existing fatty liver, or worsening in severity of existing fatty liver) is associated with markedly variable risks of incident diabetes. Risk of incident diabetes over an approximately 5-year period increased with the following: 1) development of new fatty liver during that period and 2) was not increased among people in whom fatty liver resolved over time. Progression of fatty liver between baseline and follow-up examination was also associated with an increased risk of incident diabetes. Although the design of this observational study cannot prove causality, these data strongly support the notion that increases or decreases in liver fat influence glucose homeostasis.

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K.-C.S. analyzed the data, wrote the methods, and contributed to the discussion; C.D.B. devised the hypothesis and wrote the introduction, the results, and the discussion; and S.H.W. reviewed/edited the manuscript and contributed to the discussion. K.-C.S. is the guarantor for the article.

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