Baseline and change in serum uric acid level over time and resolution of nonalcoholic fatty liver disease in young adults

Baseline and change in serum uric acid level over time and resolution of NAFLD in young adults: The Kangbuk Samsung Health Study

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Abbreviations

NAFLD: Nonalcoholic fatty liver disease

SUA: Serum uric acid

HR: Hazard ratios

CI: Confidence intervals

CVD: Cardiovascular disease

BMI: Body mass index

HEPA: Health-enhancing physical activity

BP: Blood pressure

HbA1c: Glycated hemoglobin

HOMA-IR: homeostatic model assessment of insulin resistance

hs-CRP: High-sensitivity C-reactive protein

ABSTRACT

Aims: Whether changes in serum uric acid (SUA) are associated with resolution of nonalcoholic fatty liver disease (NAFLD) is uncertain. We aimed to determine the association between (i) baseline SUA and (ii) SUA changes over time, and NAFLD resolution.

Materials and Methods: A retrospective cohort study, comprising 38,483 subjects aged <40 years with pre-existing NAFLD, were undertaken. The effects of SUA changes over time were studied in 25,266 subjects. Participants underwent a health examination between 2011 and 2019, and had at least one follow-up liver ultrasound until December 2020. Exposures included baseline SUA levels, and SUA changes between baseline and subsequent visits, categorized into quintiles. The reference group was the third quintile (Q3) containing zero change. The primary endpoint was resolution of NAFLD.

Results: During a median follow-up of 4 years, low baseline SUA and decreases in SUA over time, were independently associated with NAFLD resolution (p for trend <0.001). Using SUA as a continuous variable, the likelihood of NAFLD resolution was increased by 10% and 13% in men and women, respectively, per 1 mg/dL decrease in SUA. In a time-dependent model with changes in SUA treated as a time-varying covariate, the aHRs (95%CIs) for NAFLD resolution comparing Q1 (highest decrease) and Q2 (slight decrease) to Q3 (reference) were 1.63 (1.49-1.78) and 1.23 (1.11-1.35) in men and 1.78 (1.49-2.12) and 1.18 (0.95-1.46) in women, respectively.

Conclusions: Low baseline SUA levels and a decrease in SUA levels over time were both associated with NAFLD resolution in young adults.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become a global public health burden, mainly attributed to unhealthy lifestyle-induced obesity and metabolic syndrome [1,2], and prevalence has rapidly increased in young adults [3]. NAFLD in young adults is often unrecognized and, if untreated, can eventually progress to cirrhosis requiring liver transplantation even before the age of 40 years [4]. The mortality rate in young patients with NAFLD is five times higher than that in the general population, emphasizing the urgent need for prevention, early detection and proper management of this disease in young adults [5,6]. However, the lack of NAFLD–specific pharmacological treatments [7] means that it is imperative to recognize risk factors that can be modified and implement effective interventions to prevent NAFLD.

Serum uric acid (SUA), the end-enzymatic product of purine metabolism, is associated with increased oxidative stress and increased reactive oxygen species [8-10]. Unhealthy dietary habits, including high consumption of sugary foods containing fructose, which is becoming increasingly prevalent, particularly among young populations, may result in elevated SUA levels [11,12]. Epidemiological studies suggest that hyperuricemia is associated with cardiometabolic diseases, including cardiovascular diseases (CVD), and related mortality as well as all-cause mortality [13-16].

There is some evidence of a positive and independent association between either hyperuricemia at a single point in time or increasing SUA over a period and both prevalent and incident NAFLD [17-20]. A previous study of 3,822 Chinese participants with 500 incident NAFLD events found that an increase in SUA over a period of two years was linked to a dose-

response increase in the development of NAFLD [20]. This study categorized SUA changing trajectories into four trajectories, identified by a group based trajectory modeling, and increasing SUA trajectory was positively associated with incident NAFLD risk. However, it remains unclear whether monitoring initial or changes in SUA levels can aid in predicting NAFLD resolution or persistence of NAFLD. Therefore, our study aimed to investigate the longitudinal association between baseline SUA levels and changes in SUA levels over time, on NAFLD resolution in a large cohort study of young individuals under the age of 40 years, all of whom had pre-existing NAFLD.

MATERIALS AND METHODS

The present cohort study was performed as part of the Kangbuk Samsung Health Study, a large-scale cohort study of Korean adults aged 18 or older who underwent annual or biennial health screening examinations at Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea [21]. This study focused on young adults under the age of 40 years who had pre-existing ultrasound–defined fatty liver during a comprehensive health examination between 2011 and 2019, and had at least one follow-up liver ultrasound until December 2020 (n = 99, 898).

We excluded participants who met the following criteria: had excessive alcohol consumption, liver steatogenic medication, medication for hyperuricemia or gout, serologic positivity for hepatitis B virus and hepatitis C virus, history of liver cirrhosis or liver cirrhosis based on ultrasound, history of liver disease or medication for liver disease, or history of malignancy (n= 12,069). Then, we excluded missing information on alcohol consumption, fatty liver, body mass index, serum uric acid, HOMA-IR, or hs-CRP (n= 3,496). Some participants satisfied more than 1 exclusion criterion. The analytic sample of the primary cohort study

included a total of 38,483 with baseline NAFLD in whom we were able to assess the relationship between SUA at baseline and the resolution of existing NAFLD. For the second cohort study, SUA changes between 1st to 2nd visit and the subsequent NAFLD resolution, we further excluded individuals; the majority of whom did not comply with the follow-up visit after the 2nd visit or had already experienced NAFLD resolution at the 2nd visit (n =13,217). Ultimately, the analytic sample of the secondary cohort study included a total of 25,266 to assess the SUA changes between 1st and 2nd visit and the subsequent resolution of pre-existing NAFLD (**Figure 1**).

This study was conducted following the principles stated in both the Declarations of Helsinki and Istanbul and was authorized by the Institutional Review Board of Kangbuk Samsung Hospital (IRB No. KBSMC 2023-03-029). Since the study utilized anonymous retrospective data that were routinely collected during health examinations, the need for informed consent was waived.

Data collection

The dataset consisted of self-reported socio-demographic, health-related behaviors, and medical history, as well as anthropometric and laboratory measurements and liver ultrasounds taken during the initial and subsequent visits [21]**.** The smoking status of each participant was categorized as never, former, or current smoker. Their alcohol consumption frequency and quantity per drinking day were also collected in standard units used to calculate the average alcohol consumption per day. To evaluate the physical activity levels of the participants, the Korean version of the International Physical Activity Questionnaire short form was used, and the results were converted to metabolic equivalents (min/week). The physical

160 activity levels were then calssified as inactive, minimally active, or health enhancing physical
161 activity (HEPA) based on the results of the questionnaire[22]. Self-reported data of medications
162 for dyslipidemia or glucose-lowering agents for diabetes (classified as insulin and non-insulin
163 agents) were collected.Obesity was defined as a BMI of ≥25 kg/m^2 according to Asian-specific
164 criteria [23]. Abdominal obesity was defined as waist circumference of ≥85 cm for women and
165 ≥90 cm for men [24]. Hypertension was defined as BP of ≥140/90 mmHg or the use of BP-
166 lowering medication.

167 Laboratory data, including fasting serum uric acid, glycemic parameters, lipid profiles,
168 liver enzyme, and hs-CRP levels, were measured from blood samples collected after at least 10
169 hours of fasting. SUA level was measured enzymatically using an automatic analyzer (Modular
170 DP analyzer, Roche Diagnostics, Tokyo, Japan), with the values expressed in mg/dL to the first
171 decimal place. We used SUA values in mg/dL unit, treating as a continuous variable in our
172 study, to avoid inducing rounding errors or further measurement errors that may result from
173 converting the values to SI units. Homeostatic Model Assessment for Insulin Resistance
174 (HOMA-IR) was estimated and IR was defined by a HOMA-IR ≥ 2.5 [25]. We calculated
175 estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration
176 equation.

177 A 103-item self-administered FFQ, validated for application in Korea, was designed
178 to capture dietary habits during the previous year [3]. Participants were asked how often, on
179 average, they consumed each type of food or beverage during the past year. The FFQ included
180 three predefined categories of portion sizes (small, medium, and large) and nine predefined
181 categories of frequency, ranging from never or seldom to ≥3 times a day for food (to ≥5 times
182 a day for beverages). Participants were also questioned to specify the consumption period (3,

6, 9, or 12 months) for the seasonal intake of fruits. The total consumption of each food and beverage was calculated by multiplying the frequency of consumption by specific portion sizes. Total energy and nutrient intake was determined using the food composition table developed by the Korean Nutrition Society [27].

Definition of pre-existing NAFLD and NAFLD resolution

Diagnosis of fatty liver was made based on an abdominal ultrasonography conducted by experienced radiologists who were not informed of the study's objectives. The standard criteria used to diagnose fatty liver were as follows: a diffuse increase in fine echoes in the liver parenchyma relative to those in the kidney or spleen parenchyma, deep beam attenuation, and bright vessel walls. The grade of fatty liver was also documented as either mild, modera te, or severe steatosis on sonography as follows: 1) mild, slight diffuse liver echogenicity with normal visualization of the diaphragm and portal vein wall; 2) moderate, moderately increased liver echogenicity with slightly impaired appearance of the portal vein wall and diaphragm; 3) severe, a marked increase in liver echogenicity with poor or no visualization of the portal vein wall, diaphragm, and posterior part of the right liver lobe. Please note that excessive alcohol use (<20 and <30 g/day for women and men, respectively) or any other potential causes of fatty liver were initially excluded (refer to the exclusion criteria in **Figure 1**) and the presence of fatty liver were considered indicative of NAFLD. The inter-observer and intra-observer reliability values for fatty liver diagnosis were substantial (kappa statistic = 0.74) and excellent (kappa statistic = 0.94), respectively [21]. The resolution of NAFLD was defined as the presence of hepatic steatosis (with any grade of hepatic steatosis) assessed by liver ultrasound at initial visit, but its absence during follow-up.

205 **Statistical analysis**

206 Descriptive statistics were used to summarize the participants according to sex-specific
207 groups based on their SUA levels at baseline: <5.0, 5.0-to-5.9, 6.0-to-6.9, 7.0-to-7.9 or ≥ 8.0
208 mg/dL in men and <4.0, 4.0-to-4.9, 5.0-to-5.9, 6.0-to-6.9 or ≥ 7.0 mg/dL in women. This
209 categorization was chosen due to previous studies suggesting that SUA levels even in normal
210 range can increase the risk of developing NAFLD, as well as the need for sample sizes large
211 enough for each category while considering a difference of 1 mg/dL between sexes for the
212 diagnosis of hyperuricemia [28,29].

213 We conducted two distinct analyses: (1) SUA levels at baseline and resolution of
214 NAFLD at subsequent follow-up, starting from 2nd visit to last available visit; and (2) changes
215 in SUA levels between the 1st visit (baseline) and 2nd visit and subsequent resolution of NAFLD,
216 starting from the 3rd visit to last available visit. For individuals who showed resolution of
217 NAFLD, subsequent visits following the resolution of NAFLD were not included in the
218 analysis. For those who did not show resolution of NAFLD, the follow-up continued until their
219 last recorded visit.

220 The primary endpoint for both analyses was the resolution of pre-existing NAFLD.
221 The occurrence of NAFLD resolution was measured in terms of the number of cases per 1000
222 person-years, and the follow-up period extended from the baseline visit until the date of the
223 primary endpoint or the last health screening examination (December 31, 2020), whichever
224 came first. To examine relationship between changes in SUA levels between baseline and
225 second visits and NAFLD resolution, the time of second visit was used as the start of the follow-
226 up period. The study design of our study is depicted in **Figure 2**.

Changes in SUA levels were determined as the difference in SUA levels between the 1st (baseline) visit and the 2nd visit (**Figure 2**). Main exposure was the difference in SUA levels from baseline to subsequent visit (2nd visit) and categorized into quintiles with the 3rd quintile (containing zero change) as the reference group; 1) highest decrease (Q1), 2) slight decrease (Q2), 3) slight increase (Q4), and 5) highest increase (Q5).

To assess the relationship between baseline and change in SUA status and resolution of pre-existing NAFLD, cox proportional hazard models were used to calculate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for the primary endpoint. The multivariable-adjusted model was gradually adjusted for covariates, including age, center (Seoul or Suwon), examination year, education level (below college graduate, college graduate or higher, or unknown), smoking status (never, former, current smoker, or unknown), alcohol consumption (<10 or ≥10 g/day), physical activity level (inactive, minimally active, HEPA, or unknown), medication use for hyperlipidemia, glucose lowering agent use, history of hypertension, BMI, waist circumference, eGFR, hs-CRP, and HOMA-IR. We estimated aHRs for NAFLD resolution according to the 1 mg/dL decrease in SUA levels compared to the highest SUA level, as well as 1 mg/dL decrement in SUA as a continuous variable. An increase in the aHR describes a greater likelihood for resolution of fatty liver in the group characterized by the baseline SUA or the change in SUA (either an increase or a decrease over time) relative to the reference group. For the change in SUA as an exposure, the reference group contained 'no change' in SUA level over time. For both analyses of baseline and change in SUA status and resolution of pre-existing NAFLD, we initially adjusted for age. Model 1 was further adjusted for the study center, BMI, year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, history of hypertension, medication for

dyslipidemia and use of glucose lowering agent use (insulin and/or OHA). Model 2 was further adjusted for waist circumference, hs-CRP, HOMA-IR and eGFR.

We performed the time-dependent analyses, wherein SUA levels and covariates were measured repeatedly during the follow-up and included as time-varying covariates. Specifically, time-dependent Cox proportional hazard models incorporated the updated status of SUA levels, smoking, alcohol consumption, physical activity, total energy intake, BMI, insulin use, OHA use, history of hypertension, medication for dyslipidemia, hs-CRP, HOMA-IR, waist circumference, and eGFR as time-dependent variables. Baseline age, center, year of the screening exam, and education level were included as time-fixed variables. We further assessed the association between changes in SUA levels and the resolution of pre-existing NAFLD using time-dependent Cox proportional hazards modeling, with changes in SUA levels treated as a time-dependent variable. Changes in SUA levels were calculated for each subject as the differences in SUA levels from visit n+1 to visit n. For example, from visit 2 to baseline (visit 1), from visit 3 to visit 2, from visit 4 to visit 3, and so on.

Additionally, we performed sensitivity analyses to reinforce the association between SUA and NAFLD resolution under the following conditions: 1) defining the primary outcome as persistent NAFLD resolution, specifically when NAFLD resolution first occurred and persisted until the subsequent follow-up, and 2) categorizing pre-existing NAFLD based on the severity of ultrasound-defined fatty liver into mild and moderate-to-severe, considering both baseline SUA levels and changes in SUA.

We also performed sensitivity analyses to see whether the associations between SUA or changes in SUA levels and NAFLD resolution preserved after excluding individuals with prevalent diabetes or incident diabetes. STATA version 17.0 (Stata Corp LP, College Station,

TX, USA) was used to perform statistical analyses. A two-sided P-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of participants according to a sex-specific uric acid level

After excluding those who met the exclusion criteria, 38,483 participants (32,321 men and 6,162 women) with NAFLD at baseline were included in the study (**Figure 1**). Participants with higher SUA levels tended to be younger, and have lower education levels, higher alcohol intake, increased BMI and waist circumference, and more unfavorable metabolic profiles including higher insulin resistance and hs-CRP levels, compared to those with lower SUA levels (**Table 1 and Table 2).**

Relationship between baseline SUA levels and resolution of NAFLD

During 152,333 person-years of follow-up, 8,451 cases of NAFLD resolution were identified in men (resolution rate, 55.5 cases per 10^3 person-years). During 21,818 person-years of follow-up, 2,801 cases of NAFLD resolution were identified in women (resolution rate, 128.4 cases per 10^3 person-years). The relationship between baseline SUA levels and NAFLD resolution is shown in **Table 3**.

Lower baseline SUA levels were positively associated with increased NAFLD resolution in men and women (*p* for trend <0.001) with slightly stronger association in women than in men (P for interaction = 0.006). These associations remained after adjusting confounders, hs-CRP and HOMA-IR (models 1 and 2). In time-dependent models where SUA levels, BMI and other confounders were included as time-varying covariates, the multivariable

aHRs (95% CIs) for NAFLD resolution, comparing the lowest SUA level (<5 mg/dL for men and <4 mg/dL for women) to the highest SUA level (reference; ≥8 mg/dL for men and ≥7 mg/dL for women) was 1.51 (1.35-1.69) and 1.35 (1.09-1.67) in men and women, respectively. In an analysis using SUA as a continuous variable in the models, the likelihood of NAFLD resolution was increased by 10 % in men and by 13% in women per 1 mg/dL decrease in SUA concentration, in a time dependent model that takes account not only of change in SUA over time but also allows for adjustment of change in potential key confounders over time.

Relationship between short-term changes in SUA levels and resolution of NAFLD

During 134,147 person-years of follow-up 4,494 cases of NAFLD resolution (167.1 cases per 10^3 person-years) were identified in men. During 16,991 person-years of follow-up, 996 cases of NAFLD resolution (293 cases per 10^3 person-years) were identified in women (**Table 4**). The interval between the first and second visits for participants receiving health screening examinations, including SUA samplings, was 1.9 years (interquartile range, 1.6-2.1). Overall, changes in SUA levels over time were inversely associated with NAFLD resolution in both men and women (P for trend <0.05) without significant interaction by sex (P for interaction = 0.632). In a time-dependent model including change in SUA level over time, treated as a time-varying covariate, the multivariable aHRs (95% CIs) for NAFLD resolution, comparing the first quintile (Q1, highest decrease) and second quintile (Q2, slight decrease) to reference (Q3, stable SUA) were 1.63 (1.49-1.78) and 1.23 (1.11-1.35) in men and 1.78 (1.49-2.12) and 1.18 (0.95-1.46) in women. In men, even a slight decrease in SUA level was associated with increased NAFLD resolution. Although a similar association was observed in women, it was not statistically significant.

316 **Sensitivty Analysis**

317 We performed additional analyses, where the primary outcome was defined as
318 persistent NAFLD resolution (indicating NAFLD resolution first occurred and persisted
319 through subsequent follow-up) to evaluate the link between SUA at baseline and its changes
320 and persistent NAFLD resolution. In the analysis, we observed a sustained inverse association
321 between SUA levels or their changes and persistent NAFLD resolution, with a more robust
322 effect size observed in both men and women (**Table S1 and S2**). The persistent NAFLD
323 resolution was 1.60 (1.36-1.89) and 2.07 (1.52-2.81) in men and women, respectively, comparing
324 the lowest SUA level (<5 mg/dL for men and <4 mg/dL for women) to the highest SUA level
325 (reference; ≥8 mg/dL for men and ≥7 mg/dL for women). In an analysis using SUA as a
326 continuous variable in the models, the likelihood of persistent NAFLD resolution was increased
327 by 12 % in men and by 23% in women per 1 mg/dL decrease in SUA concentration (Table S1).
328 For changes in SUA levels, the persistent NAFLD resolution was 1.15 (1.03-1.29) and 1.31
329 (1.04-1.65) in men and women, respectively, comparing the first quintile (Q1, decrease SUA)
330 and third quintile (Q3, increase SUA) to reference (Q2, stable SUA) (**Table S2**).

331 Moreover, we categorized pre-existing NAFLD based on the severity (mild vs.
332 moderate-to-severe) and followed-up until its resolution occurred (**Table S3–S6**). For those
333 with pre-existing mild NAFLD, the inverse association between baseline SUA levels and
334 NAFLD resolution remained significant in both men and women, though the incident NAFLD
335 resolution with decreased SUA level during the short-time interval was attenuated (**Table S3**
336 **and S4**). Among those with pre-existing moderate-to-severe NAFLD, the NAFLD resolution
337 rate based on SUA levels was insufficient to establish a significant association during the 4-
338 year follow-up period. Therefore, no significant association was observed for either men or

339 women (**Table S5 and S6**). After excluding participants with prevalent diabetes at baseline or
340 incident diabetes during follow-up period, the association between SUA levels and the
341 resolution of NAFLD remained significant although it was attenuated by decreased SUA levels
342 over time (**Table S7 and S8**).

343 **DISCUSSION**

344 Our large cohort study of subjects with pre-existing NAFLD at baseline is the first to
345 demonstrate that lower initial SUA levels and short-term decrease in SUA levels in men and
346 women with pre-existing NAFLD were independently associated with NAFLD resolution,
347 highlighting the importance of maintaining SUA levels within the normal range.In this large
348 population-based study, comprising approximately 38,000 young adults with pre-existing
349 NAFLD, our findings extend the existing evidence on the relationship between SUA and
350 NAFLD risk by showing a novel association between SUA decrease over time and NAFLD
351 resolution.

352 Previous meta-analyses showed that increased SUA levels are independently
353 associated with increasing risk of NAFLD in a dose-response manner [28,30]. Several longitudinal
354 studies have evaluated an association between hyperuricemia and the development of NAFLD
355 [19,31-33], with evidence suggesting that elevated SUA levels precede the development of hepatic
356 steatosis [34]. However, there are few descriptions of the effects of changes in SUA level on
357 NAFLD, except for the association of SUA changing trajectory and NAFLD risk [20] which
358 showed that increasing SUA trajectory was positively associated with incident NAFLD risk.
359 However, until the present study it remained unclear whether monitoring initial or changes in
360 SUA levels can aid in predicting NAFLD resolution or persistence of NAFLD. Furthermore,

361 little evidence on the resolution of NAFLD in both men and women with pre-existing NAFLD
362 according to SUA; a couple of cohort studies evaluated the NAFLD remission by baseline SUA
363 levels, without considering SUA changes over time, and only included men with a small sample
364 size of about 800 [35,36]. Moreover, the inverse relationship between hyperuricemia and NAFLD
365 remission was only significant in those without obesity [35]. However, our large cohort study of
366 men and women aged <40 years with NAFLD at baseline showed consistent results across all
367 analyses in a time-varying manner, supporting the independent role of both initial SUA levels
368 and their changes on NAFLD resolution, irrespective of potential metabolic compoments
369 including BMI, waist circumference, HOMA-IR and hs-CRP.

370 Both men and women with SUA levels that decreased by a moderate amount during
371 the 1.9-year short-term interval had a higher rate of NAFLD resolution. These data have shown
372 that the likelihood of NAFLD resolution was increased by 10 % in men and 13% in women,
373 even with a small decrement from baseline SUA, suggesting also that women, despite having
374 relatively lower levels of baseline SUA, may also benefit from achieving a reduction in SUA
375 levels with regard to NAFLD resolution. However, we acknowledge that further studies with
376 larger sample sizes of women with NAFLD in particular are needed to provide additional
377 evidence to support this finding.

378 Based on biomolecular aspects, several possible mechaisms have been suggested to
379 support a pathophysiological relationship between SUA and NAFLD. Insulin resistance
380 induced by excessive SUA has been reported to cause hepatic lipid accumulation, which is an
381 early indicator of NAFLD development [37]. Elevated SUA levels can also induce endoplasmic
382 reticulum stress and trigger lipogenesis [38], generate mitochondrial oxidative stress [39], resulting
383 in the release of reactive oxygen species [40], and stimulate activation of the NLRP3

inflammasome [41]. These mechanisms may worsen the progression of disease activity in NAFLD, ultimately resulting in the development of NASH and liver fibrosis [31,42]. For NAFLD resolution, it is plausible that those potential pathophysiological factors may be also affected by lowering SUA levels; SUA reduction with allopurinol improved insulin resistance, defined as HOMA-IR, as well as hs-CRP in a radomized study [43], although our findings remained irrespective of two factors.

Given that our study participants were relatively young and generally healthy compared to individuals with hyperuricemia (defined as SUA >7 mg/dL for men and > 6.5 mg/dL for women) in a clinical study [43], it is plausible that the potential impact of insulin resistance or inflammation on the association between SUA or its changes and NAFLD resolution within our study might be less pronounced. Also, the relatively short follow-up period (about 4 years) might have limited our ability to observe the confounding or mediating effects of insulin resistance or inflammation, defined as HOMA-IR or hs-CRP, respectively. Moreover, we used Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) that is accepted as a good measure for assessment of whole body insulin sensitivity. However, the correlation between HOMA-IR and glucose disposal rate, a measure of peripheral insulin resistance, can vary depending on the characteristics of study population and these insulin sensitivity measures are not free of measurement errors [44-46]. Therefore, in our study, we cannot rule out the potential confounding or mediating effect of insulin resistance or inflammation in SUA or its change and NAFLD resolution. An alternative explanation may involve direct fat accumulation in hepatocytes and release of pro-inflammatory cytokines following activation of NLRP3 inflammasome. Uric acid has been found to directly induce intracellular triglyceride accumulation in hepatocytes, both in vivo and vitro [41], inferring that lowering SUA levels could

potentially hinder this fat accumulation in hepatocytes. Moreover, pro-inflammatory cytokines such as IL-1β and IL-18 [47] which are released upon activation of NLRP3 inflammasome triggered by uric acid, might be alleviated by lowering SUA levels potentially contributing to NAFLD resolution. Further studies engaging potential biomarkers are required to clarify the mechanical pathways involved in NAFLD resolution through changes in SUA levels.

The present study has some limitations that should be acknowledged. Firstly, we were unable to collect data for high intake of certain foods and beverages –those rich in purines or fructose – can elevate uric acid levels, and potentially affect fatty liver. Although our study employed a 103-item self-administered food frequency questionnaire (FFQ) [26] and estimated total energy intake, it was not specifically designed for the assessment of dietary fructose intake, a major source of uric acid. Secondly, our dataset lacked specific information about specific classes of glucose-lowering medications, such as sodium-glucose cotrasporter-2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RAs), which could potentially act as confounders, exhibiting beneficial effects in NAFLD treatment or contributing to the reduction of SUA levels [50,51]. However, when restricting to individuals without prevalent diabetes or incident diabetes, likely not exposed to SGLT-2 inhibitors or GLP-1RA at baseline, the significant inverse association between SUA levels and NAFLD resolution persisted, although it was attenuated by decreased SUA levels over time in our study. Third, as a retrospective study relying on collected date, we were unable to account for participants' all behavior or lifestyle changes during the follow-up period. However, we performed time-dependent analyses, in which the changes in SUA levels and other covariates including changes in certain lifestyle behaviors available in our cohort data such as smoking, alcohol consumption, physical activity, and total energy intake were treated as time-varying covariates. Additionally,

the database for fructose in Korea was limited, which further hindered our ability to rule out the possibility of residual confounding in relation to fructose intake affecting both uric acid levels and liver fat. Therefore, further research is needed to better understand the interrelationship between fructose intake, uric acid levels, and liver fat. In addition, some measurement errors, including HOMA-IR which is an imperfect measure of IR, may still be present and other confounding factors such as smoking, alcohol use and medication history were also collected via a self-administered structured questionnaire, used in health checkup programs under the National Health Insurance plan in Korea. Although efforts were made to adjust for these potential confounders, there may still be other unmeasured confounders that could have influenced the observed associations. Finally, since our study subjects consisted of healthy young Korean men and women with easy access to health care facilities, further research is needed to confirm our results in different populations to determine the extent to which they can be extrapolated to other groups.

Despite those limitations, our findings suggest that monitoring SUA levels can identify individuals at risk of NAFLD persistence or resolution in young adults with pre-existing NAFLD. However, further research is needed to determine the effectiveness of targeted management to lower SUA levels for resolving NAFLD. To date, there is very limited data in patients with NAFLD and hyperuricaemia, from RCTs testing the effects of uric acid lowering agents. One study testing regression of hepatic steatosis in NAFLD patients with hyperuricaemia, with either low dose allopurinol (100mg/day) or febuxostat (40mg/day) has not yet reported. These treatments both lower serum uric acid concentrations [52] and the trial results will inform the efficacy of these agents to lower liver fat, after 3 months treatment.

In summary, our data in a very large cohort of young men and women, all of whom

had pre-existing NAFLD at study entry, shows that both a low baseline SUA level and a reduction in SUA level over time are both associated with NAFLD resolution.

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Conflict of interest

All authors declare that they have no conflict of interest.

Data Availability Statement

The data are not publicly available outside the hospital because of institutional review board restrictions (the data were not collected in a manner that could be widely distributed). However, the analytical methods are available from the corresponding author upon request.

Author contributions

All authors planned, designed, and implemented the study, including quality assurance and control. S Ryu analyzed the data and developed the analytical strategy. Y Chang and S Ryu supervised the field activities. Y Cho and Y Chang drafted the manuscript with additional writing input from C Byrne and S Wild. All authors interpreted the results and contributed to critical revisions of the manuscript.

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Legends of figures

Figure 1. Flow chart of the study population

Figure 2. Timeline of the study design. NAFLD resolution according to a short-term change in serum uric acid (SUA) level. 25,266 subjects <40 years of age with baseline ultrasound defined-NAFLD, with repeat measurements of SUA over time, were included. Subjects were categorized by quintiles of SUA changes during a median 1.9–year interval. Cox proportional hazards models were used to determine adjusted hazard ratios (aHRs) for NAFLD resolution by SUA changes

Table 1. Baseline characteristics of study participants by serum uric acid levels among men under the age of 40 years with NAFLD at baseline (n = 32,321)

Characteristics	Overall	Serum uric acid levels (mg/dL)					*P* for trend
		<5	5.0-5.9	6.0-6.9	7.0-7.9	≥8	
Number	32,321	1,195	3,548	9,359	10,111	8,108	
Age (years) [a]	34.1 (3.5)	34.5 (3.5)	34.6 (3.4)	34.3 (3.5)	34.1 (3.5)	33.6 (3.5)	<0.001
BMI (kg/m^2) [a]	26.4 (3.1)	25.8 (3.0)	25.5 (2.9)	25.9 (2.9)	26.4 (3.0)	27.4 (3.3)	<0.001
Obesity (%) [b]	64.6	56.4	53.4	58.9	65.4	76.3	<0.001
Waist circumference (cm) [a]	90.7 (7.9)	89.2 (7.6)	88.7 (7.4)	89.5 (7.3)	90.8 (7.7)	93.1 (8.3)	<0.001
Current smoker (%) [b]	31.8	34.6	34.7	33.1	31.1	29.5	<0.001
Alcohol intake (%) [b,c]	45.4	45.4	43.5	44.8	45.3	47.1	0.001
HEPA (%)[b]	13.6	12.9	15.1	13.6	13.1	13.7	0.265
Education level (%) [b,d]	92.7	90.3	92.9	92.4	93.1	92.7	0.086
Glucose-lowering agents (%) [b]	0.9	2.5	1.8	1.2	0.5	0.5	<0.001
Insulin (%) [b]	0.08	0.08	0.25	0.11	0.05	0.02	0.001
OHA (%) [b]	0.87	2.43	1.66	1.10	0.46	0.52	<0.001
Hypertension (%) [b]	13.0	11.3	11.6	11.5	12.3	16.5	<0.001
Medication for dyslipidemia (%)	1.6	2.3	1.9	1.7	1.3	1.5	0.002
Systolic BP (mmHg) [a]	116.8 (11.1)	115.1 (10.9)	115.2 (11.1)	115.7 (10.8)	116.8 (10.9)	118.9 (11.4)	<0.001
Diastolic BP (mmHg) [a]	74.3 (9)	73.2 (8.8)	73.1 (8.9)	73.5 (8.8)	74.4 (8.9)	75.8 (9.2)	<0.001
Glucose (mg/dL)[a]	97.2 (15.1)	103.6 (34.5)	98.9 (20.5)	97.0 (14.8)	96.4 (11.3)	96.6 (11.4)	<0.001
Total cholesterol (mg/dL) [a]	204.8 (34.8)	196.9 (34.4)	198.9 (34.2)	200.9 (33.5)	206.1 (34.5)	211.3 (35.9)	<0.001
LDL-C (mg/dL) [a]	137.0 (31.4)	129.8 (31.2)	131.5 (31)	133.5 (30.2)	138.4 (31.1)	142.6 (32.1)	<0.001
HDL-C (mg/dL) [a]	47.7 (10.4)	48.5 (11)	49.5 (11.1)	48.4 (10.6)	47.5 (10.3)	46.3 (9.8)	<0.001
Triglycerides (mg/dL) [e]	137 (99-191)	126 (91-178)	121 (89-170)	129 (93-179)	138 (101-192)	153 (111-214)	<0.001
ALT (U/L) [e]	34 (24-52)	30 (22-45)	29 (21-43)	31 (23-45)	35 (25-52)	41 (28-64)	<0.001
AST (U/L) [e]	24 (20-32)	23 (19-29)	22 (18-28)	23 (19-29)	25 (20-32)	27 (22-37)	<0.001

GGT (U/L) [e]	36 (25-55)	31 (22-48)	31 (22-47)	32 (23-48)	37 (26-56)	43 (30-66)	<0.001
HOMA-IR[e]	1.82 (1.26-2.63)	1.75 (1.21-2.54)	1.68 (1.16-2.37)	1.71 (1.18-2.41)	1.84 (1.27-2.63)	2.06 (1.41-2.99)	<0.001
hs-CRP (mg/L) [e]	0.8 (0.4-1.4)	0.6 (0.4-1.3)	0.6 (0.4-1.2)	0.7 (0.4-1.2)	0.8 (0.4-1.4)	1 (0.5-1.8)	<0.001
eGFR (mL/min/1.73 m^2) [e]	101.5 (12.6)	104.9 (12.0)	103.8 (11.8)	102.9 (12.0)	101.2 (12.6)	98.7 (13.2)	<0.001
Total energy intake (kcal/d)[e, f]	1515.3 (1158.4-1940.8)	1539.2 (1164.9-1943.7)	1510.3 (1163.3-1940.3)	1517.2 (1165.7-1936.2)	1519.3 (1161.8-1936.7)	1507.4 (1144.0-1946.3)	<0.001

Note: Data are presented as [a]means (standard deviation), [e]medians (interquartile range), or [b] percentages. Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48 ; glucose in mg/dL to mmol/L, ×0.05551; cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129

[c] ≥ 20 g of ethanol per day; [d]≥ College graduate; [f] among 103,514 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake).

Abbreviations: BMI, body mass index; BP, blood pressure; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HEPA, health-enhancing physical activity; OHA; oral hypoglycemic agents; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate.

Table 2. Baseline characteristics of study participants by serum uric acid levels among women under the age of 40 years with NAFLD at baseline (n = 6,162)

Characteristics	Overall	Serum uric acid levels (mg/dL)					*P* for trend
		<4	4.0-4.9	5.0-5.9	6.0-6.9	≥7	
Number	6,162	393	1,619	2,335	1,290	525	
Age (years) [a]	33.9 (4.0)	35.1 (3.5)	34.5 (3.8)	34 (3.8)	33.3 (4.2)	31.8 (4.3)	<0.001
BMI (kg/m^2) [a]	26.2 (4.2)	23.7 (3.4)	24.9 (3.5)	26.1 (3.9)	27.4 (4.3)	29.4 (5.0)	<0.001
Obesity (%) [b]	55.9	29.5	43.5	56.3	68.1	82.3	<0.001
Waist circumference (cm) [a]	86.4 (9.8)	81.2 (8.2)	83.7 (8.8)	86.4 (9.2)	88.8 (9.69)	93.0 (11.2)	<0.001
Current smoker (%) [b]	2.7	2.6	2.8	2.6	2.9	3.0	0760
Alcohol intake (%) [b,c]	12.5	11.7	11.1	12.8	13.4	13.5	0.052
HEPA (%)[b]	9.3	9.6	8.8	9.3	9.3	10.4	0.456
Education level (%) [b,d]	73.7	77.7	76.6	74.9	71.2	62.8	<0.001
Glucose-lowering agents (%) [b]	1.2	0.8	1.2	1.1	1.3	1.1	0.667
Insulin (%) [b]	0.23	0.00	0.25	0.26	0.23	0.19	0.767
Non-insulin (%) [b]	1.07	0.76	1.11	1.03	1.16	1.14	0.658
Hypertension (%) [b]	5.5	2.8	3.3	5.1	7.8	10.9	<0.001
Medication for dyslipidemia (%)[b]	1.5	0.3	0.7	0.9	1.0	1.9	0.007
Systolic BP (mmHg) [a]	107.5 (12.2)	103 (11.4)	105.1 (11.3)	107.3 (11.8)	109.8 (12.4)	113.1 (13)	<0.001
Diastolic BP (mmHg) [a]	68.2 (9.2)	65.4 (8.7)	66.6 (8.5)	68.1 (8.9)	69.6 (10)	71.5 (9.7)	<0.001
Glucose (mg/dL)[a]	96.9 (18.4)	99.3 (31.4)	96.4 (20.0)	96.2 (15.7)	97.3 (15.2)	99.1 (18.5)	0.270
Total cholesterol (mg/dL) [a]	195.0 (34.1)	184.9 (32.7)	190.5 (33.1)	194.1 (33.1)	201.2 (34.3)	205.0 (37.3)	<0.001
LDL-C (mg/dL) [a]	124.9 (31.1)	113.9 (29.8)	119.8 (29.9)	124.3 (30.2)	131.4 (30.8)	136.0 (33.7)	<0.001
HDL-C (mg/dL) [a]	54.1 (12.9)	58.6 (14.1)	56.5 (13.2)	54.0 (12.6)	51.9 (12.2)	49.3 (10.9)	<0.001
Triglycerides (mg/dL) [e]	106 (76-149)	82 (63-120)	93 (68-130)	107 (78-147)	121 (85-167)	132 (95-184)	<0.001
ALT (U/L)	18 (13-27)	14 (11-19)	16 (12-22)	18 (14-26)	22 (15-33)	28 (18-51)	<0.001
AST (U/L)	18 (15-23)	16 (14-19)	17 (15-20)	18 (15-22)	20 (16-25)	23 (18-35)	<0.001
GGT (U/L)	18 (13-27)	14 (10-21)	15 (12-22)	18 (14-26)	21 (16-33)	27 (19-42)	<0.001

HOMA-IR[e]	2.14 (1.40-3.24)	1.68 (1.16-2.44)	1.84 (1.22-2.66)	2.17 (1.42-3.11)	2.48 (1.66-3.82)	3.13 (1.98-4.75)	<0.001
hs-CRP (mg/L) [e]	1.0 (0.5-2.2)	0.5 (0.2-1.1)	0.7 (0.3-1.6)	1 (0.5-2.1)	1.4 (0.7-2.9)	2.1 (1.0-4.1)	<0.001
eGFR (mL/min/1.73 m^2) [e]	112.1 (11.2)	114.8 (9.8)	113.5 (9.95)	112.0 (11.1)	110.9 (11.7)	109.1 (13.8)	<0.001
Total energy intake (kcal/d)[e, f]	1308.3 (940.9-1721.7)	1317.7 (957.4-1746.2)	1298.0 (938.9-1723.0)	1316.1 (949.5-1728.8)	1308.6 (932.4-1729.6)	1295.6 (932.9-1653.3)	0.802

Note: Data are presented as [a]means (standard deviation), [e]medians (interquartile range), or [b] percentages. Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48; glucose in mg/dL to mmol/L, ×0.05551; cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129

[c] ≥ 20 g of ethanol per day; [d]≥ College graduate; [f] among 103,514 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake).

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; BP, blood pressure; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HEPA, health-enhancing physical activity; OHA; oral hypoglycemic agents; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate

Table 3. Resolution of NAFLD according to baseline serum uric acid levels among subjects with NAFLD at baseline (n = 38,483)

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)		HR (95% CI)[b] in a model with time-dependent variable
					Model 1	Model 2	
Men (n=32,321)							
<5	5,514.8	387	70.2	1.53 (1.37-1.71)	1.43 (1.28-1.6)	1.44 (1.29-1.61)	1.51 (1.35-1.69)
5.0-5.9	16,506.1	1,128	68.3	1.49 (1.38-1.61)	1.36 (1.26-1.47)	1.35 (1.25-1.46)	1.36 (1.26-1.47)
6.0-6.9	43,559.5	2,760	63.4	1.39 (1.31-1.48)	1.29 (1.21-1.37)	1.28 (1.20-1.36)	1.34 (1.26-1.43)
7.0-7.9	48,333.8	2,455	50.8	1.13 (1.06-1.20)	1.07 (1.01-1.14)	1.07 (1.002-1.14)	1.13 (1.06-1.20)
≥8	38,418.5	1,721	44.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
P for trend				<0.001	<0.001	<0.001	<0.001
Per 1 mg/dl decrease				1.13 (1.11-1.14)	1.10 (1.08-1.12)	1.10 (1.08-1.12)	1.10 (1.08-1.12)
Women (n=6,162)							
<4	1,170.9	228	194.7	2.37 (1.93-2.91)	1.53 (1.24-1.89)	1.61 (1.30-1.99)	1.35 (1.09-1.67)
4.0-4.9	5,178.6	896	173	2.11 (1.78-2.50)	1.52 (1.28-1.81)	1.56 (1.30-1.86)	1.35 (1.13-1.61)
5.0-5.9	8,626.5	1,033	119.7	1.51 (1.28-1.79)	1.19 (1.01-1.42)	1.22 (1.02-1.44)	1.17 (0.98-1.38)
6.0-6.	4,824.5	486	100.7	1.27 (1.06-1.52)	1.10 (0.92-1.32)	1.11 (0.93-1.34)	0.99 (0.83-1.19)
≥7	2,017.3	158	78.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
P for trend				<0.001	<0.001	<0.001	<0.001
Per 1 mg/dl decrease				1.27 (1.23-1.32)	1.16 (1.11-1.2)	1.17 (1.12-1.22)	1.13 (1.09-1.18)

The P-value for the interaction of sex, and serum uric acid levels (continuous variable) with resolution of NAFLD was 0.006 (Model 2).

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI (body mass index), year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension and medication for dyslipidemia; model 2: model 1 plus adjustment for hs-CRP, HOMA-IR, waist circumference and eGFR.

[b] Estimated from Cox proportional hazard models with uric acid levels, smoking, alcohol consumption, physical activity, total energy intake, BMI, insulin use, OHA use, history of hypertension, medication for dyslipidemia, hs-CRP, HOMA-IR, waist circumference and eGFR as time-dependent variables, baseline age, center, year of screening exam, and education level as time-fixed variables.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio

Table 4. Resolution of NAFLD according to quintiles of change in serum uric acid levels among participants with NAFLD at baseline (n = 25,266)

Serum uric acid change (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/10^3 PY)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)		HR (95% CI)[b] in a model with time-dependent variables
					Model 1	Model 2	
Men (n=22,108)							
Q1 (<▼0.5)	27,273.6	961	35.2	1.08 (0.99-1.18)	1.16 (1.06-1.27)	1.15 (1.05-1.26)	1.63 (1.49-1.78)
Q2 (▼0.5-▼0.2)	25,506.5	872	34.2	1.04 (0.94-1.13)	1.06 (0.97-1.16)	1.07 (0.97-1.16)	1.23 (1.11-1.35)
Q3 (▼0.1-0.2)	29,056.7	956	32.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q4 (0.3-0.7)	29,139.9	996	34.2	1.05 (0.96-1.15)	1.04 (0.95-1.14)	1.04 (0.96-1.14)	0.96 (0.87-1.06)
Q5 (≥0.8)	23,169.9	709	30.6	0.96 (0.87-1.05)	0.95 (0.86-1.04)	0.96 (0.87-1.06)	0.91 (0.82-1.02)
P for trend				0.049	<0.001	0.001	<0.001
Women (n=3,158)							

Q1 (<▼0.4)	4,236.3	247	58.3	0.94 (0.79-1.13)	1.05 (0.87-1.27)	1.15 (1.05-1.26)	1.78 (1.49-2.12)
Q2 (▼0.4-▼0.2)	2,502.3	159	63.5	0.99 (0.81-1.21)	1.05 (0.86-1.28)	1.07 (0.97-1.16)	1.18 (0.95-1.46)
Q3 (▼0.1-0.2)	3,809.5	245	64.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q4 (0.3-0.5)	2,651.5	140	52.8	0.81 (0.66-1.00)	0.81 (0.66-0.99)	1.04 (0.96-1.14)	0.89 (0.70-1.13)
Q5 (≥0.6)	3,791.6	205	54.1	0.88 (0.73-1.06)	0.87 (0.72-1.05)	0.96 (0.87-1.06)	0.77 (0.61-0.96)
P for trend				0.188	0.009	0.001	<0.001

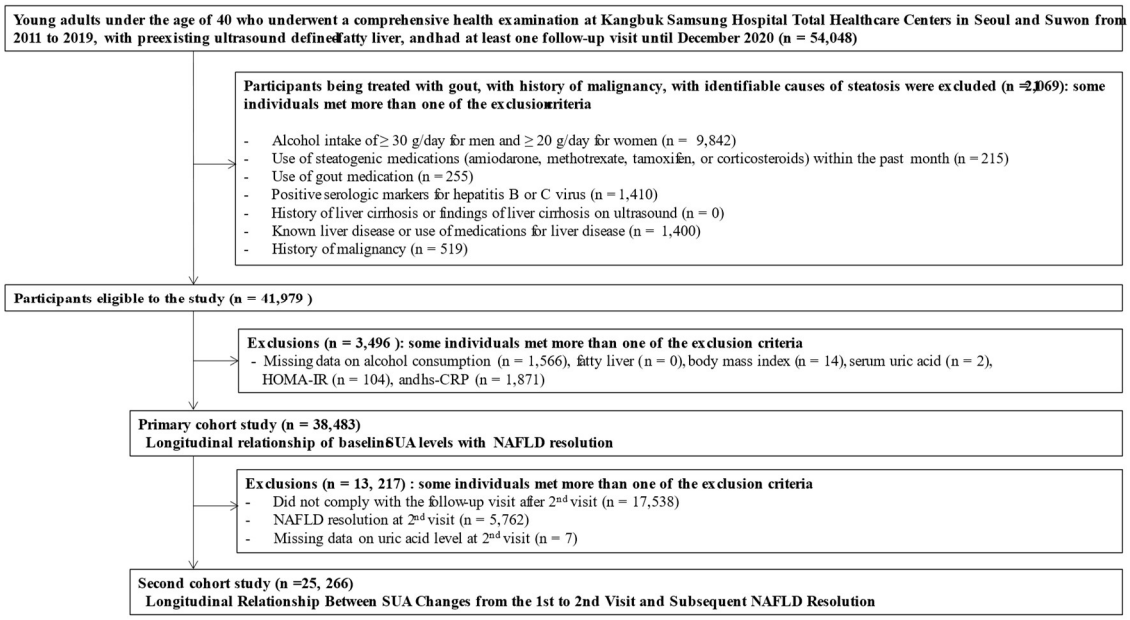
The P-value for the interaction of sex, and serum uric acid change (continuous variable) with the risk of NAFLD was 0.632 (Model 2).

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI, year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, and baseline uric acid; model 2: model 1 plus adjustment for hs-CRP, HOMA-IR, waist circumference and eGFR.

[b] Estimated from Cox proportional hazard models with uric acid levels, smoking, alcohol consumption, physical activity, total energy intake, BMI, insulin use, OHA use, history of hypertension, medication for dyslipidemia, hs-CRP, HOMA-IR, waist circumference and eGFR time-dependent variables, baseline age, baseline uric acid, center, year of screening exam, and education level as time-fixed variables.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio. ▼negative


Young adults under the age of 40 who underwent a comprehensive health examination at Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon from 2011 to 2019, with preexisting ultrasound defined fatty liver, and had at least one follow-up visit until December 2020 (n = 54,048)
Participants being treated with gout, with history of malignancy, with identifiable causes of steatosis were excluded (n = 2,069): some individuals met more than one of the exclusion criteria
- Alcohol intake of ≥ 30 g/day for men and ≥ 20 g/day for women (n = 9,842)
- Use of steatogenic medications (amiodarone, methotrexate, tamoxifen, or corticosteroids) within the past month (n = 215)
- Use of gout medication (n = 255)
- Positive serologic markers for hepatitis B or C virus (n = 1,410)
- History of liver cirrhosis or findings of liver cirrhosis on ultrasound (n = 0)
- Known liver disease or use of medications for liver disease (n = 1,400)
- History of malignancy (n = 519)
Participants eligible to the study (n = 41,979)
Exclusions (n = 3,496): some individuals met more than one of the exclusion criteria
- Missing data on alcohol consumption (n = 1,566), fatty liver (n = 0), body mass index (n = 14), serum uric acid (n = 2), HOMA-IR (n = 104), and hs-CRP (n = 1,871)
Primary cohort study (n = 38,483)
Longitudinal relationship of baseline SUA levels with NAFLD resolution
Exclusions (n = 13, 217) : some individuals met more than one of the exclusion criteria
- Did not comply with the follow-up visit after 2nd visit (n = 17,538)
- NAFLD resolution at 2nd visit (n = 5,762)
- Missing data on uric acid level at 2nd visit (n = 7)
Second cohort study (n =25, 266)
Longitudinal Relationship Between SUA Changes from the 1st to 2nd Visit and Subsequent NAFLD Resolution

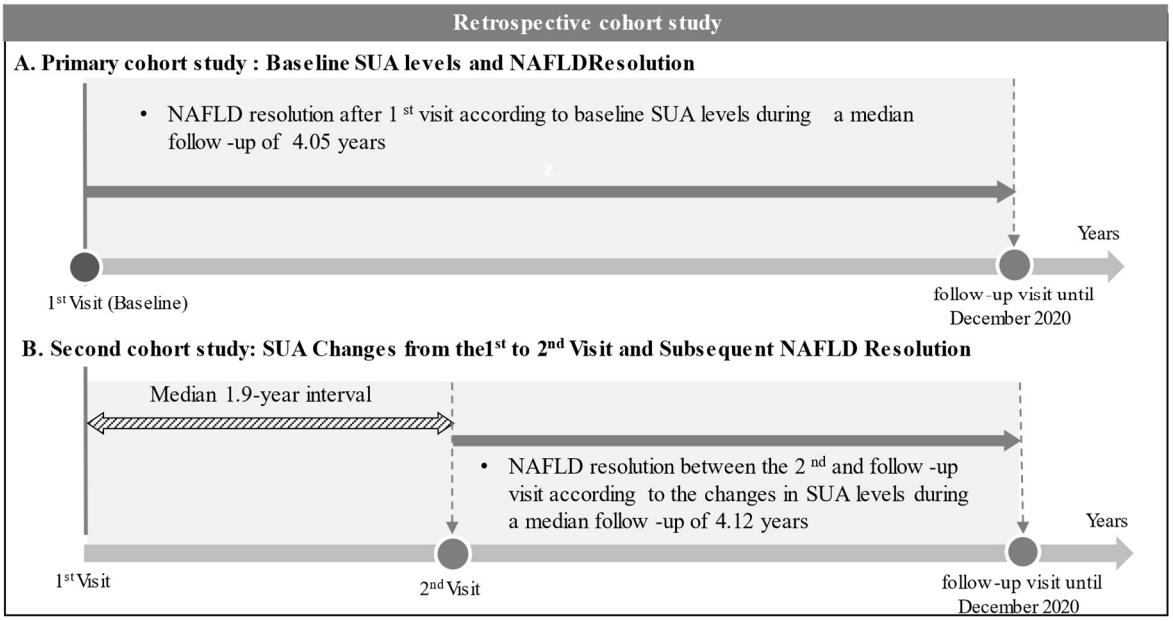

Retrospective cohort study
A. Primary cohort study : Baseline SUA levels and NAFLDResolution
• NAFLD resolution after 1 st visit according to baseline SUA levels during a median follow -up of 4.05 years
Years
1st Visit (Baseline)
follow -up visit until December 2020
B. Second cohort study: SUA Changes from the1st to 2nd Visit and Subsequent NAFLD Resolution
Median 1.9-year interval
• NAFLD resolution between the 2 nd and follow -up visit according to the changes in SUA levels during a median follow -up of 4.12 years
Years
1st Visit
2nd Visit
follow -up visit until December 2020

Table S1. Persistent resolution of NAFLD according to baseline serum uric acid levels among subjects with NAFLD at baseline (n= 38,483)

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men (n= 32,321)				
<5	6,099.0	190	31.2	1.60 (1.36-1.89)
5.0-5.9	18,329.6	544	29.7	1.45 (1.29-1.63)
6.0-6.9	47,889.0	1,283	25.4	1.36 (1.24-1.50)
7.0-7.9	52,316.3	1,062	19.1	1.11 (1.01-1.22)
≥8	41,163.2	670	15.1	1.00 (reference)
P for trend				<0.001
Per 1 mg/dl decrease				1.12 (1.09-1.15)
Women (n= 6,162)				
<4	1,330.1	153	115.0	2.07 (1.52-2.81)
4.0-4.9	6,280.1	532	84.7	1.74 (1.33-2.29)
5.0-5.9	9,950.5	547	55.0	1.34 (1.03-1.75)
6.0-6.	5,604.8	230	41.0	1.19 (0.89-1.58)
≥7	2,271.2	62	27.3	1.00 (reference)
P for trend				<0.001
Per 1 mg/dl decrease				1.23 (1.16-1.30)
P for interaction				0.004

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI(body mass index), year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, hs-CRP, HOMA-IR, waist circumference and eGFR.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio

Table S2. Persistent resolution of NAFLD according to tertiles of change in serum uric acid levels among participants with NAFLD at baseline (n= 25,266)

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men (n= 22,108)				
Q1 (<▼0.2)	55,195.7	745	13.5	1.15 (1.03-1.29)
Q2 (▼0.2-0.4)	44,204.7	543	12.3	1.00 (reference)
Q3 (≥0.4)	40,694.4	466	11.5	0.98 (0.86-1.11)
P for trend				0.005
Women (n= 3,158)				
Q1 (<▼0.2)	7,232.6	195	27.0	1.31 (1.04-1.65)
Q2 (▼0.2-0.3)	5,056.7	124	24.5	1.00 (reference)
Q3 (≥0.3)	5,936.7	132	22.2	0.98 (0.76-1.25)
P for trend				0.012
P for interaction				0.263

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, and baseline uric acid; model 2: model 1 plus adjustment for hs-CRP, HOMA-IR, waist circumference and eGFR.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio. ▼negative

Table S3. Resolution of NAFLD according to baseline serum uric acid levels among subjects with mild NAFLD at baseline (n= 29,739)

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men (n= 24,499)				
<5	4,335.5	350	80.7	1.35 (1.20-1.53)
5.0-5.9	13,570.2	1,032	76.0	1.26 (1.16-1.37)
6.0-6.9	34,614.1	2,532	73.1	1.23 (1.15-1.31)
7.0-7.9	35,534.9	2,135	60.1	1.04 (0.97-1.11)
≥8	24,156.1	1,361	56.3	1.00 (reference)
P for trend				<0.001
Per 1 mg/dl decrease				1.08 (1.06-1.10)
Women (n= 5,240)				
<4	1,064.2	225	211.4	1.69 (1.33-2.14)
4.0-4.9	4,714.2	862	182.9	1.59 (1.30-1.96)
5.0-5.9	7,248.6	953	131.5	1.26 (1.03-1.54)
6.0-6.	3,645.7	421	115.5	1.16 (0.94-1.43)
≥7	1,219.4	112	91.8	1.00 (reference)
P for trend				<0.001
Per 1 mg/dl decrease				1.17 (1.12-1.22)
P for interaction				<0.001

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI(body mass index), year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, hs-CRP, HOMA-IR, waist circumference and eGFR.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio

Table S4. Resolution of NAFLD according to quintiles of change in serum uric acid levels among subjects with mild NAFLD at baseline (n= 18,954)

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men (n= 16,371)				
Q1 (<▼0.5)	18,486.9	757	40.9	1.14 (1.03-1.27)
Q2 (▼0.5-▼0.2)	18,616.5	744	40.0	1.09 (0.98-1.20)
Q3 (▼0.1-0.2)	21,766.6	808	37.1	1.00 (reference)
Q4 (0.3-0.7)	22,201.0	851	38.3	1.04 (0.94-1.14)
Q5 (≥0.8)	17,272.1	606	35.1	0.96 (0.87-1.07)
P for trend				0.002
Women (n= 2,583)				
Q1 (<▼0.4)	3,189.9	212	66.5	1.15 (0.95-1.41)
Q2 (▼0.4-▼0.2)	2,026.2	136	67.1	1.07 (0.86-1.33)
Q3 (▼0.1-0.2)	3,188.6	216	67.7	1.00 (reference)
Q4 (0.3-0.5)	2,201.7	126	57.2	0.86 (0.69-1.07)
Q5 (≥0.6)	3,207.9	182	56.7	0.88 (0.72-1.07)
P for trend				0.003
P for interaction				0.370

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, and baseline uric acid; model 2: model 1 plus adjustment for hs-CRP, HOMA-IR, waist circumference and eGFR.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio. ▼negative

Table S5. Resolution of NAFLD according to baseline serum uric acid levels among subjects with moderate-to-severe NAFLD at baseline (n= 8,744)

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men (n= 7,822)				
<6	4,115.3	133	32.3	1.34 (1.09-1.65)
6.0-6.9	8,945.4	228	25.5	1.02 (0.86-1.21)
7.0-7.9	12,799.0	320	25.0	0.99 (0.85-1.15)
≥8	14,262.4	360	25.2	1.00 (reference)
P for trend				0.031
Per 1 mg/dl decrease				1.05 (0.99-1.10)
Women (n= 922)				
<5	571.1	37	64.8	0.92 (0.57-1.49)
5.0-5.9	1,377.9	80	58.1	0.86 (0.58-1.27)
6.0-6.	1,178.7	65	55.1	0.90 (0.60-1.33)
≥7	797.9	46	57.7	1.00 (reference)
P for trend				0.656
Per 1 mg/dl decrease				0.96 (0.84-1.10)
P for interaction				0.652

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI(body mass index), year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, hs-CRP, HOMA-IR, waist circumference and eGFR.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

Table S6. Resolution of NAFLD according to tertiles of change in serum uric acid levels among subjects with moderate-to-severe NAFLD at baseline (n= 6,312)

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men (n= 5,737)				
Q1 (<▼0.2)	15,676.7	332	21.2	1.03 (0.86-1.23)
Q2 (▼0.2-0.4)	10,436.7	219	21.0	1.00 (reference)
Q3 (≥0.4)	9,690.2	177	18.3	0.90 (0.74-1.10)
P for trend				0.178
Women (n= 575)				
Q1 (<▼0.2)	1,522.5	58	38.1	0.85 (0.54-1.33)
Q2 (▼0.2-0.3)	766.4	33	43.1	1.00 (reference)
Q3 (≥0.3)	888.1	33	37.2	0.91 (0.55-1.51)
P for trend				0.684
P for interaction				0.364

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, and baseline uric acid; model 2: model 1 plus adjustment for hs-CRP, HOMA-IR, waist circumference and eGFR.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio. ▼negative

Table S7. Resolution of NAFLD according to baseline serum uric acid levels among subjects with pre-existing NAFLD after excluding 4,490 subjects with either prevalent diabetes or incident diabetes during follow-up period

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men (n= 28,640)				
<5	4.527.9	349	77.1	1.46 (1.30-1.64)
5.0-5.9	14.265.4	1,009	70.7	1.32 (1.22-1.43)
6.0-6.9	37.840.2	2,515	66.5	1.26 (1.18-1.35)
7.0-7.9	41.851.3	2,239	53.5	1.06 (0.99-1.13)
≥8	32.265.7	1,548	48.0	1.00 (reference)
P for trend				<0.001
Per 1 mg/dl decrease				1.10 (1.08-1.12)
Women (n= 5,353)				
<4	1,016.0	217	213.6	1.61 (1.28-2.03)
4.0-4.9	4,513.5	829	183.7	1.53 (1.26-1.86)
5.0-5.9	7,205.8	955	132.5	1.24 (1.02-1.49)
6.0-6.	3,730.9	424	113.6	1.13 (0.93-1.38)
≥7	1,458.5	128	87.8	1.00 (reference)
P for trend				<0.001
Per 1 mg/dl decrease				1.16 (1.11-1.21)
P for interaction				0.014

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI(body mass index), year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, hs-CRP, HOMA-IR, waist circumference and eGFR.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio

Table S8. Resolution of NAFLD according to quintiles of change in serum uric acid levels among subjects with pre-existing NAFLD after excluding 3,613 subjects with either prevalent diabetes or incident diabetes during follow-up period

Baseline serum uric acid levels, (mg/dL)	Person-years (PY)	Resolution cases	Resolution rate (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men (n= 19,062)				
Q1 (<▼0.5)	21,902.8	806	36.8	1.13 (1.03-1.25)
Q2 (▼0.5-▼0.2)	21,623.3	772	35.7	1.06 (0.96-1.17)
Q3 (▼0.1-0.2)	25,023.6	860	34.4	1.00 (reference)
Q4 (0.3-0.7)	25,259.3	874	34.6	1.01 (0.92-1.11)
Q5 (≥0.8)	19,984.1	626	31.3	0.94 (0.85-1.05)
P for trend				0.001
Women (n= 2,591)				
Q1 (<▼0.4)	3,178.5	212	66.7	1.11 (0.91-1.35)
Q2 (▼0.4-▼0.2)	1,979.7	134	67.7	1.00 (0.80-1.24)
Q3 (▼0.1-0.2)	3,146.3	218	69.3	1.00 (reference)
Q4 (0.3-0.5)	2,114.6	120	56.7	0.79 (0.64-1.01)
Q5 (≥0.6)	3,149.1	178	56.5	0.75 (0.68-1.02)
P for trend				0.002
P for interaction				0.319

[a] Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI year of screening exam, smoking status, alcohol intake, physical activity, total energy intake, educational level, insulin use, OHA use, history of hypertension, medication for dyslipidemia, and baseline uric acid; model 2: model 1 plus adjustment for hs-CRP, HOMA-IR, waist circumference and eGFR.

Conversion factors for units: uric acid in mg/dL to μmol/L, ×59.48

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; CI, confidence interval; OHA; oral hypoglycemic agents; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; HR, hazard ratio. ▼negative