Metabolically Healthy Obesity and the Development of Nonalcoholic Fatty Liver Disease

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OBJECTIVES: **The risk of nonalcoholic fatty liver disease (NAFLD) among obese individuals without obesity-related metabolic abnormalities, a condition referred to as metabolically healthy obese (MHO), is largely unexplored. Therefore, we examined the association between body mass index (BMI) categories and the development of NAFLD in a large cohort of metabolically healthy men and women.**

METHODS: **A cohort study was conducted in 77,425 men and women free of NAFLD and metabolic abnormalities at baseline, who were followed-up annually or biennially for an average of 4.5 years. Being metabolically healthy was defined as not having any metabolic syndrome component and having a homeostasis model assessment of insulin resistance <2.5. The presence of fatty liver was determined using ultrasound.**

RESULTS: **During 348,193.5 person-years of follow-up, 10,340 participants developed NAFLD (incidence rate, 29.7 per 1,000 person-years). The multivariable adjusted hazard ratios (95% confidence intervals) for incident NAFLD comparing overweight and obese with normal-weight participants were 2.15 (2.06–2.26) and 3.55 (3.37–3.74), respectively. In detailed dose–response analyses, increasing baseline BMI showed a strong and approximately linear relationship with the incidence of NAFLD, with no threshold at no risk. This association was present in both men and women, although it was stronger in women (*P* for interaction <0.001), and it was evident in all clinically relevant subgroups evaluated, including participants with low inflammation status.**

CONCLUSIONS: **In a large cohort of strictly defined metabolically healthy men and women, overweight and obesity were strongly and progressively associated with an increased incidence of NAFLD, suggesting that the obese phenotype *per se*, regardless of metabolic abnormalities, can increase the risk of NAFLD.**

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide (1) and an emerging risk factor for type 2 diabetes mellitus, cardiovascular disease, and all-cause mortality (2–4). NAFLD may have a key role in the metabolic abnormalities associated with excess adiposity and is even considered a precursor of metabolic syndrome (5,6).

While excess adiposity is a major determinant of the high prevalence of NAFLD worldwide (6–10), the connection between overweight/obesity and NAFLD is still incompletely understood.

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Specifically, it is unclear whether obesity is a risk factor for NALFD in subjects who do not have any of the metabolic abnormalities associated with excess adiposity, a group often described as metabolically healthy obese (MHO) (11,12). The health implications of MHO are controversial (13–15). Only one study has evaluated the association of MHO with NAFLD (16). In this study, MHO subjects had an increased prevalence of NAFLD compared with metabolically healthy non-obese subjects, but the cross-sectional design of this study limited its ability to establish a temporal relation between obesity and NAFLD.

No cohort study has evaluated the role of MHO as a determinant of incident NAFLD among subjects free of NAFLD at baseline. Therefore, we examined the association between body mass index (BMI) categories and the development of NAFLD in a large cohort of metabolically healthy men and women who participated in a health screening examination program.

METHODS

Study population

The Kangbuk Samsung Health Study is a cohort study of men and women 18 years of age or older who underwent a comprehensive annual or biennial health examination at the clinics of the Kangbuk Samsung Hospital Total Healthcare Screening Center in Seoul and Suwon, South Korea, between 1 January 2002 and 31 December 2013. More than 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health screening exams of all employees, offered free of charge. The remaining participants voluntarily purchased screening exams at the health exam center.

The present analysis included all study participants with at least one follow-up visit through 31 December 2013 (n=233,676). We selected metabolically healthy participants by excluding any participant with at least one of the following metabolic abnormalities at baseline (11,17): (i) fasting blood glucose ≥100 mg/dl or current use of blood glucose-lowering agents (n=49,634) (18); (ii) blood pressure ≥130/85 mm Hg or current use of blood pressure-lowering agents (n=48,596) (18); (iii) triglyceride levels ≥150 mg/dl or current use of lipid-lowering agents (n=58,629) (18); (iv) high-density lipoprotein-cholesterol (HDL-C) <40 mg/dl in men or <50 mg/dl in women (n=32,880) (18); or (v) insulin resistance defined as homeostasis model assessment of insulin resistance (HOMA-IR) ≥2.5 (n=40,559) (19).

We further excluded participants who had any of the following conditions at baseline: fatty liver on ultrasound (n=60,522); history of malignancy (n=2,484); history of known liver disease (n=30,380); alcohol intake ≥30 g/day for men and ≥20 g/day for women (n=20,506); (1) positive serologic markers for hepatitis B or C virus (n=9,585); or use within the past 1 year of medications that could induce fatty liver such as amiodarone, tamoxifen, methotrexate, or corticosteroids (n=720) (1). Finally, we excluded participants with missing data for anthropometric measures, metabolic parameters, or liver ultrasonography (n=6,331). As some individuals met more than one criterion for exclusion, the total number of metabolically healthy subjects without NAFLD at baseline included in the study was 77,425 (30,502 men and 46,923 women; **Figure 1**).

The study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital, which waived the requirement for informed consent as we used only de-identified data obtained as part of routine health-screening exams.

Data collection

All examinations were conducted at Kangbuk Samsung Hospital Total Healthcare Screening Center clinics in Seoul and Suwon. At each clinic visit, demographic characteristics, smoking status, alcohol consumption, regular exercise, medical history, and medication use were collected by standardized, self-administered questionnaires. Smoking status was categorized into never, former, and current. Alcohol consumption was categorized into none, ≤10 g/day, and >10 g/day. We also assessed the weekly frequency of moderate- or vigorous-intensity physical activity.

Height and weight were measured by trained nurses with the participants wearing a lightweight hospital gown and no shoes. Height was measured to the nearest 1 mm using a stadiometer with the participant standing barefoot. Weight was measured to the nearest 0.1 kg on a bioimpedance analyzer (InBody 3.0 and Inbody 720, Biospace Co., Seoul, Korea) that was validated with regards to reproducibility and accuracy for body composition (20) and calibrated every morning before the testing started. BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured by trained nurses while subjects were in a sitting position with the arm supported at heart level.

Laboratory analyses

Blood specimens were sampled from the antecubital vein after at least a 10-h fast. Methods for measuring serum levels of glucose, uric acid, total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, HDL-C, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, insulin, and high-sensitivity C-reactive protein (hsCRP) have been reported elsewhere (21,22). The Laboratory Medicine Department of the Kangbuk Samsung Hospital is accredited by the Korean Society of Laboratory Medicine (KSLM) and the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL), and participates in the College of American Pathologists (CAP) Survey Proficiency Testing. Insulin resistance was assessed with the HOMA-IR equation: fasting blood insulin (μU/ml)×fasting blood glucose (mmol/l)/22.5.

Abdominal ultrasound for NAFLD assessment

Abdominal ultrasounds were performed using a Logic Q700 MR 3.5-MHz transducer (GE, Milwaukee, WI) by 11 experienced radiologists unaware of the study aims. Images were captured in a standard manner with the patient in the supine position with the right arm raised above the head. An ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or

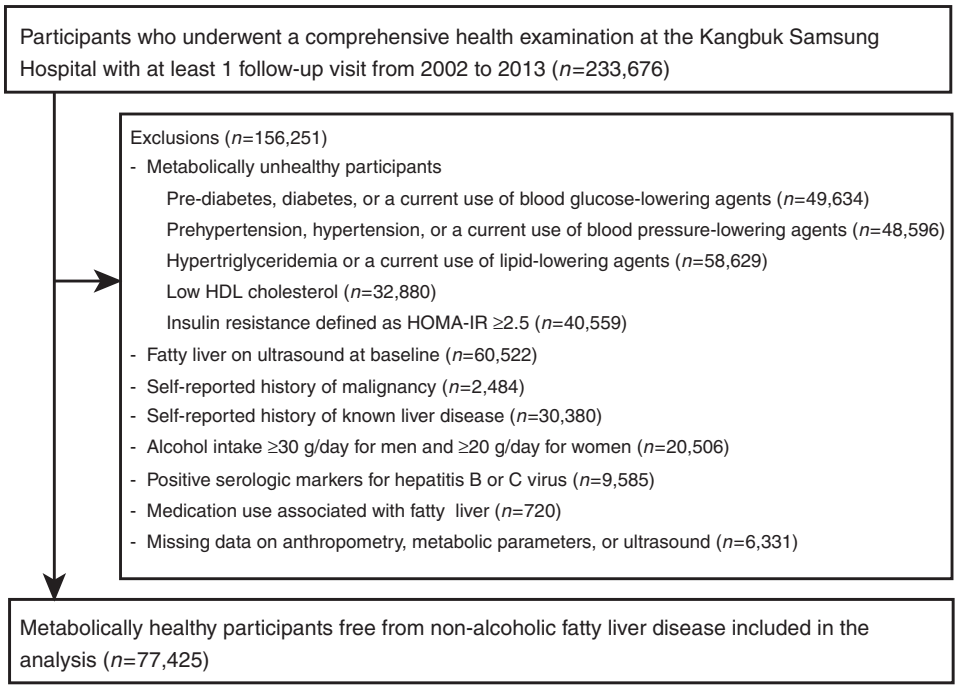

Figure 1. Flow chart of study participants.

spleen parenchyma (23). The inter- and intra-observer reliability for the diagnosis of fatty liver was very high (kappa statistics of 0.74 and 0.94, respectively) (24). Because we had already excluded participants with excessive alcohol use (≥20 g/day for women and ≥30 g/day for men) (1) as well as other identifiable causes of fatty liver at baseline as described in the exclusion criteria, incident cases of fatty liver were considered NAFLD.

Statistical analysis

BMI was categorized on the basis of criteria established for Asian populations (25,26): underweight, BMI <18.5 kg/m^2; normal-weight, BMI 18.5–23 kg/m^2; overweight, BMI 23–25 kg/m^2; and obesity, BMI ≥25 kg/m^2. The primary endpoint was the development of incident NAFLD. Follow-up for each participant extended from the baseline exam until the development of NAFLD or the last health exam conducted prior to 31 December 2013, whichever came first. Incidence rates were calculated as the number of incident cases divided by person-years of follow-up.

Because we started follow-up with all participants free of NAFLD at baseline, we could establish the first visit at which a participant showed NAFLD, but we could not determine the precise time of outcome development (which occurred at some point between the first visit with NAFLD and the previous visit). As a consequence, we used a parametric proportional hazards model to take into account this type of interval censoring (*stpm* command in Stata) (27). In these models, the baseline hazard function was parameterized with restricted cubic splines in log time with four degrees of freedom.

The primary analysis was based on clinical BMI categories, and we estimated adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for incident NAFLD comparing BMI categories at baseline with the normal-weight category. To determine the linear trends of risk, we used a continuous variable with the category number and tested its statistical significance in the regression models. Models were initially adjusted initially for age, sex, center, and year of examination, and then further adjusted for potential confounding factors including education level, smoking status, alcohol intake and exercise. We assessed the proportional hazards assumption by examining graphs of estimated log (−log) survival.

We conducted two additional types of dose–response analyses. First, we estimated the aHRs with 95% CIs associated with a BMI increase of 1 kg/m^2 at baseline using BMI as a continuous variable in the regression models. Second, we modeled BMI using restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the baseline distribution to provide a smooth yet flexible description of the relationship between BMI and incident NAFLD.

We also conducted two additional types of analyses. First, we conducted subgroup analyses to identify interactions between BMI categories and clinically relevant groups defined by age (<40 vs. ≥40 years), sex (women vs. men), smoking (current vs. noncurrent smokers), alcohol intake (<10 vs. ≥10 g/day), regular exercise (<3 vs. ≥3 times/week), and hsCRP levels (<1.0 vs. ≥1.0 mg/l). Second, we evaluated potential mediation by intermediate physiological variables by including baseline systolic blood pressure, fasting serum glucose, triglycerides, HDL-C, LDL-C, HOMA-IR, and hsCRP in the regression models. All analyses were performed using STATA version 13.0 (StataCorp LP, College Station, TX).

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RESULTS

The mean (s.d.) age and BMI of study participants at baseline was 35.7 (6.4) years and 21.5 (2.4) kg/m^2 (BMI range 12.6–36.1 kg/m^2), respectively. Participants in higher BMI categories were more likely to be older, male, and current smokers, were more likely to exercise and to drink alcohol, and have higher levels of fasting glucose, systolic and diastolic blood pressure, total cholesterol, triglycerides, LDL-C, uric acid, hepatic enzymes, insulin, HOMA-IR, and hsCRP and lower levels of HDL-C than normal-weight or underweight participants (**Table 1**).

We identified 10,340 incident cases of NAFLD during 348,193.5 person-years of follow-up (incident rate 29.7 per 1,000 person-years). The average follow-up period for participants was 4.5 years. In this group of metabolically healthy men and women, increasing baseline BMI showed a strong and graded dose–response relationship with the incidence of NAFLD (**Table 2**). In models adjusted for age, sex, center, and year of visit, the aHRs (95% CIs) for incident NAFLD comparing underweight, overweight, and obese participants with normal-weight participants were 0.28 (0.24–0.33), 2.12 (2.03–2.22), and 3.47 (3.30–3.66), respectively. In spline regression models, the dose–response relationship between baseline BMI and incident NAFLD was approximately linear throughout the range of BMI levels, with no threshold for risk (**Figure 2**). The aHR associated with a 1 kg/m^2 increase when BMI was introduced as a continuous variable in regression models was 1.29 (1.28–1.30). The association was virtually unchanged after adjustment for smoking, alcohol intake, exercise, and education.

The association between BMI and the incidence of NAFLD was observed in both men and women, but it was significantly stronger in women (*P* for interaction <0.001; **Table 3**) although the absolute incidence rate of NAFLD was much lower in women

Table 1. Baseline characteristics of study participants by body mass index category

Characteristics	Overall	BMI category (kg/m^2)				*P* for trend
		<18.5	18.5–22.9	23.0–24.9	≥25.0	
Number	77,425	7,363	49,663	13,942	6,457	
Age (years)[a]	35.7 (6.4)	33.7 (5.3)	35.6 (6.2)	36.7 (7.0)	36.9 (7.2)	<0.001
Male (%)	39.4	15.7	33.3	61.5	65.5	<0.001
Current smoker (%)	19.0	12.2	17.0	25.8	28.1	<0.001
Alcohol intake (%)[b]	4.0	1.1	3.1	6.7	8.1	<0.001
Vigorous exercise (%)[c]	14.6	7.0	13.9	18.1	21.0	<0.001
High education (%)[d]	80.2	84.8	80.2	79.0	77.4	<0.001
Systolic BP (mm Hg)[a]	106.7 (9.7)	103.1 (9.8)	106.0 (9.7)	109.3 (9.0)	110.7 (8.7)	<0.001
Diastolic BP (mm Hg)[a]	68.4 (7.6)	65.9 (7.3)	67.8 (7.5)	70.3 (7.3)	71.4 (7.2)	<0.001
Glucose (mg/dl)[a]	88.3 (6.3)	86.9 (6.6)	88.1 (6.3)	89.2 (6.1)	89.4 (6.1)	<0.001
Uric acid (mg/dl)[a]	4.8 (1.3)	4.2 (1.0)	4.6 (1.2)	5.3 (1.3)	5.5 (1.3)	<0.001
Total cholesterol (mg/dl)[a]	185.2 (29.8)	176.7 (27.7)	183.5 (29.2)	191.2 (30.6)	195.5 (30.8)	<0.001
LDL-C (mg/dl)[a]	105.1 (26.7)	93.5 (23.1)	102.8 (25.7)	113.5 (27.3)	118.5 (27.4)	<0.001
HDL-C (mg/dl)[a]	62.4 (12.1)	67.4 (12.1)	63.5 (12.0)	58.5 (11.0)	56.9 (10.7)	<0.001
Triglycerides (mg/dl)[d]	74 (57–96)	64 (52–80)	71 (56–92)	84 (65–108)	91 (70–115)	<0.001
ALT (U/l)[d]	16 (12–21)	14 (11–18)	15 (12–20)	19 (14–24)	21 (16–28)	<0.001
AST (U/l)[d]	20 (17–23)	19 (17–22)	19 (17–23)	21 (18–24)	21 (18–25)	<0.001
GGT (U/l)[d]	14 (10–20)	12 (10–16)	13 (10–18)	17 (12–25)	19 (13–28)	<0.001
Insulin (uIU/ml)[d]	6.2 (4.3–7.9)	5.5 (3.5–7.4)	6.1 (4.2–7.8)	6.5 (4.7–8.2)	6.8 (5.1–8.6)	<0.001
HOMA-IR[d]	1.3 (0.9–1.7)	1.2 (0.7–1.6)	1.3 (0.9–1.7)	1.4 (1.0–1.8)	1.5 (1.1–1.9)	<0.001
hsCRP (mg/l)[d]	0.3 (0.1–0.6)	0.2 (0.1–0.4)	0.2 (0.1–0.5)	0.4 (0.2–0.8)	0.5 (0.3–1.0)	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol.
[a]Data are means (s.d.).
[b]≥10 g of ethanol per day.
[c]≥3 times per week.
[d]Data are medians (interquartile range) or percentages.

Table 2. Development of nonalcoholic fatty liver disease (NAFLD) by body mass index category in metabolically healthy participants

BMI category (kg/m²)	Person-years	Number of incident cases	Incidence rate (per 1,000 person-years)	Age-, sex-, center-, and year of visit-adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)
<18.5	32,302.7	157	4.9	0.28 (0.24–0.33)	0.27 (0.23–0.32)
18.5–22.9	227,431.5	4,627	20.3	1.00 (reference)	1.00 (reference)
23.0–24.9	61,887.4	3,273	52.9	2.12 (2.03–2.22)	2.15 (2.06–2.26)
≥25.0	26,572.0	2,283	85.9	3.47 (3.30–3.66)	3.55 (3.37–3.74)
P for trend				<0.001	<0.001
Per 1 kg/m² increase in BMI				1.29 (1.28–1.30)	1.30 (1.29–1.31)

BMI, body mass index; CI, confidence intervals; HR, hazard ratio.
[a]Estimated from parametric proportional hazards models adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise and education level at baseline.

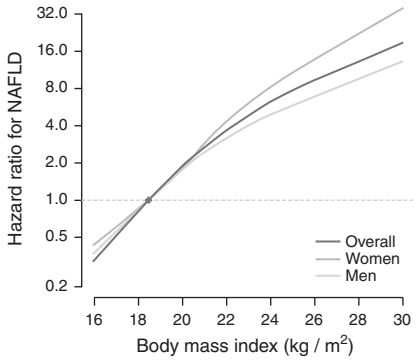

Figure 2. Multivariable-adjusted hazard ratios for incident nonalcoholic fatty liver disease by level of body mass index. Curves represent adjusted hazard ratios for incident nonalcoholic fatty liver disease based on restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the body mass index distribution. The reference value (diamond dot) was set at 18.5 kg/m² (corresponding to the 10th percentile in the overall population, 14th percentile in women, and 4th percentile in men). Models were adjusted for age, sex (overall analysis only), study center, year of visit, education, smoking, alcohol, and physical activity.

than in men (15.5 vs. 50.6 per 1,000 person-years, respectively). None of the other interactions tested was statistically significant (not shown). The association between BMI and incident NAFLD was evident even among the 66,642 participants with low hsCRP levels (<1.0 mg/l) at baseline. In this subgroup, the aHRs (95% CIs) for NAFLD comparing underweight, overweight, and obese participants to normal-weight participants were 0.28 (0.24–0.33), 2.16 (2.05–2.28), and 3.41 (3.20–3.62), respectively.

In order to explore whether the increased risk of NAFLD associated with increased BMI levels was mediated by residual metabolic components in MHO participants, we performed additional analyses adjusted for metabolic risk factors. Adjusting for fasting blood glucose, systolic blood pressure, triglyceride levels, HDL-C, HOMA-IR, hsCRP, and LDL-C slightly reduced the associations but they remained strong and statistically significant (**Appendix Table A1**).

DISCUSSION

In this large cohort study of metabolically healthy men and women without fatty liver at baseline, overweight and obesity were associated with an increased risk of incident NAFLD compared with normal weight. The association between BMI and incident NAFLD was strong and progressive, and was observed across the whole range of BMI values and in all subgroups evaluated. Furthermore, this association could not be explained by residual levels of metabolic risk factors below the standard cutoffs used to define metabolic abnormalities. Our findings indicate that excess adiposity is not a harmless condition and can induce the development of NAFLD even in subjects with no metabolic abnormalities.

A major strength of our study is that we used a strict definition of metabolic health to focus on a large cohort of men and women with no metabolic abnormalities and with no insulin resistance (11). Although there is no general agreement on the criteria to define MHO (13,15), other studies have typically focused on subjects with two or fewer metabolic components, but the risk of cardiovascular disease increases progressively with the number of metabolic syndrome components, beginning with one component (28,29). Indeed, each metabolic syndrome criterion is an established cardiovascular risk factor (30) and has been associated with increased risk of diabetes (31). Even though we used very strict criteria to define metabolically healthy participants using both metabolic syndrome criteria and insulin resistance, we still found a strong association between BMI and incident NAFLD that persisted after adjusting for metabolic components and after excluding participants with increased levels of inflammatory markers. As a consequence, our findings support that obesity *per se*, irrespective of insulin resistance or metabolic abnormalities, is a crucial element in the development of NAFLD.

To our knowledge, this is the first cohort study to evaluate the association between the MHO phenotype and the risk of developing NAFLD. Although obesity, insulin resistance, and metabolic abnormalities are well-known risk factors for NAFLD (32,33), the effect of excess adiposity in the absence of metabolic abnormalities

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Table 3. Development of nonalcoholic fatty liver disease (NAFLD) by body mass index categories in men and women

BMI category (kg/m^2)	Person-years	Number of incident cases	Incidence rate (per 1,000 person-years)	Multivariable-adjusted HR[a] (95% CI)
Men (n=*30,502*)				
<18.5	6,287.8	74	11.8	0.31 (0.24–0.39)
18.5–22.9	79,765.0	2,924	36.7	1.00 (reference)
23.0–24.9	37,666.2	2,437	64.7	1.82 (1.73–1.92)
≥25.0	17,216.5	1,690	98.2	2.87 (2.70–3.05)
P for trend				<0.001
Per 1 kg/m^2 increase in BMI				1.25 (1.23–1.26)
Women (n=*46,923*)				
<18.5	26,014.9	83	3.2	0.28 (0.22–0.35)
18.5–22.9	147,666.5	1,703	11.5	1.00 (reference)
23.0–24.9	24,221.2	836	34.5	3.03 (2.79–3.30)
≥25.0	9,355.5	593	63.4	5.76 (5.23–6.34)
P for trend				<0.001
Per 1 kg/m^2 increase in BMI				1.38 (1.36–1.39)

BMI, body mass index; CI, confidence intervals; HR, hazard ratio.

P value <0.001 for the interaction between sex and BMI categories for incident NAFLD.

[a]Estimated from parametric proportional hazards models adjusted for age, center, year of screening exam, smoking status, alcohol intake, regular exercise, and education level at baseline.

on the risk of NAFLD has rarely been reported in previous studies. A previous cross-sectional study showed a higher prevalence of fatty liver among MHO individuals, but this study did not consider other risk factors for fatty liver such as excessive alcohol consumption, or compare obese with non-obese participants (including overweight and underweight participants in the reference group) (16). Furthermore, the cross-sectional design resulted in temporal ambiguity of exposure and outcome.

The mechanisms whereby obesity contributes to NAFLD remain incompletely elucidated. Obesity is characterized by expanded adipose tissue that can increase free fatty acid delivery to the liver, possibly contributing to lipid accumulation in the liver (7). Furthermore, adipose tissue is an active endocrine organ that produces and releases adipokines with a number of pro-inflammatory and other potentially harmful effects (34). Adipocyte-derived hormones and cytokines including leptin, adiponectin, interleukin-6, and tumor necrosis factor-alpha may be involved in the pathogenesis of NAFLD (7). Indeed, the expression of inflammatory genes was similarly altered in both MHO and metabolically unhealthy obese subjects, highlighting that MHO individuals may exhibit an adverse profile comparable with that of metabolically unhealthy obese patients and that the MHO concept should be applied with caution (35). Finally, recent studies suggest that the MHO phenotype is transient and progresses to overt metabolic abnormalities in a significant proportion of individuals (36,37), although the association between BMI and incident NAFLD in our study was evident across all BMI levels and was not restricted to MHO participants. Further mechanistic studies, however, are needed to further understand why the MHO phenotype is associated with an increased incidence of NAFLD.

In the current study, the association between BMI and incident NAFLD was observed in both men and women but was stronger in women, even though the absolute incidence of NAFLD was over three times higher in men. Previous population-based studies also reported a significantly higher prevalence of NAFLD in men than in women (38), possibly related to more favorable lifestyle factors and the protective effect of sex hormones in women. The reasons for a stronger association of BMI with incident NAFLD in women are unclear, but excess adiposity may be a more important contributor to fatty liver in women than in men. Further research is needed to understand this sex-related difference.

Several limitations of our study need to be considered. First, our study used ultrasonography to detect incident fatty liver as the study endpoint: we did not perform histological confirmation or use more accurate measures such as MR spectroscopy to detect incident fatty liver, as these methods are not feasible in large population-based epidemiological studies (1,39). Abdominal ultrasound, however, has a high diagnostic accuracy for steatosis (40) and many population-based studies have relied on ultrasound assessment of NAFLD (39–41). Second, the definition of insulin resistance used in this study was based on HOMA-IR levels, not on invasive and time consuming euglycemic insulin clamp analyses. HOMA-IR and euglycemic insulin clamp data are strongly correlated (42), but we cannot discard some misclassification of insulin resistance status in our study. Third, we used BMI as a measure of obesity, but BMI does not distinguish fat tissue from lean tissue. If

the MHO group had a higher proportion of lean mass compared with normal-weight participants, the association between MHO and incident NAFLD in our study could be attenuated. In addition, waist circumference measurements were available for only a small fraction of study participants, limiting our ability to examine the role of fat distribution on the development of NAFLD. Fourth, we were unable to include dietary information, which could confound the association between BMI and NAFLD. Fifth, duration of obesity has been shown to be an independent risk factor for adverse health outcomes (43,44), but this information was not available in this study. Finally, our study was conducted in asymptomatic relatively young Korean men and women and our findings may not apply to other populations.

In addition to the large sample size that allowed us to select a group of participants with no metabolic abnormalities or insulin resistance at baseline, other strengths of our study included the prospective design, the use of carefully standardized clinical, imaging, and laboratory procedures, and the availability of detailed phenotyping of study participants. The relatively young age of our study cohort is also an advantage of our study, as findings in this group are less likely to be affected by survivor bias, biases induced by comorbidities, or use of multiple medications than findings in older cohorts.

In conclusion, overweight and obesity were strongly and progressively associated with an increased incidence of NAFLD in a strictly selected group of metabolically healthy men and women. These findings provide compelling evidence to support to the hypothesis that MHO is not a harmless condition and that the obese phenotype *per se*, regardless of metabolic abnormalities, can increase development of NAFLD. As a consequence, physicians should adequately address the increased risk of NAFLD and of other cardiovascular and metabolic abnormalities in metabolically healthy obese individuals in addition to counseling them about healthy weight and lifestyle.

CONFLICT OF INTEREST

Guarantors of the article: Seungho Ryu, MD, PhD and Eliseo Guallar, MD, DrPH.

Specific author contributions: Y. Chang, H.S. Jung, S. Ryu, and E. Guallar planned and designed the study, and directed its implementation, including quality assurance and control. Y. Chang and S. Ryu analyzed the data and designed the study's analytic strategy. S. Ryu, J. Cho, E.C. Chung, and H. Shin helped supervise the field activities. Y. Chang, H.S. Jung, S. Ryu, E. Guallar, Y. Zhang, K.E. Yun, M. Lazo, R. Pastor-Barriuso, J. Ahn, C.W. Kim, M. Cainzos-Achirica, D. Zhao, B.S. Suh, S. Rampal, and J. Cho helped conduct the literature review and prepare the Materials and Methods and the Discussion sections of the text. Y. Chang, H.S. Jung, S. Ryu, and E. Guallar drafted the manuscript. Y. Chang, H. Jung, J. Cho, Y. Zhang, K.E. Yun, M. Lazo, R. Pastor-Barriuso, J. Ahn, C.W. Kim, S. Rampal, M. Cainzos-Achirica, D. Zhao, B.S. Suh, E.C. Chung, B.S. Suh, H. Shin, E. Guallar, and S. Ryu interpreted the results. All authors contributed to critical revision of the manuscript.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Obesity is a strong risk factor for nonalcoholic fatty liver disease (NAFLD).
- ✓ There is controversy on the health implications of metabolically healthy obesity, that is, subjects who are obese but do not have metabolic abnormalities in spite of excessive adiposity.
- ✓ The risk of NAFLD among metabolically healthy obese individuals is unknown.

WHAT IS NEW HERE

- ✓ Overweight and obesity were strongly and progressively associated with an increased incidence of NAFLD even in metabolically healthy individuals.
- ✓ Obese phenotype *per se*, regardless of metabolic abnormalities, can increase the risk of NAFLD.

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APPENDIX

Mediation analysis of the association between body mass index and the development of nonalcoholic fatty liver disease

	Body mass index category (kg/m²)				*P* for trend
	Underweight (<18.5)	Normal-weight (18.5–22.9)	Overweight (23.0–24.9)	Obese (≥25.0)	
Model 1—aHR[a] (95% CI)	0.30 (0.26–0.35)	Reference	1.94 (1.85–2.03)	2.98 (2.83–3.15)	<0.001
Model 2—aHR[a] (95% CI)	0.31 (0.27–0.37)	Reference	1.86 (1.77–1.95)	2.81 (2.66–2.97)	<0.001

[a]Estimated from parametric proportional hazards models.

Model 1: adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, and education level at baseline, glucose, systolic blood pressure, triglycerides, HDL cholesterol, and HOMA-IR.

Model 2: further adjusted for LDL cholesterol and hsCRP.