Nonalcoholic fatty liver disease and risk of incident young-onset hypertension: effect modification by sex

Running title: Sex dimorphism, NAFLD and hypertension

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Abbreviation list

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; GGT, gamma-glutamyl transpeptidase; HR, hazard ratio; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PY, person-years; RAS, renin-angiotensin system; T2D, type 2 diabetes

Data availability statement

The data are not available to be shared publicly as we do not have IRB permission for distributing the data. However, data is available from the corresponding author on reasonable request.

ABSTRACT

Background and aims: Although nonalcoholic fatty liver disease (NAFLD) and hypertension are increasingly common among young adults, it is uncertain if NAFLD affects incidence of young-onset hypertension, and if the association is modified by sex. We investigated potential effect modification by sex on the association between NAFLD and incident hypertension in young adults (<40 years).

Method and results: This cohort study comprised 85,789 women and 67,553 men aged <40 years without hypertension at baseline. Hepatic steatosis was assessed by liver ultrasound and classified as mild or moderate/severe. Hypertension was defined as blood pressure (BP) ≥130/80 mmHg; self-reported history of physician-diagnosed hypertension; or current use of BP-lowering medications. Cox proportional hazard models were used to estimate hazard ratios (HRs; 95% confidence intervals [CIs]) for incident hypertension by NAFLD status (median follow-up 4.5 years). A total of 25,891 participants developed incident hypertension (incidence rates per 10^3 person-years: 15.6 for women and 63.5 for men). Multivariable-adjusted HRs (95% CIs) for incident hypertension comparing no NAFLD (reference) with mild or moderate/severe NAFLD were 1.68 (1.56–1.80) and 1.83 (1.60–2.09) for women and 1.21 (1.17–1.25) and 1.23 (1.17–1.30) for men, respectively. Stronger associations were consistently observed between NAFLD and incident hypertension in women, regardless of obesity/central obesity (all *p*-values for interaction by sex <0.001).

Conclusions: NAFLD is a potential risk factor for young-onset hypertension with a relatively greater impact in women and in those with more severe hepatic steatosis.

Keywords: Nonalcoholic fatty liver disease, sex dimorphism, sex difference, young-onset hypertension, cohort study

INTRODUCTION

Hypertension in young adults (<40 years of age) is estimated to occur in about 1 in 8 adults between 20 and 40 years of age [1]. Increasing prevalence of young-onset hypertension parallels that of obesity and other lifestyle- or metabolic-related diseases [1]. Hypertension at a young age can have detrimental consequences, including increased cardiovascular (CV) risks in middle age, early end-organ damage, as well as mortality [2-5]. With age being one of the strongest risk factors in the traditional model for estimating cardiovascular risk, the risk of uncontrolled blood pressure (BP) in young people is often underestimated, leading to delays in adequate management.

An approximately 7-fold increase in the incidence of nonalcoholic fatty liver disease (NAFLD) has been observed in young adults aged 18-39 years over a 20-year period [6]. Given the strong link between NAFLD and a wide range of CV complications including hypertension [7-9], the recent increase in NAFLD incidence is likely to be contributing to the recent rise in cardiovascular disease (CVD) incidence among young individuals [9]. However, previous literature investigating risk factors for hypertension has mainly focused on middle-aged or older adults, and the role of NAFLD on the risk of hypertension in young adults remains unclear.

Both NAFLD and BP show sexually dimorphic traits and prevalence of these conditions varies by sex across the lifespan [10, 11]. It is well established that women are protected from cardiometabolic risk due to female sex- and sex-related factors [12]. However, whether disparities by sex also apply to the association between NAFLD and hypertension in young adults aged <40 years has not been investigated. Given fundamental etiological differences in vascular physiology between men and women [13, 14], an accurate understanding of the role of sex as a risk modifier is essential in risk stratification, disease prevention, and optimizing therapeutic approaches to hypertension in young adults.

The present study aimed to investigate in young adults: a) the association between NAFLD (specifically mild and moderate/severe steatosis) and risk of incident hypertension and b) whether there was effect-modification by sex on these associations.

METHODS

Study participants

This cohort study is part of the Kangbuk Samsung Health Study, consisting of Korean men and women aged ≥18 years who underwent comprehensive annual or biennial examinations at the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea, as previously described [15]. The participants under 40 years of age who underwent a comprehensive health examination between January 2011 and December 2019 and had at least one follow-up visit before December 31, 2020 (n = 235,193) were initially included. After applying exclusion criteria (see Supplementary Materials), the final sample yielded 153,342 participants, comprising 85,789 women and 67,553 men.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB No. KBSMC 2022-04-058), which waived the need for informed consent owing to the use of de-identified retrospective data from routine health screening. All procedures performed in the study were in accordance with the Declaration of Helsinki regarding ethical standards for research involving human subjects.

Data collection

Standardized, self-administered questionnaires, physical measurements, abdominal ultrasonography results, and serum biochemical measurements were collected at each visit during the basic health check-up program [15] (see Supplementary Materials for further details).

Sitting BP, height, weight, and waist circumference were measured by trained nurses. Waist circumference was measured by trained personnel in the horizontal plane around the unclothed abdomen to the nearest 0.1 cm at the midpoint between the bottom of the rib cage and the top of the iliac crest, with the subjects standing with their weight equally distributed on both feet, their arms at their sides, and head facing straight forward. Abdominal obesity was defined as waist circumference ≥90 cm for men and ≥85 cm for women, which are specific for Korean populations [16, 17]. BP was measured using an automated oscillometric device (Model 53000; Welch Allyn, New York, NY) while participants were in a seated position with the arm supported at heart level. Three BP readings were

recorded for each participant, and the average of the second and third readings was used in the analyses to minimize measurement error. Hypertension was defined as systolic BP ≥130 mmHg, diastolic BP ≥80 mmHg (using the threshold for diagnosis of stage 1 hypertension), self-reported history of physician-diagnosed hypertension, or current use of antihypertensive medication, on the basis of the 2017 American College of Cardiology and American Heart Association Hypertension guidelines [18, 19]. A higher threshold of ≥140/90 mmHg was also used for supplementary analyses [18, 19].

Overweight was defined according to the Asian-specific criteria [20]: body mass index (BMI) of ≥23 kg/m^2.

Blood specimens were collected after at least 10 h of fasting. Levels of lipid profiles, liver enzymes, glucose, and high sensitivity C-reactive protein (hsCRP) were measured (see Supplementary Materials for further details).

Diagnosis of NAFLD

NAFLD was defined as the presence of fatty liver in the absence of excessive alcohol use (<20 g/day and <30 g/day for women and men, respectively) or any other identifiable cause [21]. Fatty liver was diagnosed on the basis of an abdominal ultrasound performed by experienced radiologists who were unaware of the study aim, using standard criteria, including a diffuse increase in fine echoes in the liver parenchyma in comparison with the kidney or spleen, deep beam attenuation, and bright vessel walls [22]. Radiologists graded hepatic steatosis as mild, moderate, or severe [23]. Mild hepatic steatosis was identified by a slight increase in liver echogenicity. Moderate hepatic steatosis was identified by a slightly impaired image of the intrahepatic vasculature and diaphragm, accompanied by increased liver echogenicity. Severe hepatic steatosis was identified by a marked increase in liver echogenicity, impaired penetration of the posterior segment of the right lobe, and poor or no image of the intrahepatic vasculature and diaphragm [24]. Degree of hepatic steatosis was categorized as mild or moderate/severe. The inter- and intra-observer reliability values for diagnosis of hepatic steatosis were substantial (kappa statistic of 0·74) and excellent (kappa statistic of 0·94), respectively [15].

Statistical analyses

The participants' characteristics according to the presence of NAFLD separately for women and men were summarized using descriptive statistics.

The primary exposure was any NAFLD and ultrasound-based assessment of severity of hepatic steatosis at baseline. The primary endpoint was incident hypertension during follow-up: (1) hypertension based on the threshold for stage 1 hypertension defined as ≥130/80 mmHg (details of the definition described earlier); and (2) hypertension based on stage 2 hypertension defined as ≥140/90 mmHg [18, 19] for the sensitivity analyses.

The follow-up duration for each participant was extended from the baseline examination until the development of the endpoint or the last health examination conducted prior to December 31, 2020, whichever came first. Incidence rates were calculated as the number of incident cases divided by follow-up person-years (PY). Cox proportional hazard models were used to estimate the hazard ratios (HRs) with 95% CIs for the development of incident hypertension. Initially, we adjusted for age. In multivariable-adjusted model, further adjustment was made for the study center (Seoul, Suwon), year of the screening examination, alcohol consumption, smoking status, physical activity, education level, lipid-lowering medication, and BMI (continuous). To evaluate the effects of NAFLD status changes between baseline and follow up, and also change in other covariates during the follow-up period, we performed additional analyses by introducing NAFLD status and other covariates/potential confounding factors, as time-varying covariates in the models (time-dependent models). The proportional hazards assumption was assessed via estimated log (-log) survival curves, and no violation of the assumption was found.

To assess the interaction effect by sex, the multivariable model included the presence of NAFLD, sex and the product term, as well as the potential confounders in the multivariable model. We calculated stratum-specific effect estimates with confidence intervals using the *–lincom* command in STATA after performing multivariable analysis. Since NAFLD is strongly associated with general and abdominal obesity, we also performed stratified analyses based on binary categories of overweight (defined as BMI of <23 and≥23 kg/m^2)[20] and abdominal obesity (waist circumference of <90 and

≥90 cm in men and <85 and ≥85 cm in women[25]). To account for potential confounding effects of metabolic comorbidities, additional analyses restricted to metabolically health individuals were also performed. The interactions between NAFLD status and sex on the risk of hypertension were assessed using likelihood ratio tests, comparing models with and without multiplicative interaction terms.

Statistical analyses were performed using STATA version 16.0 (StataCorp LP, College Station, TX, USA). Statistical significance was set at $p < 0.05$.

RESULTS

The baseline characteristics of the study population stratified by sex and NAFLD status are presented (**Table 1**). The mean (SD) age of women and men were 31.9 (3.7) and 32.0 (3.2) years, respectively. Age, lipid-lowering medication usage, obesity parameters (BMI, obesity, waist circumference), BP, glycemic parameters (glucose, HbA1c), total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), liver enzymes (gamma-glutamyl transpeptidase [GGT], alanine aminotransferase [ALT], and aspartate aminotransferase [AST]), hs-CRP levels, and HOMA-IR were higher in the NAFLD groups than in the non-NAFLD group, while high-density lipoprotein cholesterol (HDL-C) was higher in the non-NAFLD group than NAFLD groups both in men and women.

Table 2 presents the absolute and relative risks of incident hypertension based on NAFLD status and sex. Within over 700,000 person-years of follow-up (median follow-up 4.5 years), 25,891 subjects developed incident hypertension (incidence rates per 10^3 person-years were 35.3 [95% CI, 35.1-36.1] overall; 15.6 [95% CI, 15.2-15.9] for women and 63.5 [95% CI, 62.6-64.4] for men. In the age-adjusted model, NAFLD was positively associated with incident hypertension in both men and women, and hazard ratios were significantly higher for women than men. After further adjustments for sex, center, year of screening, alcohol consumption, smoking status, physical activity, education level, lipid-lowering medication, and BMI, the multivariable-adjusted HRs (95% CIs) for incident hypertension comparing NAFLD to no NAFLD were 1.67 (1.56–1.80) in women and 1.24 (1.20–1.28) in men (p for interaction by sex <0.001). The association was virtually unchanged in both groups when changes in status of NAFLD or other covariates during the follow-up period were treated as time-

varying covariates. Similar findings were observed in the sensitivity analyses where the risk of incident stage 2 hypertension was assessed as an outcome (**eTable 1**) and when HOMA-IR was further adjusted for (**eTable 2**).

The risk of incident hypertension according to NAFLD and its severity (assessed by the ultrasound) were also investigated (**Table 3**). In the age-adjusted model, the degree of NAFLD severity was positively associated with incident hypertension in a dose-response manner among men and women. After further adjustments for confounders, these associations were attenuated, but the trends persisted in both sexes; the multivariable-adjusted HRs (95% CIs) for incident hypertension comparing mild NAFLD and moderate/severe NAFLD to no NAFLD group as the reference were 1.67 (1.54–1.80) and 1.78 (1.52–2.08) in women and 1.23 (1.19–1.27) and 1.28 (1.22–1.35) for men, respectively. These associations remained similar when the covariates were treated as time-dependent variables (as reported in the final column of **Table 3**). After further adjustment for HOMA-IR (**eTable 3**), increased excess risks of hypertension was found in women with mild NAFLD. However, the associations were no longer significant in women with moderate/severe NAFLD. When risks of stage 2 hypertension were assessed based on NAFLD severity (**eTable 4**), the associations between mild and moderate/severe NAFLD at baseline and incident stage 2 hypertension were even stronger compared with corresponding risks of stage 1 hypertension. In a model with time-dependent variables, HRs (95% CIs) for incident hypertension defined by the higher threshold ≥140/90 mmHg, comparing no NAFLD (reference) to mild, or moderate/severe NAFLD were 2.01 (1.63–2.48) and 2.45 (1.73–3.45) for women; and 1.45 (1.28–1.64) and 1.55 (1.31–1.82) for men.

Table 4 presents the association between NAFLD and stage 1 hypertension in BMI strata. In both overweight and non-overweight groups with NAFLD, HRs for hypertension were higher in women than in men. Similar patterns of associations were consistently observed when participants were stratified based on abdominal obesity instead of overweight status (all *p*-values for interaction by sex <0.001).

When we performed analyses restricted to metabolically healthy individuals (n = 91,628), the association between NAFLD and development of stage 1 hypertension remained similar to the original

analyses both in women and men (**eTable 5**). Similarly, overall stronger relative excess risks of stage 1 hypertension were found in women with increasing severity of NAFLD compared with men.

In the analyses evaluating the risks of hypertension by NAFLD severity based on NFS (**eTable 6**) and FIB-4 (**eTable 7**), overall similar results were observed, with stronger excess risks among women compared with men. However, significance was not detected for the groups with intermediate/high FIB-4.

DISCUSSION

In this cohort study of 153,342 Korean young adults with a median follow up of almost five years, our novel data shows that NAFLD is a potential risk factor for young-onset hypertension. The relative impact of NAFLD as a risk factor is greater in women, and moderate/severe hepatic steatosis is associated with a greater risk of developing incident hypertension than mild liver steatosis.

Previous epidemiological studies have shown that NAFLD and its severity are associated with prevalent and incident hypertension in general populations [8, 26, 27]. A recent meta-analysis of 11 cohort studies suggests that NAFLD is associated with approximately a 1.6-fold increased risk of incident hypertension [28]. However, limited data are available on the role of NAFLD in the development of hypertension in younger adults under 40 years. Most of the existing studies to date have also not considered sex-specific effects of NAFLD, which is known to be crucial in understanding the incidence, progression and management of cardiometabolic diseases [11, 29-31]. Our study, to the best of our knowledge, is the first to demonstrate that NAFLD is associated with increased risk of incident hypertension in young adults. In addition, our study has revealed that the NAFLD-hypertension relationship differs by sex, thus underscoring the need to consider the role of sex in estimating risk of cardiovascular and other outcomes associated with NAFLD in young people.

Our data are consistent with the notion that cardiometabolic protection in women is diminished in the presence of an underlying metabolic condition, as consistently reported in other studies conducted in the context of obesity, type 2 diabetes (T2D), or metabolic syndrome [32-34]. In our study, the absolute incidence of hypertension in women with NAFLD was similar to that of men without NAFLD.

The finding aligns with several lines of evidence including a previous systematic review that found no differences in prevalence of NAFLD between men and women with T2D, in contrast to the general population, in which men are more frequently affected than women [35]. Other studies have shown that the presence of NAFLD attenuated protection against CVD in premenopausal women [32, 33]. Similar patterns were also observed in our recent work demonstrating sex-specific associations between NAFLD and T2D [36]. Taken together, in young women, whose cumulative exposure to metabolic risks is relatively low, NAFLD may represent an increased cardiometabolic burden in these individuals that may directly or indirectly contribute to higher BP, which needs to be further confirmed in additional work.

Previously, the extent to which NAFLD is associated with increased risk of incident hypertension beyond obesity or diabetes mellitus [9] has been uncertain. Our study addressed this issue by restricting the study sample to individuals without diabetes or other known comorbidities at baseline as well as evaluating the association in lean and overweight people using both general and abdominal measures of obesity. In the stratified analyses higher hazard ratios of NAFLD for hypertension were consistently observed in women than men regardless of overweight and abdominal obesity. The significant excess risks associated with NAFLD in groups without abdominal obesity suggest that the effect of NAFLD on blood pressure is not solely attributed to overall or central obesity [37]. Moreover, in our analyses of a sample with metabolically healthy individuals only, the associations did not change. These data suggest that, although the NAFLD group had a greater number of individuals with a range of unfavorable metabolic abnormalities, these cardiometabolic comorbidities may not fully account for the observed association. Further exploration is required to elucidate whether there are potentially independent effects of NAFLD on hypertension development beyond central obesity.

While pathophysiological links between NAFLD and hypertension in the general population have been relatively well described in previous literature [9], with some of the key mediators involving insulin resistance, altered adipokine profiles, sympathetic nerve activation, and renin-angiotensin system (RAS), mechanisms underlying sex dimorphism in the association between NAFLD and hypertension are less clear and complex. NAFLD is associated with increased leptin levels [37-39].

298 Leptin may act in a sexually dimorphic fashion by promoting sympathetic activation in males and
299 stimulates aldosterone production in females [37]. Another mechanism may be related to the activation
300 of RAS by systemic inflammation in NAFLD [9]. RAS components such as renin are responsive to the
301 altering levels of estradiol [40], and there are also sex differences in the basal levels of several key
302 molecules involved in RAS activation (e.g., renin, angiotensin-converting enzyme) [14], suggesting the
303 effects of NAFLD on RAS may be different between sexes. In addition, while NAFLD may increase
304 vasoconstriction by decreasing the production of nitric oxide (NO) [41], estrogen may counteract this
305 effect by increase NO bioavailability by upregulating endothelial NOS. Moreover, inherent sex
306 differences in the balancing of sympathetic nerve activity [42] and responses to oxidative stress [43,
307 44], which are implicated as potential mechanisms linking NAFLD and hypertension [9], have been
308 reported. Further studies are necessary to determine whether there is a role of hepatic steatosis and its
309 severity in the pathogenesis of hypertension and whether there are inherent differences by sex in the
310 mechanisms.

311 There are some limitations to our study. First, NAFLD and its severity were assessed based on
312 ultrasound, instead of liver biopsy. The use of liver biopsy, however, for the purpose of routine
313 screening is considered unethical and not feasible. Moreover, liver ultrasound is widely accepted tools
314 in epidemiologic studies and reliably identifies NAFLD [45]. That said, further studies using diagnostic
315 tools with improved accuracy are needed to confirm our findings. Second, the determination of BP was
316 based on a single-day measurement, although it should be noted three readings were taken in our study.
317 This approach may lead to a misclassification of BP categories, possibly underestimating true
318 associations between NAFLD and incident hypertension. Third, causality cannot be determined owing
319 to the observational nature of our study, and a possibility of residual confounding remains due to
320 unmeasured confounders. Fourth, although we excluded postmenopausal women including those with
321 surgical/radiation-induced menopause, we did not exclude women with other potential causes of
322 menstrual irregularities, such as synthetic hormone use, intrauterine devices, or premature menopause
323 during follow-up, which may lead to a possibility of residual confounding. Considering these
324 reproductive factors would be important since the extent of cardioprotection in women can be dictated

by reproductive hormonal status in women. However, in our sample, none of the women were taking oral contraceptives or using intrauterine devices. In addition, only 1.1% of the women reached menopause during follow-up. Thus, it is unlikely that these factors had a substantial impact on our results. Other conditions, such as polycystic ovary syndrome (PCOS), that may affect the menstrual cycle as well as metabolic status [46] were not considered owing to the lack of data. Lastly, our study of young Koreans means that the findings may not be generalizable to other populations of different ages, ethnicities, or with different comorbidities.

Our study has several notable strengths. The longitudinal, prospective design enabled us to observe the temporal associations between NAFLD, with the risk of incident hypertension. Furthermore, the large sample size, the use of carefully standardized clinical, imaging, and laboratory procedures, and the inclusion of lifestyle factors, and the repeated measurements allowed us to account for changes in possible confounders over time, between baseline and follow up, as time-varying covariates. In addition, the outcome was ascertained using multiple BP measurements, which reduced the potential errors in diagnosis (e.g., white coat hypertension). Lastly, the inclusion of relatively healthy, younger individuals i) reduced the potential for survivor bias caused by selecting subjects with severe diseases as well as comorbidity-related bias, which is a common limitation of previous studies involving patients with biopsy-proven advanced stage NAFLD and ii) eliminated the potential confounding effects of menopause which is known to affect both NAFLD pathophysiology [29, 47] as well as BP [42], allowing us to better determine sex-specific differences in the associations.

Conclusion

Our results demonstrate that NAFLD and its severity increase the risk of young-onset incident hypertension, even in lean individuals, showing a stronger association in young women than in men. As NAFLD is becoming an important public health concern, especially among young adults, the sex-specific multisystem consequences of NAFLD in younger people deserves more attention.

Author Contributions

Yejin Kim: interpretation of data, drafting and critical revision of the manuscript.

Yoosoo Chang: study concept and design, acquisition of data, interpretation of data, drafting and critical revision of the manuscript

Seungho Ryu: study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript

Soyoung Park: study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript

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Sarah H. Wild: interpretation of data, writing and critical revision of the manuscript

Christopher D Byrne: study concept and design, interpretation of data, writing and critical revision of the manuscript

All authors confirm that they had full access to all the data.

Conflict of interest

All authors declare that they have no conflict of interests.

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Table 1. Estimated mean values (95% CI) and adjusted[a] proportions (95% CI) of baseline characteristics for population strata defined by sex and NAFLD status among young adults under the age of 40 years (n = 153,342)

Characteristics	Women		P value	Men		*p*-value
	No NAFLD	NAFLD		No NAFLD	NAFLD	
Number of participants	80,593	5,196		45,102	22,451	
Age (years)	32.8 (32.8-32.8)	33.8 (33.7-33.9)	< 0.001	32.8 (32.8-32.9)	33.9 (33.9-34.0)	< 0.001
Alcohol intake (%) [b]	11.8 (11.6-12.1)	13.0 (12.1-13.9)	0.014	43.5 (43.0-43.9)	43.1 (42.5-43.8)	0.378
Current smoker (%)	1.7 (1.6-1.8)	2.7 (2.3-3.2)	< 0.001	28.6 (28.2-29.1)	30.7 (30.1-31.3)	< 0.001
Higher education (%) [d]	85.2 (84.9-85.4)	73.8 (72.5-75.1)	< 0.001	93.2 (93.0-93.4)	93.3 (92.9-93.6)	0.790
HEPA (%) [c]	11.0 (10.8-11.2)	11.4 (10.5-12.2)	0.449	17.8 (17.5-18.2)	14.0 (13.5-14.5)	< 0.001
Lipid-lowering medication use (%)	0.1 (0.1-0.1)	0.3 (0.2-0.5)	< 0.001	0.4 (0.4-0.5)	1.0 (0.9-1.1)	< 0.001
Obesity (%) [e]	5.4 (5.3-5.6)	52.5 (51.2-53.9)	< 0.001	19.2 (18.9-19.6)	59.9 (59.3-60.6)	< 0.001
Body mass index (kg/m^2)	20.7 (20.7-20.8)	25.7 (25.6-25.8)	< 0.001	23.1 (23.1-23.1)	25.9 (25.9-26.0)	< 0.001
Waist circumference (cm)	73.1 (73.1-73.2)	85.1 (84.9-85.3)	< 0.001	81.7 (81.7-81.8)	89.6 (89.5-89.6)	< 0.001
SBP (mmHg)	98.9 (98.8-98.9)	104.3 (104.0-104.5)	< 0.001	109.2 (109.2-109.3)	112 (111.9-112.1)	< 0.001
DBP (mmHg)	62.9 (62.9-63.0)	65.6 (65.4-65.7)	< 0.001	67.9 (67.8-67.9)	69.7 (69.7-69.8)	< 0.001
Glucose (mg/dl)	89.2 (89.2-89.3)	93.6 (93.4-93.8)	< 0.001	92.2 (92.2-92.3)	94.5 (94.4-94.6)	< 0.001
HbA1c (%)	5.4 (5.4-5.4)	5.6 (5.6-5.6)	< 0.001	5.4 (5.4-5.4)	5.5 (5.5-5.5)	< 0.001
Total cholesterol (mg/dl)	179.8 (179.6-180.0)	192.9 (192.1-193.7)	< 0.001	188.0 (187.7-188.3)	201.6 (201.1-202.0)	< 0.001
LDL-C(mg/dl)	103.9 (103.7-104.1)	123.1 (122.4-123.8)	< 0.001	120.2 (120.0-120.5)	135.1 (134.7-135.5)	< 0.001
HDL-C (mg/dl)	68.1 (68.0-68.2)	55.3 (54.9-55.6)	< 0.001	57.0 (56.9-57.2)	48.4 (48.2-48.5)	< 0.001
Triglycerides (mg/dl)	71.6 (71.4-71.9)	117.0 (116.0-118.0)	< 0.001	97.8 (97.2-98.5)	148.0 (147.1-148.9)	< 0.001
GGT (U/L)	14.0 (14.0-14.1)	22.7 (22.4-23.0)	< 0.001	26.6 (26.3-26.9)	42.8 (42.3-43.2)	< 0.001
ALT (U/L)	13.6 (13.5-13.7)	23.4 (23.1-23.7)	< 0.001	22.2 (22.0-22.3)	40.4 (40.1-40.6)	< 0.001
AST (U/L)	17.5 (17.5-17.6)	20.8 (20.5-21.0)	< 0.001	21.6 (21.4-21.7)	27.2 (27.0-27.4)	< 0.001
hs-CRP (mg/L)	0.76 (0.74-0.78)	1.77 (1.70-1.84)	< 0.001	0.96 (0.93-0.99)	1.36 (1.32-1.40)	< 0.001
HOMA-IR	1.19 (1.19-1.20)	2.43 (2.41-2.46)	< 0.001	1.18 (1.17-1.19)	1.94 (1.93-1.95)	< 0.001

[a]Adjusted for age; [b] ≥10 g/day; [c] health-enhancing physical activity; [d] ≥college graduate; [e] BMI ≥25 kg/m^2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; GGT, gamma-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physical activity; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure

Table 2. Absolute and relative estimates of stage 1 hypertension incidence for population strata defined by sex and NAFLD status among young adults under the age of 40 years (n = 153,342)

	Person-years	Incident cases	Incidence density (/ 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
Women (n = 85,789)						
No NAFLD	408,783	5,701	13.9	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD	23,981	1,035	43.2	2.99 (2.79-3.19)	1.67 (1.56-1.80)	1.70 (1.59-1.81)
Men (n = 67,553)						
No NAFLD	208,605	10,727	51.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD	93,083	8,428	90.5	1.69 (1.64-1.74)	1.24 (1.20-1.28)	1.21 (1.17-1.25)

The *P*-value for the interaction of sex and NAFLD status with the risk of hypertension was <0·001 (Multivariable-adjusted model).
[a] Estimated from Cox proportional hazards models; multivariable Model 1 was adjusted for age, center, year of screening examination, alcohol consumption, smoking status, physical activity, education level, lipid-lowering medication, and BMI.
[b] Estimated from Cox proportional hazard models with NAFLD status, smoking status, alcohol consumption, physical activity, BMI, and lipid-lowering medication, as time-dependent categorical variables, and baseline age, center, year of screening examination, and education level as time-fixed variables.
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PY, person-years

Table 3. Absolute and relative estimates of stage 1 hypertension incidence for population strata defined by sex and NAFLD severity status based on ultrasound among young adults under the age of 40 years (n = 153,342)

	Person-years (PY)	Incident cases	Incidence density (/ 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
Women (n = 85,789)						
No NAFLD	408,783	5,701	13.9	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, mild	21,357	859	40.2	2.76 (2.57-2.97)	1.67 (1.54-1.80)	1.68 (1.56-1.80)
NAFLD, moderate/severe	2,624	176	67.1	4.91 (4.23-5.71)	1.78 (1.52-2.08)	1.83 (1.60-2.09)
p for trend				< 0.001	< 0.001	< 0.001
Men (n = 67,553)						
No NAFLD	208,605	10,727	51.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, mild	76,071	6,495	85.4	1.58 (1.54-1.63)	1.23 (1.19-1.27)	1.21 (1.17-1.25)
NAFLD, moderate/severe	17,012	1,933	113.6	2.16 (2.06-2.27)	1.28 (1.22-1.35)	1.23 (1.17-1.30)
p for trend				< 0.001	< 0.001	< 0.001

The *p-value* for the interaction of sex and NAFLD categories for the risk of hypertension was <0·001 (Multivariable-adjusted model).

[a] Estimated from Cox proportional hazards models; multivariable model was adjusted for age, center, year of screening examination, alcohol consumption, smoking status, physical activity, education level, lipid-lowering medication, and BMI.

[b] Estimated from Cox proportional hazard models with NAFLD categories, smoking, alcohol consumption, physical activity, BMI, medication for lipid-lowering as time-dependent categorical variables and baseline age, center, year of screening examination, and education level as time-fixed variables.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PY, person-years

Table 4. Absolute and relative estimates of stage 1 hypertension incidence for population strata defined by sex and adiposity status by NAFLD among young adults under the age of 40 years

	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Strata by overweight	Non-overweight (n = 94,910)				Overweight[b] (n = 58,432)			
Women								
No NAFLD	348,462	4,061	11.7	1.00 (reference)	60,321	1,640	27.2	1.00 (reference)
NAFLD	6,949	170	24.5	1.95 (1.67-2.28)	17,032	865	50.8	1.83 (1.68-1.98)
Men								
No NAFLD	109,440	4,557	41.6	1.00 (reference)	99,165	6,170	62.2	1.00 (reference)
NAFLD	14,281	835	58.5	1.35 (1.25-1.45)	78,802	7,593	96.4	1.50 (1.45-1.55)
p for interaction by sex				<0.001				<0.001
Strata by abdominal obesity	No abdominal obesity (n = 131,314)				Abdominal obesity[c] (n = 22,028)			
Women								
No NAFLD	385,740	4,961	12.9	1.00 (reference)	23,042	740	32.1	1.00 (reference)
NAFLD	12,758	431	33.8	2.44 (2.21-2.69)	11,222	604	53.8	1.65 (1.48-1.84)
Men								
No NAFLD	188,134	9,105	48.4	1.00 (reference)	20,471	1,622	79.2	1.00 (reference)
NAFLD	54,273	4,111	75.7	1.49 (1.44-1.55)	38,811	4,317	111.2	1.38 (1.30-1.46)
p for interaction by sex				<0.001				<0.001

[a] Estimated from Cox proportional hazards models; multivariable Model 1 was adjusted for age, center, year of screening examination, alcohol consumption, smoking status, physical activity, education level, and lipid-lowering medication.

[b] Overweight was defined as body mass index (BMI) of ≥23 kg/m^2.

[c] Abdominal obesity was defined as waist circumference ≥90 cm for men and ≥85 cm for women.

Abbreviations: CI, confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PY, person-years

FIGURE LEGENDS

Figure 1. Selection of study participants