Original Article

Association between MRI-derived hepatic fat fraction and blood pressure in participants without history of cardiovascular disease

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Objectives: We assessed whether liver fat content, as determined by MRI, correlates with blood pressure (BP), a major vascular risk factor, in individuals from the general population without history of stroke and coronary or peripheral artery disease.

Methods: Cross-sectional data from 384 participants (161 women; aged 39–73 years) of a MRI substudy of the KORA FF4 survey were used. Hepatic fat fraction (HFF) was measured in the left and right lobe of the liver using single voxel multiecho ^{1}H-spectroscopy and at the level of the portal vein using a multiecho Dixon-sequence. Associations of HFF with SBP and DBP as well as hypertension were assessed by right censored normal regression (accounting for antihypertensive treatment) and by logistic regression, respectively.

Results: High levels of HFF measured on the level of the portal vein (90th percentile, 21.8%), compared with low HFF levels (10th percentile, 1.7%), were associated with higher SBP (131 vs. 122 mmHg; overall $P = 0.001$), higher DBP (82 vs. 76 mmHg, $P < 0.001$) and with higher odds of hypertension [odds ratio (OR) = 2.16, $P = 0.025$]. A level of 5.13% (54th percentile) was identified as optimal HFF cut-off for the prediction of hypertension (OR = 2.00, $P = 0.015$). Alcohol consumption emerged as an effect modifier for the association between HFF and hypertension (nonalcohol drinker: OR = 3.76, $P = 0.025$; alcohol drinker: OR = 1.59, $P = 0.165$).

Conclusion: MRI-derived subclinical HFF is associated with SBP and DBP as well as with hypertension in participants from the general population without history of cardiovascular disease.

Keywords: blood pressure, hepatic fat fraction, hypertension, MRI, population

Abbreviations: BP, blood pressure; FLD, fatty liver disease; HFF, hepatic fat fraction; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio

INTRODUCTION

The burden of nonalcoholic fatty liver disease (NAFLD) has increased in recent decades in the Western world and globally [1,2]. Mounting evidence suggests that NAFLD is associated with subclinical cardiovascular disorders like atherosclerosis [2–4] and also with symptomatic cardiovascular diseases [3,4].

Some prior studies reported that NAFLD is associated with higher DBP [5,6], SBP [7,8] and hypertension [5,9]. However, in most studies, FLD was coded as a binary (present or absent) or categorical (absent, mild, moderate or severe) variable so that the continuous cardiovascular risk associated with hepatic fat is not well established.

Invasive liver biopsy remains the standard of reference for the diagnosis of FLD including quantification of liver fat content as well as evaluation of hepatic fibrosis [3]. In clinical and epidemiological studies, however, such invasive approaches are not appropriate so that FLD is most commonly determined by imaging methods such as sonography [5,6,8] and computed tomography [4] in combination with serum levels of liver enzymes including alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase [3,6].

Magnetic resonance (MR) measurements of hepatic fat have successfully been used to investigate continuous and subclinical levels of FLD with excellent correlations with liver biopsy [10]. Until now, only few studies have examined the association between MR-derived hepatic fat and BP [7,11–13]. So far, the associations of MR-derived hepatic fat with SBP and DBP as well as with hypertension were not yet investigated in individuals without prior history of cardiovascular disease from the general population. Therefore, we conducted analyses within a subset of the population-based KORA study (Cooperative Health

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Research in the Region of Augsburg) to investigate the association of MR-derived HFF with SBP and DBP as well as hypertension, to derive an optimal cut-off value for HFF to predict hypertension, to assess the effect of alcohol consumption on the association between hepatic fat and BP, and to evaluate the hepatic fat distribution according to hypertension management categories.

METHODS

Study sample

The KORA FF4 study is the second follow-up examination of the KORA S4 study, a population-based health survey conducted in the city of Augsburg (south Germany) and two surrounding counties between 1999 and 2001. A total sample of 6640 participants was drawn from the target population consisting of all German residents of the region aged 25–74 years [14].

Of all 4261 participants of the S4 baseline study, 2279 participants also participated in the 14-year follow-up FF4 study conducted between 2013 and 2014. Participants were considered ineligible for FF4 if they had passed away ($n = 447$, 10.5%), moved too far outside of the study region or were lost to follow-up ($n = 303$, 7.1%) or had demanded deletion of their contact data ($n = 198$, 4.6%). Of the remaining 3313 eligible participants, 159 could not be reached, 499 were unable to participate because of bad health condition or lack of time and 376 were not willing to participate in this follow-up, resulting in a final response rate of 68.8%.

KORA FF4 included an MRI substudy aimed at investigating subclinical cardiovascular disorders [15]. Exclusion criteria for this MRI substudy included age more than 73 years ($n = 428$), a history of cardiovascular disease defined as validated stroke, myocardial infarction or arterial vessel occlusion and any contraindication for MRI examinations reported previously ($n = 569$) [15,16]. According to these criteria, 1282 participants were eligible to undergo MRI. Among those, 337 participants did not consent to the study, 171 refused the telephone invitation, 39 could not be reached by telephone and 327 were not considered because of limited examination slots. A number of eight participants could not realize the MRI examination because of technical defects or contraindications that were newly established on site. Finally, participants with missing data for hepatic fat ($n = 16$) were excluded from the present analysis, yielding an analysis sample of 384 participants (161 women) aged 39–73 years.

The investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. All study methods were approved by the ethics committee of the Bavarian Chamber of Physicians, Munich, Germany (S4: EC no. 99186 and for genetic epidemiological questions 05004, F4 and FF4: EC no. 06068). The MRI examination protocol was further approved by the ethics committee of the Ludwig Maximilian University Hospital, Munich, Germany.

Magnetic resonance examination and liver fat measurements

MR examinations were performed at a 3-T Magnetom Skyra (Siemens AG, Healthcare Sector, Erlangen, Germany) using an 18-channel body coil in combination with the table-mounted spine matrix coil [15]. Participants were scanned in the supine position. The liver imaging protocol consisted of two sequences: multiecho Dixon and multi-echo hydrogen magnetic resonance spectroscopy (^{3}H MRS)

Multiecho Dixon: The multiecho Dixon was based on a volume interpolated body examination sequence with the following parameters: repetition time 8.90 ms, six echo times ranging from 1.23 to 7.38 ms, flip angle 4°, matrix 256×256. Slice thickness was 4 mm. For the estimation of liver proton density fat fraction, confounding effects of $T2^+$ decay and the spectral complexity of fat were taken into account [17]. Acquisition time was approximately 15 s. Data were analysed using Osirix (Vers. 4.1 64-bit, Pixmeo SARL, Bernex, GE, Switzerland). A region of interest was manually drawn on one slice at the height of the portal vein including the whole liver parenchyma avoiding large vessels and surrounding extrahepatic tissue to measure HFF at the level of the portal vein.

Multiecho ^{1}H MRS: A single-voxel spectroscopy sequence with stimulated-echo acquisition mode was used for ^{1}H MRS [18]. The sequence used a high-speed T2-corrected multiecho technique with the following parameters: repetition time 3000 ms, mixing time between second and third radiofrequency pulses 10 ms, and five echo times between 12.00 and 72.00 ms, respectively. A total of 1024 points were acquired at a bandwidth of 1200 Hz, with one signal acquired by using a voxel size of $30 \times 30 \times 30$ μl. Voxels were placed in the right (segment VIII) and left (segment II) liver lobe to measure right liver lobe HFF and left liver lobe HFF. The sequence lasted about 15 s. Spectrum postprocessing and lipid content estimation were automatically performed by a dedicated software package.

Blood pressure and hypertension

SBP and DBP measurements were obtained three times at the right arm of seated participants after a 5-min resting period. The resting period between readings was 3 min. An oscillometric digital BP monitor (HEM-705CP, Omron Corporation, Tokyo, Japan) was used, and one of two cuff sizes was applied according to the circumference of the participant's arm. The mean of the second and third BP measurements was used for the present analyses [19]. Pulse pressure (PP) was calculated as the difference between SBP and DBP. Hypertension was defined as increased SBP (≥140 mmHg) or increased DBP (≥90 mmHg) [20] or use of antihypertensive medication under awareness of having hypertension. Medication intake of the last 7 days was recorded during the medical interview by computer-based software, when participants were asked to show their medication packages. Anatomical Therapeutic Chemical codes were used. Antihypertensive medication was defined according to the recommendations of the German Hypertension Association that include antihypertensives (C02), diuretics (C03), beta blocking agents (C07), calcium channel blockers (C08) or agents acting on the renin–angiotensin system (C09) [21]. If participants reported that they had ever been told that they have high or elevated BP, they were characterized as being aware of hypertension. All hypertensive participants were categorized as either

1. controlled hypertensive participants (individuals who are aware of their hypertension and who are treated and reach BP levels of SBP < 140 mmHg and DBP < 90 mmHg)
2. uncontrolled hypertensive participants (individuals aware of and treated for hypertension, but with BP levels of SBP ≥ 140 mmHg or DBP ≥ 90 mmHg)
3. untreated hypertensive participants (individuals aware of being hypertensive, but not on treatment and with BP levels of SBP ≥ 140 mmHg or DBP ≥ 90 mmHg)
4. unaware hypertensive participants (individuals unaware of their hypertension, receiving no treatment and with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg)

Covariables measurements

In addition to age and sex, a broad range of health-related variables were measured in KORA FF4 by standardized interview, basic health examinations, laboratory analyses and medication record. Participants were classified as never-smoker, ex-smoker or current smoker; and as being physically active if they did regular sports in summer and winter for at least 1 h/week or as physically inactive if they did less than 1 h of sports per week. Alcohol consumption was measured in grams per day and was derived from a quantity-frequency index.

BMI was calculated as weight divided by squared height (kg/m^2), and waist circumference was measured in cm to the closest 0.1 cm at the smallest position between the lower rib and the upper margin of the iliac crest.

Diabetes was defined according to the WHO definition as a 2-h plasma glucose concentration measured by OGTT equal or above 200 mg/dl and/or a fasting glucose level above 125 mg/dl [22]. Laboratory measurements including glucose and haemoglobin A1c as well as total cholesterol, HDL and LDL cholesterol were described elsewhere [23].

Statistical analyses

Variables were summarized separately for women and men using median and interquartile range for continuous measurements and absolute numbers and percentage values for categorical measurements.

HFF was quantified at three locations (left liver lobe, right liver lobe and at the level of the portal vein) and used as main exposure variables. Each of these continuous HFF variables was separately associated with SBP and DBP and with PP by censored normal regression. This methodological approach was used to account for possible bias caused by antihypertensive medication [24,25]. We adjusted the regression models for age, sex, BMI and diabetes mellitus and calculated predicted BP values for selected HFF levels (10th, 30th, 50th, 70th and 90th percentile) using centred covariables. In sensitivity analysis, regression models were adjusted for waist-to-hip ratio (WHR) instead of BMI. Furthermore, age-adjusted and sex-adjusted linear regression models were applied in subgroups of treated and untreated hypertension. Nonlinear associations between HFF levels and BP outcomes were evaluated by restricted cubic splines [26]. The distribution of errors of the censored regression model was checked visually for normality.

The association between continuous HFF and prevalent hypertension (modelled dichotomous) was assessed using logistic regression models. The same HFF percentiles and confounders were used as detailed above. Wald tests were used to test overall significance of the associations. Effect modification by alcohol consumption was tested using marginal effects for different alcohol consumption levels [27], and stratified results were presented by linear regression models. Optimal HFF cut-off for the prediction of hypertension was calculated by maximal Youden Index (sensitivity + specificity − 1), and sensitivity and specificity were presented.

Adjusted medians calculated from quantile regression models were used to compare HFF variables between hypertension categories (defined as detailed above based on the individual's awareness, treatment and BP control) and were graphically displayed in bar charts. Power analysis revealed that the study sample had 80% power to detect a mean HHF difference of 2.7% between the nonhypertensive control group ($n = 252$) and the hypertension group ($n = 132$) and to detect an increase in R^2 of 0.014 upon adding HFF to a linear regression model [outcome = SBP; seven predictor variables including one tested predictor (HFF)].

All analyses were additionally adjusted for sampling weights considering differences in age, sex and diabetic status between the study sample ($n = 400$) and the entire KORA FF4 cohort ($n = 2279$, median age = 60 years, 48% men, 15% participants with diabetes) yielding no substantially changed findings. A P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using Stata 13.1 (Stata Corporation, College Station, Texas, USA).

RESULTS

Baseline characteristics of the study sample are shown in Table 1 for women ($n = 161$, median age = 58 years) and men ($n = 223$, median age = 55 years). Levels of HFF measured at the right liver lobe revealed the highest median of 4.2 and 8.1% for women and men, respectively, compared with left lobe HFF (3.3 and 6.7%) and HFF at the portal vein (3.2 and 6.5%). Median SBP and the proportion of hypertension were higher in men (126 mmHg, 39%) compared with women (113 mmHg, 29%).

Association of hepatic fat fraction with blood pressure

In primary analyses, levels of HFF were positively associated with SBP and DBP (Table 2, overall $P < 0.01$) across all three locations where HFF was measured. For example, low HFF levels of the left liver lobe (10th percentile; 1.4% HFF) revealed an adjusted mean SBP of 120.8 mmHg compared with high HFF levels (90th percentile; 19.8% HFF) with an SBP of 130.7 mmHg ($P = 0.002$). Figure 1 displays the nonlinear relation between left lobe HFF and SBP. Similar results were detected for DBP [76.5 mmHg (10th HFF percentile) vs. 81.1 mmHg (90th HFF percentile), $P = 0.003$] and PP (46.0 vs. 50.4 mmHg, $P = 0.016$, Table 2). Sensitivity analysis adjusting for WHR (Supplemental Table 1, http://links.lww.com/HJH/A720), instead of BMI, did not change the results.

TABLE 1. Baseline characteristics of the study sample

	Women $n = 161$	Men $n = 223$
Covariates		
Age (years)	58 (48; 64)	55 (48; 63)
Smoking status		
Never-smoker	65 (40.4%)	74 (33.2%)
Ex-smoker	61 (37.9%)	107 (48.0%)
Current smoker	35 (21.7%)	42 (18.8%)
Alcohol consumption (g/day)	2.9 (0; 12.3)	20.0 (3.7; 40.2)
BMI (kg/m^2)	26.8 (23.0; 30.8)	28.0 (25.4; 30.8)
Waist circumference (cm)	90 (79; 103)	102 (95; 110)
Waist-to-hip ratio	0.86 (0.80; 0.91)	0.96 (0.92; 1.01)
Physically active	105 (65.2%)	124 (55.6%)
Diabetes mellitus	13 (8.1%)	39 (17.5%)
HbA1c (%)	5.4 (5.3; 5.7)	5.4 (5.3; 5.7)
Glucose (mg/dl)	95 (88; 105)	102 (95; 113)
HDL-C (mg/dl)	68 (57; 82)	54 (45; 64)
LDL-C (mg/dl)	134 (112; 157)	140 (118; 162)
Total cholesterol (mg/dl)	217 (195; 242)	216 (189; 237)
TG (mg/dl)	94 (68; 120)	126 (87; 187)
ALT (μkat/l)	0.35 (0.27; 0.47)	0.52 (0.43; 0.68)
AST (μkat/l)	0.33 (0.28; 0.42)	0.42 (0.35; 0.52)
GGT (μkat/l)	0.33 (0.23; 0.52)	0.59 (0.40; 0.95)
Outcome variables		
SBP (mmHg)	113 (104; 122)	126 (115; 138)
DBP (mmHg)	72 (66; 77)	78 (71; 83)
Heart rate (1/min)	71 (66; 76)	69 (63; 78)
Use of antihypertensive medication	44 (27.3%)	54 (24.2%)
Hypertension	46 (28.6%)	86 (38.6%)
Exposure variables		
HFF, left liver lobe (%)	3.3 (1.9; 6.7)	6.7 (3.6; 14.7)
HFF, right liver lobe (%)	4.2 (2.4; 8.7)	8.1 (5.1; 16.9)
HFF, at the portal vein (%)	3.2 (1.9; 6.7)	6.5 (3.7; 13.8)

Data are given as number (percentage) or median (25th and 75th percentile). ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HbA1c, haemoglobin A1c; HDL-C, HDL cholesterol; HFF, hepatic fat fraction; LDL-C, LDL cholesterol; TG, triglycerides.

Association of hepatic fat fraction with prevalent hypertension

Comparing the 10th (reference) vs. 90th percentile, high levels of right lobe HFF and HFF at the portal vein were linearly associated with higher odds for hypertension [odds ratio (OR) = 2.15, $P = 0.029$, Fig. 2; OR = 2.16, $P = 0.025$, respectively, Table 3]. The association between high levels of left lobe HFF and hypertension was less strong and borderline nonsignificant (OR = 1.80, $P = 0.085$).

The evaluation of the optimal HFF cut-off value for dividing the study sample into groups with low and high hypertension risk revealed different cut-off points for left lobe HFF (3.57%; sensitivity: 86%, specificity: 50%), right lobe HFF (6.8%; sensitivity: 72%, specificity: 66%) and HFF at the portal vein (5.13%; sensitivity: 70%, specificity: 66%). The best prediction for hypertension of all HFF variables was observed for the left lobe HFF cut-off value (OR = 2.62, $P = 0.003$; right lobe HFF: OR = 2.17, $P = 0.008$, HFF at the portal vein: OR = 2.00, $P = 0.015$, Table 3).

Effect modification by alcohol consumption

In our analyses, alcohol consumption emerged as an additive and a multiplicative effect modifier for the association of HFF with SBP and with hypertension, respectively. There was a positive association between HFF and SBP for nonalcohol drinkers ($\beta = 0.34$, $P = 0.012$, $n = 91$) and no association between HFF and SBP for participants with alcohol consumption of 40 g alcohol/day ($\beta = -0.02$, $P = 0.902$, Fig. 3). Using the cut-off value of 5.13%, increased HFF at the portal vein was positively associated with hypertension in nonalcohol drinkers (OR = 3.76, $P = 0.025$), but not in participants with alcohol consumption greater than 0 g alcohol/day (OR = 1.59, $P = 0.165$).

TABLE 2. Association of hepatic fat fraction with blood pressure

HFF percentiles (%)	SBP (95% CI) (mmHg)	DBP (95% CI) (mmHg)	Pulse pressure (95% CI) (mmHg)
Left liver lobe			
10th (1.4)	120.8 (117.9–123.6)	76.5 (75.1–78.0)	46.0 (44.2–47.9)
30th (2.9)	122.6 (120.4–124.8)	76.9 (75.6–78.2)	47.0 (45.6–48.4)
50th (5.1)	124.9 (123.1–126.7)	77.5 (76.4–78.5)	48.2 (47.1–49.4)
70th (8.9)	128.0 (125.6–130.4)	78.4 (77.4–79.4)	49.8 (48.2–51.3)
90th (19.8)	130.7 (126.9–134.5)	81.1 (78.9–83.3)	50.4 (47.9–52.9)
Overall *P* value	0.002	0.003	0.016
Right liver lobe			
10th (2.0)	122.6 (120.1–125.0)	76.2 (74.7–77.7)	47.1 (45.6–48.6)
30th (3.9)	123.2 (121.1–125.3)	76.7 (75.4–78.0)	47.4 (46.0–48.7)
50th (6.3)	124.0 (122.3–125.8)	77.3 (76.2–78.4)	47.7 (46.5–48.8)
70th (11.2)	125.8 (124.1–127.5)	78.6 (77.6–79.7)	48.3 (47.2–49.4)
90th (22.8)	129.8 (126.1–133.5)	81.7 (79.4–84.0)	49.9 (47.5–52.2)
Overall *P* value	0.006	0.001	0.094
Level of the portal vein			
10th (1.7)	122.4 (120.1–124.7)	76.2 (74.8–77.6)	47.0 (45.5–48.5)
30th (3.0)	122.9 (120.9–125.0)	76.6 (75.3–77.8)	47.2 (45.9–48.5)
50th (4.6)	123.6 (121.7–125.4)	77.0 (75.9–78.2)	47.5 (46.3–48.7)
70th (9.6)	125.7 (124.0–127.3)	78.5 (77.5–79.5)	48.3 (47.2–49.4)
90th (21.8)	130.7 (127.0–134.4)	82.1 (79.8–84.4)	50.3 (47.9–52.8)
Overall *P* value	0.001	<0.001	0.042

Data are adjusted values from right censored normal regression (accounting for antihypertensive treatment), adjusted for age, sex, BMI and diabetes mellitus. BP, blood pressure; CI, confidence interval; HFF, hepatic fat fraction.

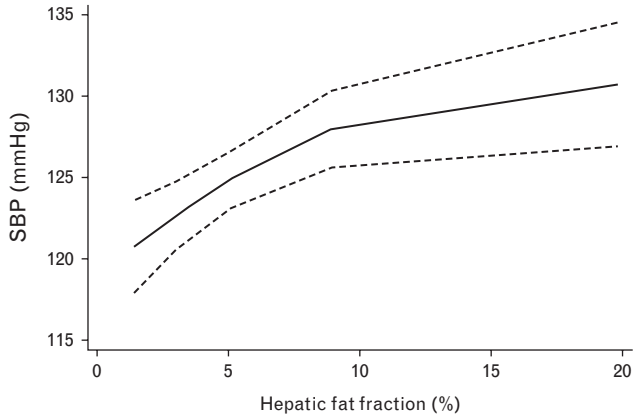

FIGURE 1 Predicted SBP values according to hepatic fat fraction of the left liver lobe (solid line) with 95% confidence interval (dashed line), from the regression model adjusted for age, sex, BMI and diabetes mellitus using restricted cubic splines.

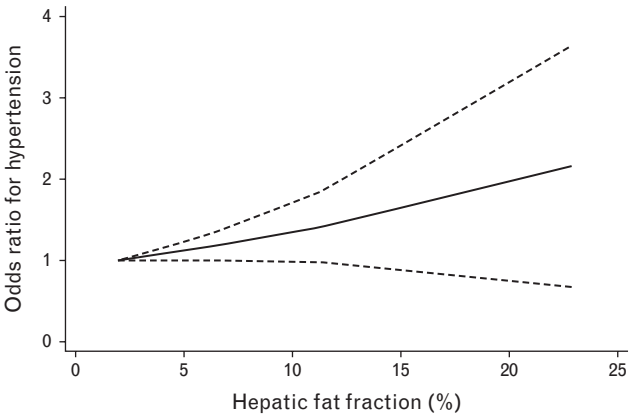

FIGURE 2 Odds ratios for hypertension according to hepatic fat fraction of the right liver lobe (solid line) with 95% confidence interval (dashed line) referred to the reference of hepatic fat fraction = 2%, from the logistic regression model adjusted for age, sex, BMI and diabetes mellitus.

Association of hypertension category with hepatic fat fraction

Participants unaware of their hypertension ($n = 15$) demonstrated the highest adjusted median levels of HFF (left HFF: 9.3%, right HFF: 16.0%, and HFF at the portal vein: 13.8%) (Supplemental Fig. 1, http://links.lww.com/HJH/A720).

Median levels of HFF did not differ substantially between participants without hypertension, with controlled and uncontrolled hypertension and participants who were untreated but aware of hypertension (Supplemental Fig. 1, http://links.lww.com/HJH/A720). The age-adjusted and sex-adjusted association between HFF at the portal vein and SBP was stronger in the subgroup of untreated hypertension ($n = 34$; $\beta = 0.41$, $P = 0.036$) compared with the subgroup of treated hypertension ($n = 98$; $\beta = 0.20$, $P = 0.258$).

DISCUSSION

The current study investigated the association between MRI-determined HFF and BP in a general population sample and revealed the following main results: higher levels of HFF were associated with higher levels of SBP and DBP, the risk for hypertension increased with higher levels of HFF, the risk for hypertension and the optimal cut-off value for prediction of hypertension differed slightly between HFF measured at different locations (left lobe, right lobe and at the level of the portal vein), participants with unknown hypertension showed highest HFF, and the positive association between HFF and BP is stronger in abstainers compared with alcohol drinkers.

Hepatic fat and blood pressure in the literature

Most evidence for the association between hepatic fat and BP is available for NAFLD measured by ultrasound [5,6,8,9,28,29], in which FLD is inconsistently considered either as an outcome [5,8,9] or as a risk factor for BP [6,29,30]. Our results are in good agreement with the cross-sectional results of Lau *et al.* [30] revealing FLD, defined as a hyperechogenic pattern of the liver and increased serum alanine transferase levels, as a risk factor for hypertension [OR: 2.8; 95% confidence interval (CI): 1.30–6.20].

Furthermore, a longitudinal study supports the finding of a higher hypertension risk for a group with moderate-to-severe degree of NAFLD (hazard ratio: 1.14; 95% CI: 1.00–1.30) compared with a normal group [29]. In most prior studies, FLD was modelled as a binary (present vs. absent) or categorical trait so that evidence for the association between a *continuous* measure of hepatic fat and BP is rare [7,11,13]. In a cross-sectional study of 156 adults, sex-adjusted and age-adjusted correlation coefficient for HFF and SBP was $r = 0.191$ ($P = 0.002$), but further adjustment for visceral adipose tissue rendered the association non-significant ($\beta = 0.11$, $P = 0.120$) [7]. A similar result was observed in another sample of 425 healthy individuals reporting a rather weak correlation between HFF and SBP ($r = 0.140$, $P < 0.05$) in a statistical model without multivariable adjustment [11]. In addition, a positive unadjusted association between MRI-determined HFF (defined dichotomous using a cut-off value of 9%) and SBP (but not DBP) was also found in a small sample including 60 obese children aged 6–14 years [13].

Compared with the latter MRI studies, our study could demonstrate consistent associations of continuous HFF levels with SBP and DBP as well as with PP and hypertension, adjusted not only for age and sex but also for BMI and diabetes mellitus. As an appropriate statistical method, we applied censored normal regression for optimal consideration of BP values affected by antihypertensive medication [24]. Furthermore, we measured and analysed HFF values obtained at three different locations in the liver: in the left liver lobe, in the right liver lobe and at the level of the portal vein based on either multiecho ^{1}H MRS or multiecho Dixon sequences with consistent results for all three measurements.

Hepatic fat as a risk factor for high blood pressure

FLD has been linked to hypertension by several pathways: it is associated with the development of insulin resistance and diabetes mellitus [31,32]. Furthermore, FLD leads to

TABLE 3. Association of hepatic fat fraction with hypertension

	Hypertension, $n = 132$ (34%)				
HFF, left liver lobe (%) percentiles	OR (95% CI)	HFF, right liver lobe (%)	OR (95% CI)	HFF, portal vein (%)	OR (95% CI)
10th (1.4)	1	(2.0)	1	(1.7)	1
30th (2.9)	1.05 (0.99–1.11)	(3.9)	1.07 (1.01–1.14)	(3.0)	1.05 (1.01–1.09)
50th (5.1)	1.12 (0.97–1.28)	(6.3)	1.17 (1.01–1.34)	(4.6)	1.12 (1.01–1.22)
70th (8.9)	1.27 (0.92–1.62)	(11.2)	1.40 (0.98–1.83)	(9.6)	1.35 (1.00–1.71)
90th (19.8)	1.80 (0.60–3.01)	(22.8)	2.15 (0.68–3.63)	(21.8)	2.16 (0.71–3.61)
Overall *P* value	0.085		0.029		0.025
Optimal cut-off values[a]					
≤38th (3.57)	1	≤53th (6.8)	1	≤54th (5.13)	1
>38th (3.57)	2.62 (1.39–4.94)	>53th (6.8)	2.17 (1.22–3.87)	>54th (5.13)	2.00 (1.14–3.51)
P value	0.003		0.008		0.015

Odds ratios (OR) from multivariable logistic regression, adjusted for age, sex, BMI and diabetes mellitus for different levels of HFF [percentiles (%)]. CI, confidence interval; HFF, hepatic fat fraction.
[a]Optimal HFF cut-off for the prediction of hypertension was calculated by maximal Youden Index (sensitivity + specificity − 1).

increased systemic inflammation [33,34]. Both have relevant impact on the endothelium leading to vascular dysfunction and atherosclerosis with decreased vascular elasticity.

Increased hepatic fat fraction

In our study, the optimal cut-off value of increased HFF predicting hypertension differed between 3.6% (left HFF), 5.1% (HFF at the portal vein) and 6.8% (right HFF) with similar performance of sensitivity and specificity (around 70%) for the two latter ones. Different MRI techniques of estimating HFF using double-echo MRI, triple-echo MRI and MR spectroscopy showed optimal cut-off values between 11.08 and 4.73% for the diagnostic accuracy of the upper normal limit of histologic steatosis percentage (>5%) [35]. The study of Ducluzeau *et al.* [7] revealed an optimal cut-off value of increased MRI-determined HFF in the right lobe of the liver of 5.2% for identifying participants with at least three or more criteria of the metabolic syndrome including hypertension that is very similar to our cut-off value of HFF at the portal vein. Increased HFF (defined by HFF > 5.1%) was associated with a doubling of hypertension risk in our study that therefore supports a general cut-off value for increased MRI-determined HFF of more than 5%.

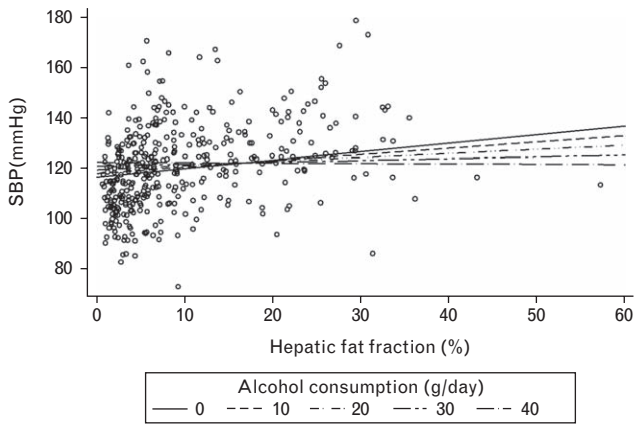

FIGURE 3 Adjusted predicted SBP according to hepatic fat fraction of the right liver lobe for different levels of alcohol consumption (lines) and observed values (dots) (interaction effect of hepatic fat fraction of the right liver lobe × alcohol consumption: $\beta = -0.009$, $P = 0.013$).

Hepatic fat fraction and alcohol consumption

As alcohol consumption and obesity are main risk factors for FLD, it is an established concept to distinguish between obesity-based nonalcoholic FLD and alcoholic FLD. However, this concept is under discussion because of similar histopathological findings and a lack of clear definitions, especially for obese participants with alcohol misuse. Therefore, a multifactorial risk concept for FLD has been suggested [36].

Nevertheless, it remains of interest how alcohol consumption contributes to the associations between FLD and chronic disease risk. In our study, alcohol consumption did not emerge as a confounder but as an effect modifier for the association between liver fat and BP, with a stronger association in abstainers compared with alcohol drinkers. This result is in contrast to the study by Lau *et al.* who used liver ultrasound and serum alanine transferase levels to define FLD. In the latter study, no significant effect modification of alcohol consumption for the association of FLD with hypertension was reported [28,30].

Strengths and limitations

Our analyses were conducted in a subsample of the population-based KORA study, a cohort study with significant long-time experience in quality assurance of a broad range of different risk factor and phenotype measurements. We applied advanced MR techniques to characterize HFF including multiecho ^{1}H MRS and multiecho Dixon sequences, and performed continuous fat measures at three different locations (left and right liver lobe, at the portal vein). MRI and ^{1}H MRS are established noninvasive modalities for accurate quantitative assessment of hepatic steatosis providing reliable measurement also for mild diseases [37,38]. In animal models, MRI and ^{1}H MRS even show higher correlation with biochemical analysis of liver triglyceride content than invasive histopathological methods [39].

Nevertheless, some limitations should be taken into account. The present analysis is of cross-sectional character precluding the identification of cause and effect. The study sample is not entirely representative for the initial cohort

sample and the population of the study region. One essential reason for nonresponse was refusal of informed consent and telephone invitation. Participants of the MRI substudy were a bit younger and more often men compared with the entire KORA FF4 cohort sample. However, after consideration of calculated sampling weights, findings of this study did not change substantially and are therefore at least applicable to the population represented by the KORA FF4 sample ($n = 2279$) characterized by mean age = 60.8 years, women = 51.7%, active smoking = 15.5%, mean BMI = 27.8 kg/m^2, mean SBP = 118.9 mmHg and hypertension = 39.1%.

In conclusion. the current study revealed a positive association of MRI-derived HFF with higher SBP and DBP as well as with hypertension independently of other risk factors in a healthy sample from the general population without prior cardiovascular events. This finding suggests that HFF as assessed by MRI is a potential biomarker candidate for a more accurate cardiovascular risk assessment, especially in participants without alcohol consumption. Longitudinal studies are warranted that investigate how predictive HFF is for incident hypertension and cardiovascular events independently of established cardiovascular risk factors and in comparison with other MRI-derived fat measurements.

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The manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract.

Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

The strengths of this article are the very careful measurements of hepatic fat fraction using accepted and informative MRI sequences, together with appropriate analyses. The limitations are its limited size, and the lack of understanding at this stage of the observed association between HFF and blood pressure, and the cross-sectional analysis, thereby limiting any useful interpretation about impact on disease progression, either cardiovascular or hepatic.

Reviewer 2

The authors investigated the association between liver fat based on MRI and BP. Although there are several limitations (e.g. cross-sectional design, somewhat limited sample size and possible selection bias) as described in the Discussion, the paper provides new insights on the risk factors of hypertension.