Received: 8 July 2021 | Revised: 30 August 2021 | Accepted: 4 September 2021

DOI: 10.1111/liv.15053

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Waist and hip circumference are independently associated with the risk of liver disease in population-based studies

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Funding information
Dr Danielsson and Dr Nissinen were supported by grants from the Helsinki University Hospital Research Fund. Dr Salomaa was supported by the Finnish Foundation for Cardiovascular Research. Dr Åberg was supported by the Academy of Finland (grant #338544), Sigrid Jusélius Foundation, Mary and Georg Ehrnrooth Foundation, Medicinska Understödsföreningen Liv och Hälsa and Finska Läkaresällskapet.

Handling Editor: Luca Valenti

Abstract

Background & Aims: While several anthropometric measures predict liver disease, the waist-hip ratio (WHR) has shown superiority in previous studies. We analysed independent and joint associations of waist circumference (WC) and hip circumference (HC) with liver disease and liver-related risk factors.

Methods: Cross-sectional study (n = 6619) and longitudinal cohort (n = 40 923) comprised individuals from Health 2000 and FINRISK 1992-2012 studies. Prevalent and viral liver diseases were excluded. Longitudinal cohort was linked with national healthcare registers for severe incident liver disease. Linear regression and Cox proportional hazards models were used to analyse anthropometric, lifestyle, metabolic and bioimpedance-related parameters; liver enzymes; and 59 liver-related genetic risk variants.

Results: WC and HC showed independent and opposite associations with both liver enzymes and incident liver disease among men (HR for liver disease: WC, 1.07, 95% CI 1.03-1.11; HC, 0.96, 95% CI 0.92-0.99; *P*-range .04 to <.001) and women (HR for liver diseases: WC, 1.06, 95% CI 1.02-1.10; HC, 0.93, 95% CI 0.89-0.98; *P*-range .005 to .004). HC modified associations between WC and liver enzymes, and between WC and incident liver disease, particularly among men. Liver enzymes and risk of liver disease increased with increasing WC, more so among individuals with high WHR compared to with low WHR. WC and HC jointly reflected both body fat distribution and muscle mass, which was largely mirrored by WHR.

Conclusions: WC and HC exhibit independent and joint associations with liver disease, which are largely reflected by WHR. Both body fat distribution and muscle mass contribute to these anthropometric measures.

KEYWORDS

anthropometric measures, body mass index, fat, sarcopenia, waist-hip ratio

Abbreviations: BMI, body mass index; BP, blood pressure; FIB-4, Fibrosis-4; HC, hip circumference; HOMA-IR, homeostasis model assessment index; MAFLD, metabolic dysfunction-associated fatty liver disease; MetS, metabolic syndrome; SMI, skeletal muscle mass index; WC, waist circumference; WHR, waist-hip ratio.

1 | INTRODUCTION

In the present era of the obesity epidemic, non-viral chronic liver disease is becoming an increasing health concern and economic burden.[1] Chronic liver disease is usually asymptomatic and may silently progress to cirrhosis and end-stage liver disease, constituting the 11th leading cause of death, worldwide.[2] Early identification of persons at risk for progressive liver disease requires that clinicians are aware of a cluster of risk factors, encompassed under the concept of non-alcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated fatty liver disease (MAFLD).[3]

Obesity, as measured by the body mass index (BMI), is a risk factor for future severe liver disease; however, the risk effect is small.[4-6] Studies comparing different anthropometric measures consistently report that liver-related outcomes are more strongly associated with measures of abdominal obesity than with BMI.[7-9] Specifically, the waist-hip ratio (WHR) reportedly predicts clinical liver-related outcomes better than waist circumference (WC) alone, BMI, or waist-height ratio.[7-9] However, it remains unclear which liver disease-relevant metabolic, lifestyle or genetic factors are better reflected by WHR than the other anthropometric measures.

WHR includes the measure of hip circumference (HC), which exhibits an independent association with metabolic factors.[10,11] HC can also independently predict all-cause mortality.[12,13] However, the association between HC and liver-related outcomes has been scarcely studied. HC may reflect both muscle mass and subcutaneous adiposity. Indeed, the loss of muscle mass (sarcopenia) has been implicated in the pathophysiology of NAFLD[14-16] and liver-related outcomes.[17,18]

An improved understanding of the anthropometric measures predictive of clinical liver disease will be important for population risk stratification, which in turn is necessary for early identification of persons at risk. In the present population-based study, we aimed to compare the WHR to BMI with regards to their associations with several lifestyle, metabolic and genetic risk factors for liver disease, and to analyse the differential associations with WC and HC. In the second part of this study, we evaluated independent associations and interactions of WC and HC with liver disease.

PLAIN SUMMARY

High values of waist-hip ratio (WHR) are risk factors for severe liver disease.

Waist circumference (WC) and hip circumference (HC) have independent and joint associations with liver disease risk particularly among those with a high WHR.

Five liver disease-related risk genotypes are associated with either WC, HC or body mass index.

2 | SUBJECTS AND METHODS

2.1 | Cross-sectional study

Cross-sectional analyses were performed using data from the Health 2000 Survey, which was coordinated by the Finnish Institute for Health and Welfare (previously National Public Health Institute). This survey originally included 8028 adults of ≥30 years of age, and the participation rate in the full examinations was 80%.[19] The cohort is generated using a regional two-stage stratified cluster sampling procedure and is considered representative of the entire Finnish population. After excluding individuals with missing WHR measurements (n = 1409), our final data-set comprised 6619 individuals.

2.2 | Longitudinal cohort

Longitudinal analyses were performed using Health 2000 Survey data along with data from FINRISK, which is a national population survey conducted in Finland every 5 years by the Finnish Institute for Health and Welfare, using random representative population samples.[20] We used data from the cohorts recruited in 1992, 1997, 2002, 2007 and 2012. The initial combined sample (FINRISK 1992-2012 and Health 2000) included 43 105 individuals. We excluded individuals with missing registry linkage (n = 1457), baseline liver disease (ICD-10 codes K70-K77 or C22; n = 299), chronic viral hepatitis at baseline or during follow-up (n = 89), or missing WHR measurements (n = 337) and then the final study cohort comprised 40 923 individuals.

To collect follow-up data, the included individuals were linked with several national registers using the unique personal identity code assigned to all Finnish residents. Data regarding hospitalisations were obtained from the Care Register for Health Care (HILMO), which registers all hospitalisations in Finland since 1969. Upon discharge, one or several ICD diagnoses are assigned to each hospitalisation, and these diagnosis codes are systematically recorded in the HILMO register. Data regarding malignancies were obtained from the Finnish Cancer Registry, which includes nationwide cancer records since 1953. Data regarding vital status and cause of death were obtained from Statistics Finland. In Finland, by law, each person who dies is assigned a cause of death (using ICD codes) on the official death certificate, which is issued by the treating physician based on medical or autopsy evidence, or forensic evidence when necessary. Then the cause-of-death codes are verified by medical experts at the register and recorded according to systematic coding principles. Data reporting to all of these registries is mandatory by law, and the general quality is consistent and virtually 100% complete.[21,22]

The study end-points were fatal and non-fatal severe liver disease (requiring hospital admission or causing liver cancer or liver-related death). Table S1 lists the ICD codes used for defining the outcomes.

2.3 | Baseline variables

At baseline, data were collected through interviews (Health 2000), questionnaires, and health examinations by trained physicians and

TABLE 1 Characteristics of the included subjects in the cross-sectional Health 2000 Study and the longitudinal combined cohort of Health 2000 and FINRISK

	Health 2000				Health 2000 + FINRISK			
	Total	Men	Women	*P*	Total	Men	Women	*P*
Number	6619	2972	3647	–	40 923	19 399	21 524	–
Age (years)[a]	53.5 ± 15.4	51.9 ± 14.2	54.9 ± 16.2	<.001	49.6 ± 13.8	49.9 ± 13.6	49.3 ± 14.0	<.001
BMI (kg/m^2)[a]	26.9 ± 4.7	27.1 ± 4.1	26.8 ± 5.1	.014	26.8 ± 4.7	27.1 ± 4.1	26.5 ± 5.1	<.001
Waist (cm)[a]	92.8 ± 13.3	97.8 ± 11.5	88.7 ± 13.3	<.001	90.3 ± 13.8	96.3 ± 11.8	84.9 ± 13.3	<.001
Hip (cm)[a]	101.7 ± 9.6	100.4 ± 7.9	102.8 ± 10.6	<.001	100.9 ± 9.1	100.4 ± 7.5	101.4 ± 10.3	<.001
Waist-hip ratio[a]	0.91 ± 0.08	0.98 ± 0.06	0.86 ± 0.06	<.001	0.89 ± 0.09	0.96 ± 0.07	0.84 ± 0.07	<.001
Total cholesterol (mmol/L)[a]	5.9 ± 1.1	5.9 ± 1.1	5.9 ± 1.1	.192	5.5 ± 1.1	5.6 ± 1.1	5.5 ± 1.1	<.001
LDL cholesterol (mmol/L)[a]	3.7 ± 1.1	3.7 ± 1.0	3.8 ± 1.1	<.001	3.4 ± 1.0	3.5 ± 1.0	3.4 ± 1.0	<.001
HDL cholesterol (mmol/L)[a]	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	<.001	1.4 ± 0.4	1.3 ± 0.3	1.5 ± 0.4	<.001
Triglycerides (mmol/L)[a]	1.6 ± 1.1	1.6 ± 1.1	1.6 ± 1.0	.059	1.5 ± 1.0	1.7 ± 1.2	1.3 ± 0.8	<.001
Percentage of diabetes n (%)	687 (10.4)	316 (10.6)	371 (10.2)	.569	3097 (7.6)	1555 (8.0)	1542 (7.2)	.001
HbA1C (%)[a]	5.4 ± 0.7	5.3 ± 0.7	5.4 ± 0.7	<.001	–	–	–	–
HOMA-IR[a]	2.5 ± 5.5	2.8 ± 7.2	2.3 ± 3.4	.001	–	–	–	–
Systolic blood pressure (mmHg)[a]	135 ± 22	136 ± 19	135 ± 23	.013	135 ± 20	138 ± 19	132 ± 21	<.001
Diastolic blood pressure (mmHg)[a]	82 ± 11	84 ± 11	80 ± 11	<.001	81 ± 11	83 ± 11	79 ± 11	<.001
γ-GT (U/L)[a]	36.6 ± 48.0	35.9 ± 46.4	37.1 ± 49.3	.350	33.9 ± 49.4	41.7 ± 59.6	26.8 ± 36.6	<.001
CRP (mg/L)[a]	2.3 ± 6.4	2.1 ± 5.4	2.4 ± 7.1	.053	2.5 ± 5.5	2.4 ± 5.4	2.5 ± 5.6	.043
Cigarettes [a]	4.8 ± 8.8	7.9 ± 10.9	2.7 ± 6.3	<.001	3.6 ± 7.7	5.0 ± 9.2	2.4 ± 5.8	<.001
Smoking:				<.001				<.001
Current n (%)	1723 (26)	968 (33)	755 (21)		9752 (24)	5609 (29)	4143 (19)	
Former n (%)	1433 (22)	936 (32)	497 (14)		9174 (23)	5713 (30)	3461 (16)	
Never n (%)	3427 (52)	1055 (36)	2372 (66)		21 621 (53)	7850 (41)	13 771 (64)	
Alcohol per week (g)[a]	73 ± 145	124 ± 190	32.0 ± 70.3	<.001	75 ± 137	115 ± 172	39 ± 77	<.001
Alcohol intake:				<.001				<.001
Lifetime abstainer n (%)	1110 (18)	210 (7)	900 (26)		3609 (9)	931 (5)	2678 (13)	
Current abstainer n (%)	351 (6)	215 (8)	136 (4)		1824 (5)	1020 (5)	804 (4)	
Alcohol user n (%)	4837 (77)	2441 (85)	2396 (70)		34 946 (87)	17 236 (90)	17 710 (84)	
Binge drinking	9.6 ± 28.2	16.6 ± 38.0	3.8 ± 13.7	<.001	–	–	–	
Exercise (%):				.178				<.001
At least 2 times a weak n (%)	3733 (58)	1660 (57)	2073 (59)		19 898 (58)	9099 (56)	10 799 (59)	

(Continues)

TABLE 1 (Continued)

	Health 2000				Health 2000 + FINRISK			
	Total	Men	Women	P	Total	Men	Women	P
2-4 times per month n (%)	1737 (27)	819 (28)	918 (26)		9193 (27)	4352 (27)	4841 (27)	
Less often n (%)	938 (15)	423 (15)	515 (15)		5521 (16)	2934 (18)	2587 (14)	
Percentage of metabolic syndrome n (%)	3001 (45.7)	1429 (48.3)	1572 (43.5)	<.001	13 628 (33.3)	7215 (37.2)	6413 (29.8)	<.001

[a]mean ± SD; HOMA-IR, homeostatic model assessment for insulin; Binge drinking, Frequency of consuming at least 5 drinks (10 g) per day during last 12 months categorised as less often/monthly/weekly.

nurses (Health 2000) and by trained nurses (FINRISK) using standardised procedures of the MONICA and European Health Risk Monitoring projects.[23,24]

Respondents were asked to report how often they consumed alcoholic beverages during the previous year and the average amount that they consumed per week during the previous month. These data were used to calculate average ethanol intake, in grams per week. To assess binge drinking, respondents were asked for the number of times during the last 12 months that they consumed ≥60 grams of ethanol per occasion. Smoking habits were categorised as current, former, or never smokers. Exercise was measured as the frequency of performing physical exercise until at least slightly out of breath and sweaty, for a minimum of 20 minutes per time.

In the Health 2000 study, diabetes was defined either by fasting serum glucose ≥7.0 mmol/L, taking diabetes medication, or a prior known diabetes diagnosis. The homeostasis model assessment index (HOMA-IR) served as an estimate of insulin resistance and was calculated using the equation [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5, as previously described.[25]

WC was measured midway between the lower rib margin and the iliac crest. HC was measured at the level of the widest circumference, which is usually the widest level of the iliac crest. WC and HC were each rounded up to the nearest 0.5 cm. WHR was calculated as WC/HC.

Metabolic syndrome (MetS) was defined according to the Joint Interim Statement criteria.[26] Blood samples were collected at baseline for a wide spectrum of laboratory measurements and were handled following a standardised protocol. The detailed study protocols have previously been published.[19,20] Fibrosis-4 (FIB-4) score was obtained from a subcohort of individuals recruited for FINRISK in 2002 and 2012 (n = 1958). All participants provided signed informed consent, and the studies were approved by the Coordinating Ethical Committee of the Helsinki and Uusimaa Hospital District. The previous studies were also approved by the institutional review board of the National Public Health Institute, Helsinki, Finland. The FINRISK and Health 2000 sample collections were transferred to THL Biobank in 2015 after approval of the Coordinating Ethical Committee of the Helsinki and Uusimaa Hospital District.

2.4 | Bioimpedance data

An eight-terminal body composition analyser was used in the Health 2000 Survey (InBody 3.0; Biospace, Seoul, South Korea).[27,28] First, individuals were weighed. This was followed by measurement of the resistance in five different body segments using alternating current frequencies of 5, 50, 250 and 500 kHz. Then the compositions of the five segments were calculated.[29,30] Skeletal muscle mass index (SMI) was defined as [skeletal muscle mass (kg)/body weight (kg)] × 100.[31] Bioimpedance data were available for 5801 participants in the Health 2000 Survey.

2.5 | Statistical analyses

For comparisons between groups, we used the chi-square or Mann–Whitney test, as appropriate. We calculated pairwise partial correlations between anthropometric measures and various other variables – with adjustment for age only, or for age plus anthropometric confounders – using the Spearman method for two continuous variables, and the point-biserial method when comparing a continuous and a dichotomous variable. To study independent associations between anthropometric measures and 59 candidate genetic risk variants associated with NAFLD/liver disease in previous studies[32-35] (Table S2), we performed linear regression analyses. The covariates were age, sex, WC, H, and BMI, and the dependent variable was the genetic risk variant, assuming an additive genetic effect. We used the genotype as the dependent variable, as it enabled the use of linear regression to identify independent predictors of genotype (which would not be possible in the converse, with genotype as the independent). Bonferroni correction was used to correct for multiple comparisons, yielding a significance level of 0.0028 (0.05/18) for clinical variables, 0.0036 (0.05/14) for bioimpedance variables and 0.00085 (0.05/59) for genetic risk variants.

To study independent associations of bioimpedance-measured fat mass and skeletal muscle mass with the WHR and HC, we performed linear regression analyses. The covariate was age, independent variables were fat mass (kg) and skeletal muscle mass (kg), and the dependent variable was either WHR or HC. These analyses were

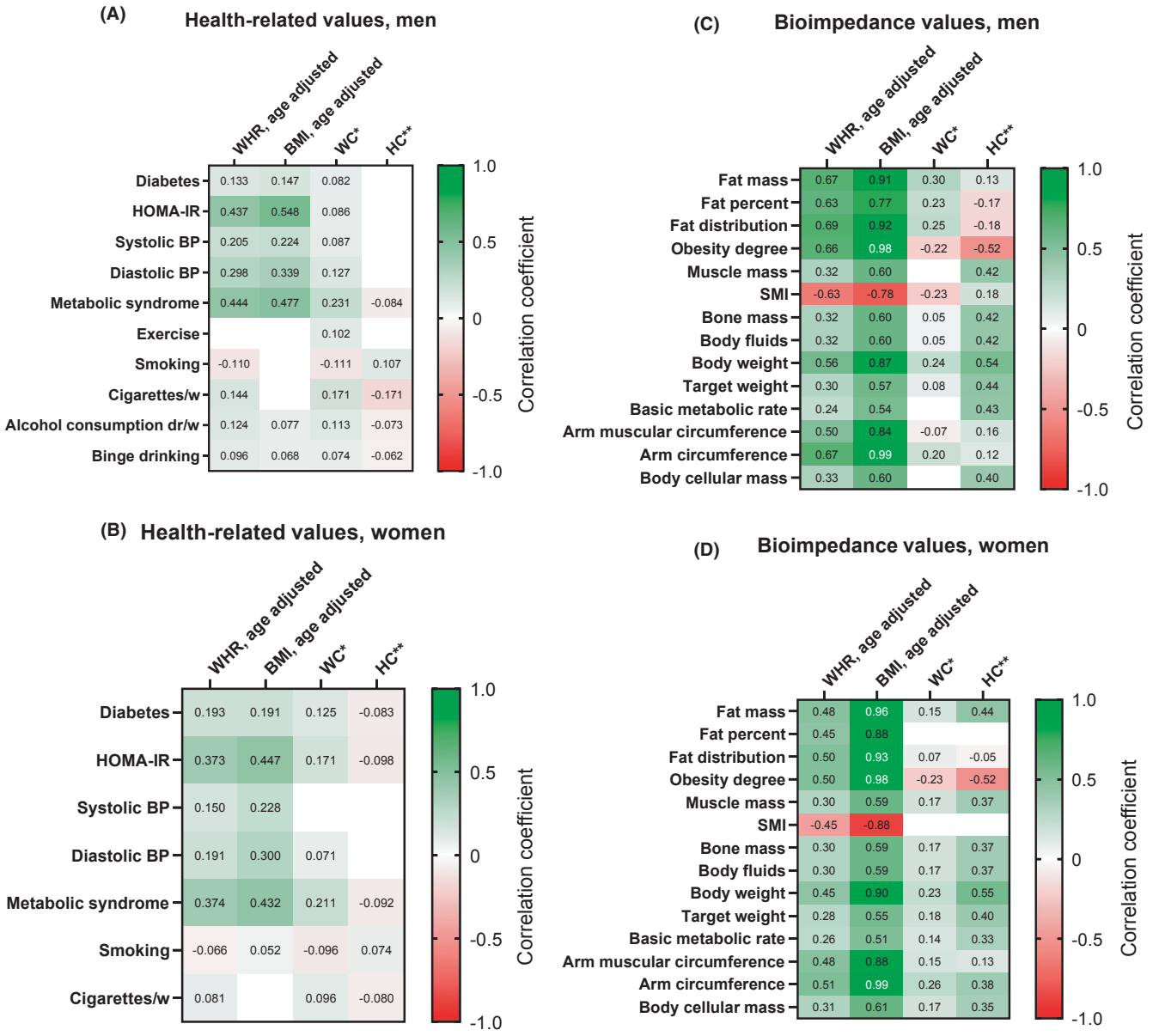

FIGURE 1 Heat-map illustrates the correlations of health-related (A: men and B: women) and bioimpedance (C: men and D: women) variables with waist-hip ratio, body mass index, waist circumference, and hip circumference. Positive values indicate positive correlation (green), and negative values indicate inverse correlation (red). The magnitude of the deviation from zero and the colour intensity indicate the strength of correlation, ranging from −1 to 1. Blank squares indicate no correlation. *P* range for given *r* values in A and B from <.0028 to <.001, and in C and D from <.0036 to <.001. *Adjusted for age, body mass index and hip circumference, **Adjusted for age, body mass index and waist circumference. WHR, waist-hip ratio; BMI, body mass index; WC, waist circumference; HC, hip circumference; BP, blood pressure

performed separately for men and women. Multicollinearity was assessed based on correlations between covariates, and the variance inflation factor.

To study independent associations of WC and HC with liver enzymes, we performed linear regression analyses. The covariant was age, the independent variables were WC, and HC, and the dependent variable was either ALT, AST or γ-GT. These analyses were performed separately for men and women. In separate regression models, we also assessed the interaction between WC and HC by additionally including the interaction term between WC and HC.

In the longitudinal dataset, we used Cox proportional hazards models – with time to first liver-related event as the outcome variable – to analyse the associations between anthropometric measures and liver outcomes. We used one Cox model with age, WC, and HC as covariates, with separate analyses for men and women. Another model additionally included the following covariates: systolic and diastolic blood pressure (BP), BMI, daily cigarette consumption, weekly alcohol consumption, diabetes, exercise habits and serum levels of cholesterol, LDL-C, HDL-C, triglycerides and CRP. To assess the two-way interaction effect between WC and HC, we included the interaction term between WC and HC in the

Genotype	WC	HC	BMI
IL1B rs1143634 A			0.000206
CD14 rs2569190 A			0.000118
TNF rs1800629 A		0.000042	
TNF rs361525 A		0.000346	
FADS1 rs174556 T	0.000496		

FIGURE 2 *P* values for independent associations between liver-related genetic risk variants and waist circumference, hip circumference and body mass index, with adjustment for age and sex. After Bonferroni correction, *P* values ≤.00085 were considered significant. Green and red indicate positive and inverse correlations, respectively – that is, greater or lesser likelihood of being a carrier of the genetic risk variant. Blank squares indicate no significant correlation. WC, waist circumference; HC, hip circumference; BMI, body mass index

Cox model. We checked the proportional hazards assumption of the Cox model using Schoenfeld residuals and detected no violations. The interaction effect between WC and HC for liver outcomes was plotted in a heat-map, with the hazard ratio on the *z*-axis. For further visualisation of interactions, we stratified the cohort into low-WHR and high-WHR subgroups based on the sex-specific median WHR (0.96 for men and 0.83 for women). *P* values of <.05 were considered statistically significant, except in genetic analyses where Bonferroni correction was used. Data were analysed with R software version 4.0.2, using the packages ppcor, survival, rms and visreg.

3 | RESULTS

3.1 | Baseline characteristics

At baseline, men and women significantly differed with regards to almost every variable, except for total cholesterol, triglycerides, percentage of diabetes, γ-GT, CRP and exercise, in the cross-sectional analysis (Table 1). Table S3 shows the baseline values of the bioimpedance measures. Table S4 reveals the amount of individuals with low, intermediate or high risk of liver fibrosis in a subcohort of FINRISK.

3.2 | Correlations between anthropometric measures and lifestyle, metabolic and bioimpedance variables

Tables S5 and S6 show the age- or multivariable-adjusted correlations between anthropometric measures and various health-related variables in the cross-sectional study. Figure 1 shows the significant correlations ($P < .0028$ in A and B and $P < .0036$ in C and D). WHR and BMI were interrelated ($r = +.656$ for men and $r = +.496$ for women, $P < .001$ for both). When comparing WHR to BMI, all correlations with a coefficient stronger than 0.3 showed similar directions for both WHR and BMI (Figure 1). Bioimpedance measures tended to correlate more strongly with BMI than WHR (Figure 1C,D). No single correlation was stronger for WHR than for BMI (Figure 1). When comparing WC to HC, correlations with health-related variables were generally weak ($r < .25$), and the directions were generally opposite for WC and HC (Figure 1; Table S5). Compared to WC, HC tended to correlate more strongly with muscle mass, but not with SMI or arm muscular circumference (Figure 1C,D).

3.3 | Associations with liver-related genetic risk variants

Age- and sex-adjusted linear regression analyses were used to assess the independent associations of BMI, WC and HC with 59 different liver disease-related risk genotypes in the cross-sectional study. These analyses revealed that five different genetic variants showed significant associations with at least one of these three anthropometric measures: one for WC, two for HC and two for BMI (Figure 2).

3.4 | Independent associations of fat mass and muscle mass with WHR and HC

Age-adjusted linear regression analysis in the cross-sectional study revealed that WHR was independently associated with both fat mass and skeletal muscle mass among women ($\beta = 0.025$, $P < .001$ for fat mass; $\beta = 0.007$, $P < .003$ for skeletal muscle mass), but only with fat mass among men ($\beta = 0.040$, $P < .001$ for fat mass; $\beta = 0.002$, $P = .11$ for skeletal muscle mass). With regards to HC, both fat mass and skeletal muscle mass were independently associated with HC among women ($\beta = 8.433$, $P < .001$; $\beta = 4.115$, $P < .001$) and among men ($\beta = 5.836$, $P < .001$; $\beta = 4.221$, $P < .001$). There was a poor correlation between fat mass and skeletal muscle mass ($r = .09$), and the variance inflation factors were <2 in all of these linear regression models, indicating no multicollinearity problem.

3.5 | Associations of WC and HC with liver enzymes

Age-adjusted linear regression analyses in the cross-sectional study revealed that WC and HC were independently associated with serum levels of ALT ($\beta = +0.839$ and -0.398 for men; $+0.392$ and -0.179 for women), AST ($\beta = +0.219$ and -0.092 for men; $+0.131$ and -0.096 for women) and γ-GT ($\beta = +1.450$ and -1.112 for men; $+0.690$ and -0.461 for women) ($P < .001$ for all). The interaction term between WC and HC was significant for AST among women ($P_{interaction} < 0.001$) and for ALT among men ($P_{interaction} < 0.001$). The interaction effect translated into a steeper rise, especially in AST, along with increasing WC, in the high-WHR group compared to the low-WHR group (Figure 3).

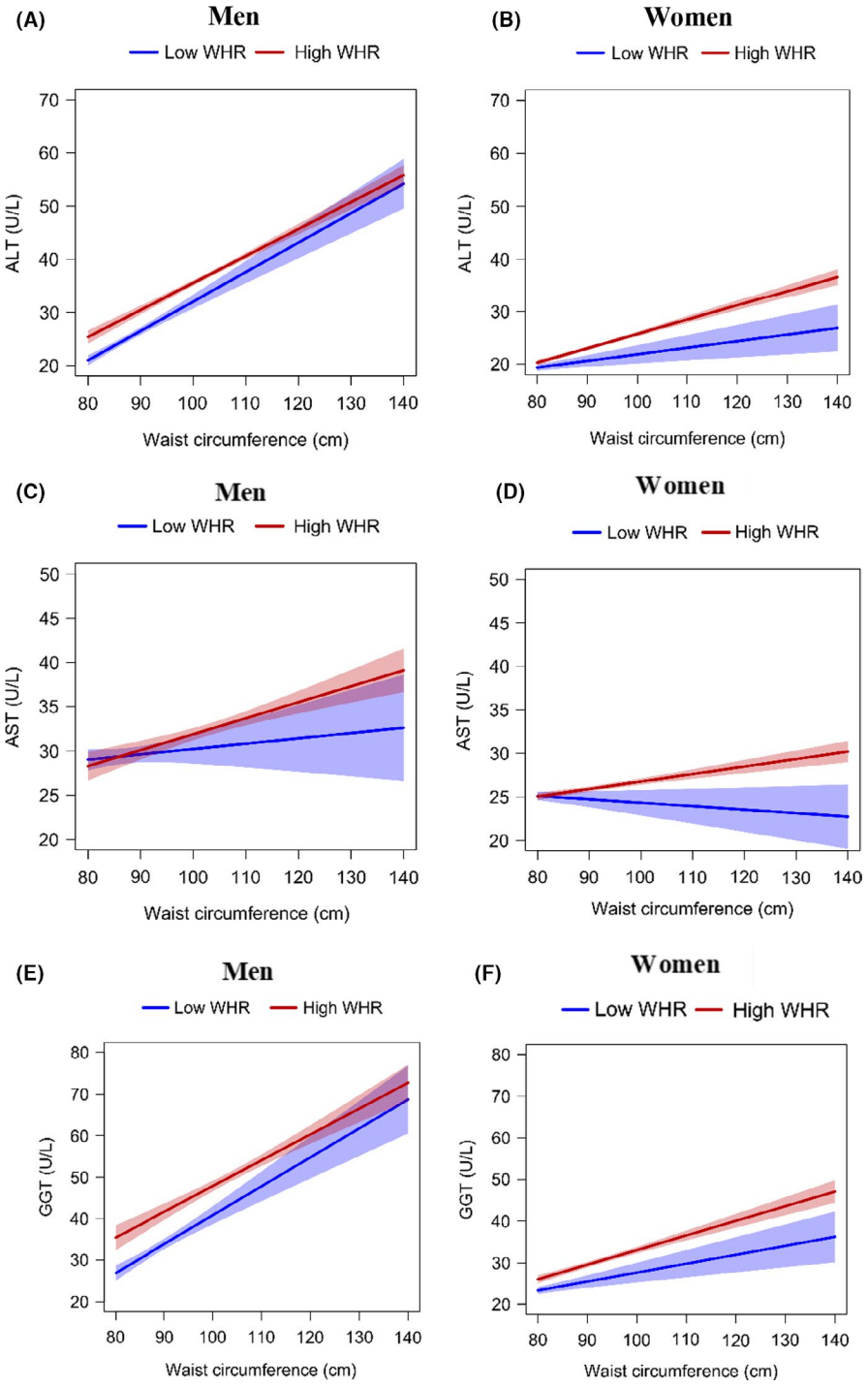

FIGURE 3 Age-adjusted association between waist circumference and serum levels of ALT (A and B), AST (C and D) and γ-GT (E and F). Analyses were performed separately for men and women, in subsets of individuals with low and high waist-hip ratio

3.6 | Association of WC and HC with incident liver disease

In the longitudinal cohort of 40 923 individuals, median follow-up until the first liver event, death, or December 2015 was 12.9 years (IQR 7.8-17.8 years, range 0-23 years, 509 055.7 person-years). During follow-up, 355 incident liver disease outcomes were registered, including 245 among men and 110 among women. Age-adjusted Cox regression analyses revealed that WC and HC were independently associated with incident severe liver outcomes among both men and women (Table 2). WC and HC remained significant in the fully adjusted Cox model (Table 2). The interaction effect between WC and HC for liver outcomes was significant for men, but not for women (Table 2).

After stratifying the cohort based on the sex-specific WHR median, the age-adjusted hazard ratios of WC and HC for liver outcomes were vastly different according to WHR strata in men. Among men, the low-WHR group had a WC-associated hazard ratio of 0.72 (95% CI 0.41-1.25, $P = .24$), while the high-WHR group had a WC-associated hazard ratio of 1.95 (95% CI 1.50-2.55, $P < .001$) (Figure 4). Among

TABLE 2 Independent associations of waist and hip circumference with incident liver outcomes by Cox Regression analyses

	Men				Women			
	HR[a] (95% CI)	*P*	HR[b] (95% CI)	*P*	HR[a] (95% CI)	*P*	HR[b] (95% CI)	*P*
WC, cm	1.08 (1.07-1.10)	<.001	1.07 (1.03-1.11)	<0.001	1.08 (1.05-1.10)	<.001	1.06 (1.02-1.10)	.004
HC, cm	0.92 (0.90-0.95)	<.001	0.96 (0.92-0.99)	0.04	0.93 (0.90-0.95)	<.001	0.93 (0.89-0.98)	.005
P int.	<0.001		<0.001		0.49		0.62	

Abbreviations: HC, hip circumference; *P* int., *P* for interaction; WC, waist circumference.

[a]Adjusted for age.

[b]Adjusted for age, systolic and diastolic blood pressure, BMI, daily cigarette consumption, weekly alcohol consumption, diabetes, exercise habits, and serum levels of cholesterol, LDL-C, HDL-C, triglycerides, and CRP.

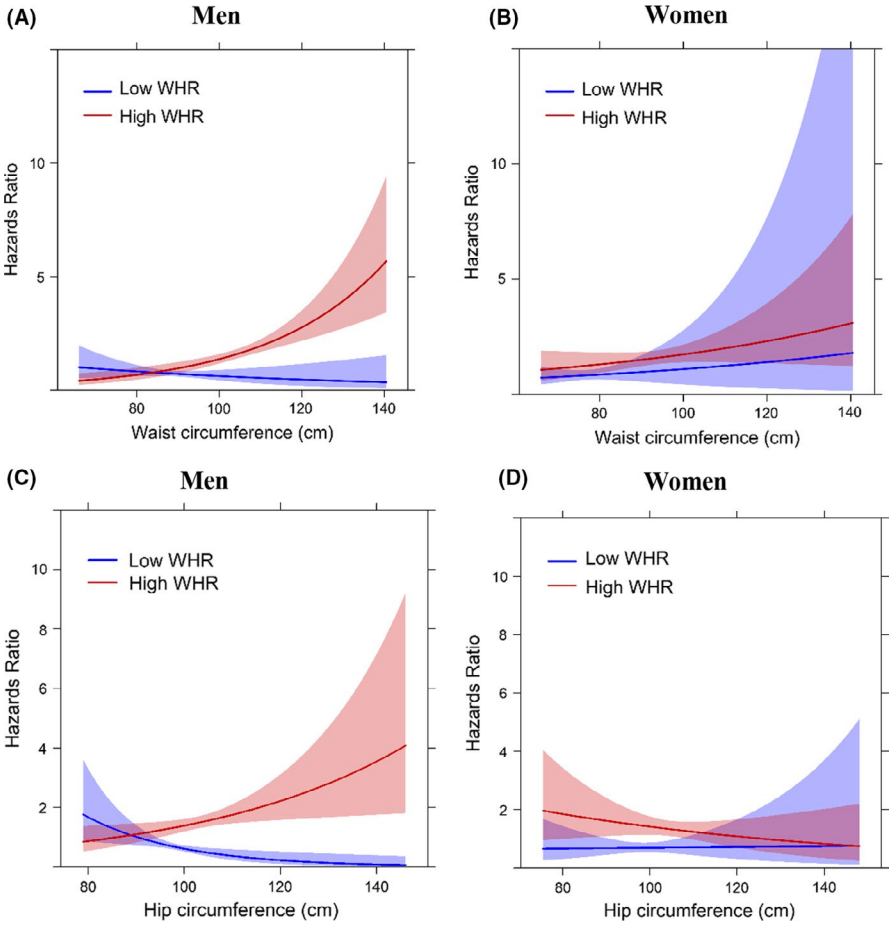

FIGURE 4 Associations between waist circumference and risk of liver outcomes among men (A) and among women (B), and associations between hip circumference and risk of liver outcomes among men (C) and among women (D) in subsets of individuals with low and high waist-hip ratio. Analyses were performed by Cox regression adjusted for age. WHR, waist-hip ratio

women, the low-WHR group had a WC-associated hazard ratio of 1.00 (95% CI 0.45-2.21, $P = 1.00$), and the high-WHR group had a WC-associated hazard ratio of 1.36 (95% CI 0.94-1.96, $P = .10$). Among men, the low-WHR group had an HC-associated hazard ratio of 0.56 (95% CI 0.38-0.84, $P = .005$), and the high-WHR group had an HC-associated hazard ratio of 1.29 (95% CI 1.06-1.57, $P = .02$). Among women, the corresponding HC-associated hazard ratios were 0.93 (95% CI 0.61-1.41, $P = .73$) and 0.89 (95% CI 0.69-1.14, $P = .36$). The age-adjusted interaction effects between WC and HC for incident liver outcomes are visualised in a heat-map plot (Figure 5), separately for men and women.

4 | DISCUSSION

In the present population-based cross-sectional and longitudinal cohort study, we found that WC and HC each exhibited independent associations with both liver enzymes and risk of liver disease, among both men and women. An interaction effect between WC and HC was evident, as especially ALT values showed a steeper rise along with increasing WC, among individuals with a visceral-type body composition (defined as a WHR above the sex-specific median) compared to those with low WHR. Similarly, among individuals with high

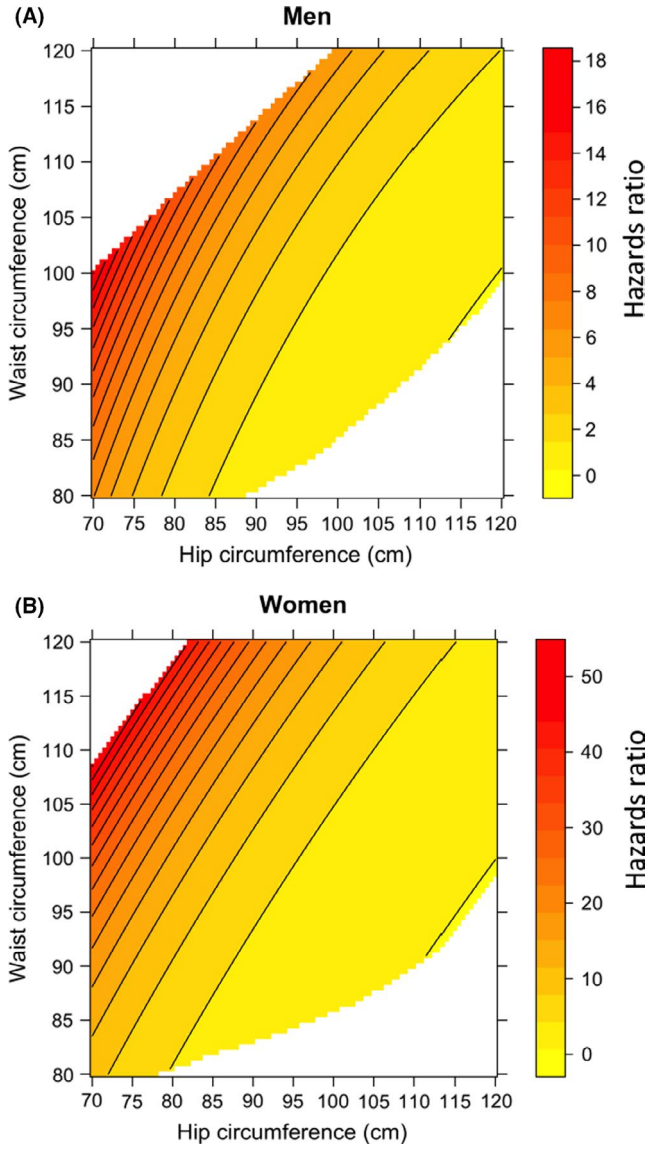

FIGURE 5 The interaction effects between waist and hip circumference for the risk of liver outcomes are visualised separately for men (A) and women (B), with adjustment for age. The colour code represents the hazard ratio (*z*-axis), with a more reddish colour indicating a higher hazard ratio

WHR, the risk of incident liver disease increased more steeply along with increasing WC values. Our interpretation is that HC modifies the association between abdominal obesity and liver disease. Although this modification effect was more apparent among men than women, the lack of significance in women may be due to insufficient statistical power (type II error). In order to estimate the possible risk profile of liver fibrosis of our study population already at enrolment, we performed a subgroup analysis applying the FIB-4 score, the results of which are in line with earlier population-based studies.[36]

In general, WC and the WHR both measure abdominal (visceral) fat, while HC reflects a combination of muscle mass, subcutaneous fat in the gluteofemoral region and skeletal structure.[10] On the other hand, BMI reflects overall obesity, but not body fat distribution.[37] Muscle mass and subcutaneous fat might have beneficial metabolic functions that partially counteract the adverse effects of visceral adiposity.[14,38,39]

Several studies indicate that hepatic steatosis is associated with central fat mass, lower extremity fat mass and appendicular lean mass.[40] A large Korean population-based study reported that sarcopenic subjects with NAFLD had an approximately two-fold increased risk of significant liver fibrosis, which was independent of obesity, insulin resistance and liver enzyme levels.[18] Two meta-analyses indicate that sarcopenia is a risk factor for NAFLD onset and is also associated with NAFLD progression to steatohepatitis and liver fibrosis.[15,16] Sarcopenic obesity seems to portend a particularly high risk.[41] Moreover, low physical activity, loss of skeletal muscle mass and strength, and low HC contribute to MetS and cardiovascular risks, and negatively affect the liver via NAFLD development.[14,17,18] The fact that HC reflects muscle mass and subcutaneous adiposity may explain the independent association of HC with liver disease, as well as why HC modifies the WC-associated risk of liver disease. Insulin resistance is a strong driver of both NAFLD and alcoholic liver disease.[42] It was recently shown that genetic loci associated with insulin resistance are also associated with lower HC, which has been interpreted as a reduced ability to expand peripheral fat compartments (low HC) when challenged by a positive energy balance.[43] Subcutaneous adiposity may indeed protect the body from the metabolic harm of visceral adiposity, by serving to store excess energy and thus avoiding fat accumulation in the liver and abdominal cavity.[44]

These findings suggest that body composition measures beyond simple WC may better reflect the metabolic harm of obesity on the liver. The WHR accounts for both WC and HC and, indeed, several epidemiological studies have concluded that the WHR predicts incident severe liver disease better than BMI, WC, or other anthropometric measures.[7-9]

Our correlation analyses revealed fairly similar findings for WHR and BMI in terms of reflecting known liver disease risk factors and bioimpedance variables. Regarding WC and HC, the correlations were generally opposite, meaning that low WC and high HC generally reflected better health. HC was inversely related to fat percent and positively related to SMI in men, with the opposite findings in women, suggesting that HC reflects muscle mass more clearly in men than in women. This might partly explain why the interaction effect between WC and HC for liver disease was stronger in men than in women. In parallel, a 12-year follow-up study of 5799 men and 6429 women demonstrated that survival among older adults was predicted by WC in men, but not in women.[36]

Smoking and number of cigarettes were consistently associated with WHR, WC and HC, but not with BMI. Smoking can induce metabolic alterations that lead to altered body fat composition, with preferential storage of excess energy in the metabolically more harmful visceral fat deposits rather than in subcutaneous deposits and further leading to insulin resistance.[45,46] Among men, alcohol consumption and binge drinking consistently reflected the anthropometric measures. Overall, our findings suggest that these

key anthropometric measures only weakly reflect alcohol consumption and binge drinking in women.

Distinct genetic mechanisms may be linked to gluteofemoral and abdominal fat distribution.[38,47] Among the 59 candidate genetic risk variants associated with liver disease in previous studies, our present study showed that two variants in the tumour necrosis factor-α (TNF-α) gene (rs1800629A and rs361525A) were strongly associated with HC, independently of WC and BMI. TNF-α has previously been linked with both non-alcoholic and alcoholic steatohepatitis.[32] Um et al previously reported that the TNF-α rs361525A variant is associated with WHR, but not with BMI, among obese Koreans.[48] We have confirmed this finding in the Finnish population, and further demonstrated that this association is specifically related to the HC. Circulating TNF-α is an inflammatory cytokine with catabolic properties predisposing to muscle wasting,[49] and genetic variation in the TNF-α locus is reportedly related to muscle mass.[50] This suggests that the association between TNF-α and HC may be secondary to differences in muscle mass, but this possibility merits further study.

The strengths of our study include the large population-based cohorts suitable for cross-sectional and longitudinal analysis, as well as the linkage with long-term outcome data with reliable national healthcare registers. The health-examination survey data enabled the combined analysis of large amounts of phenotype data, including bioimpedance data, and genotype data, along with both liver enzymes and incident liver disease. The cohorts were representative of the Finnish population and were thus ethnically homogenous. Baseline data were collected by trained healthcare professionals.

One limitation of the study was that the bioimpedance measures were performed 20 years ago with the techniques that were used at that time. Additionally, the baseline data related to alcohol, smoking and exercise relied on information provided by the individuals participating in the cohorts. Notably, this was a prospective study performed in a single country, and the analyses may need to be replicated in ethnically diverse populations.

In conclusion, the results of the present population-based study emphasise the importance of the WHR as a risk factor for severe liver disease. WC and HC have independent and joint associations with liver disease risk, which increased along with increasing WC and HC among individuals with a high WHR. Furthermore, fat mass and muscle mass were almost consistently independently associated with WHR and HC in both sexes. Five liver disease-related risk genotypes were associated with either WC, HC, or BMI. WC was associated with serum liver enzymes in a WHR-dependent manner. Moreover, high HC was associated with several beneficial health-related characteristics.

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest.

AUTHOR CONTRIBUTIONS

OD: study design, interpretation of results and writing the manuscript; MJN: study design, interpretation of results and writing the manuscript; AJ, VS, SM, AL, MP: study design, data collection, interpretation of results and critical revision of the manuscript; FÅ: study design, statistical analyses, interpretation of results and writing the manuscript. All authors revised and approved the manuscript.

STATEMENT REGARDING PERMISSION TO REPRODUCE MATERIAL

Dr Fredrik Åberg has the permission to analyse FINRISK and Health 2000 data from the THL biobank.

DATA AVAILABILITY STATEMENT

FINRISK and Health 2000 data are available from the THL biobank based on a research application, as explained on the website of the THL biobank (https://thl.fi/en/web/thl-biobank/for-researchers).

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SUPPORTING INFORMATION

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How to cite this article: Danielsson O, Nissinen MJ, Jula A, et al. Waist and hip circumference are independently associated with the risk of liver disease in population-based studies. *Liver Int*. 2021;41:2903–2913. https://doi.org/10.1111/liv.15053