Published in final edited form as:
Hepatology. 2010 June ; 51(6): 1979–1987. doi:10.1002/hep.23593.

Fatty Liver is Associated With Dyslipidemia and Dysglycemia Independent of Visceral Fat: The Framingham Heart Study

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Abstract

Obesity is not uniformly associated with the development of metabolic sequelae. Specific patterns of body fat distribution, in particular fatty liver, may preferentially predispose at-risk individuals to disease. Here we characterize the metabolic correlates of fat in the liver in a large community-based sample with and without respect to visceral fat. Fatty liver was measured by multi-detector computed tomography of the abdomen in 2589 individuals from the community-based Framingham Heart Study (FHS). Logistic and linear regression were used to determine the associations of fatty liver with cardio-metabolic risk factors adjusted for covariates with and without adjustment for other fat depots (body mass index [BMI], waist circumference [WC], and visceral adipose tissue [VAT]). The prevalence of fatty liver was 17%. Compared to participants without fatty liver, individuals with fatty liver had a higher adjusted odds ratio (OR) of diabetes (DM; OR 2.98; 95% confidence interval [CI], 2.12–4.21), metabolic syndrome (MetS; OR, 5.22; 95% CI, 4.15–6.57), hypertension (HTN; OR 2.73; 95% CI, 2.16–3.44), impaired fasting glucose (IFG; OR 2.95; 95% CI, 2.32–3.75), insulin resistance (IR; OR, 6.16; 95% CI, 4.90 – 7.76), higher triglycerides (TG) and systolic and diastolic blood pressure (SBP, DBP) and lower high density lipoprotein (HDL) and adiponectin levels ($p<0.001$ for all). After adjustment for other fat depots, fatty liver remained associated with DM, HTN, IFG, MetS, HDL, TG and adiponectin levels (all $p<.001$), whereas associations with SBP and DBP were attenuated ($p>0.05$).

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Conclusion—Fatty liver is a prevalent condition and is characterized by dysglycemia and dyslipidemia independent of VAT and other obesity measures. This work begins to dissect the specific links between fat depots and metabolic disease.

Keywords

NAFLD; lipid; glucose; fat depot

Background

Obesity is a global epidemic. In the United States more than 66% of individuals are overweight or obese and more than 33% are obese (1). Obesity affects more than a billion people worldwide and is expected to increase to 1.5 billion by 2115(2). Obesity is associated with metabolic complications, although not all obese individuals develop medical sequelae (3). Why some people develop obesity-related illnesses and others do not has not been well-characterized.

One hypothesis for why some individuals develop medical problems from obesity is that specific fat depots may predispose some individuals to getting particular ailments. Abdominal obesity, as estimated by waist circumference, has been associated with metabolic syndrome, insulin resistance, and cardiovascular complications (4). Subcutaneous and visceral adipose tissue as well as fat in liver are all correlated with waist circumference (5,6), but how these depots selectively contribute to the development of metabolic complications is not clear. One possibility is that these depots produce adipocytokines including adiponectin and resistin that can affect steatosis as well as metabolic traits. Adiponectin in rodents for example can alleviate steatosis and improve insulin sensitivity (7,8) while resistin may promote steatosis and insulin resistance (9,10). Further, fatty liver has been considered by some to be a by-product of fat deposition in the viscera, blood from which drains to the liver where it is deposited (11). Alternatively, fat in the liver may confer independent metabolic consequences above and beyond the effects of visceral fat.

Therefore, the goal of this study is to examine the correlation of fatty liver with metabolic risk factors for cardiovascular disease, and in particular to assess the association of metabolic risk factors for cardiovascular disease with fatty liver above and beyond standard anthropometric measures and visceral abdominal fat. Here we report the measurement, prevalence, metabolic and anthropometric correlates of fatty liver in the Framingham Heart Study.

Participants and Methods

Participants

Participants were drawn from the Framingham Heart study, a prospective cohort study initiated to evaluate risk factors for the development of cardiovascular disease. The selection criteria for this cohort has been previously published (12). The study was initiated in 1948 when 5209 residents of Framingham Massachusetts were enrolled. These individuals have been followed since then with multiple serial examinations and collection of risk factor data. In 1971, 5124 offspring and their spouses were recruited into the Offspring Study and have been followed every four to eight years since then (13). In 2002, 4095 Third Generation members and their spouses were enrolled (14). Between 2002 and 2005, multidetector computed tomography of the chest and abdomen were performed in 3529 individuals drawn from families including both Offspring and Third Generation participants.

Multidetector computed tomography scan cohort

Overall 3529 individuals underwent multidetector computed tomography scanning, 1418 from the Offspring and 2111 from the Third Generation. Inclusion criteria for the study favored individuals who still resided in the greater New England area and included 755 families. Minimum age cutoffs were 35 years in men and 40 years in women. All women of child-bearing age completed a pregnancy screening, and pregnant women (for risk to the fetus) and individuals >160 kg were excluded from scanning. Individuals undergoing scans were excluded from this analysis if their Multidetector computed tomography scans were not interpretable for fatty liver (n=323), did not attend Offspring Examination 7 (n=23) or if individuals reported greater than 7 drinks for men or 14 drinks for women per week (n=487). Of these, 107 were missing a complete covariate profile and were further excluded, resulting in a total sample size of 2589.

Multidetector computed tomography scan protocol and measurement of fatty liver, visceral and subcutaneous adipose tissue

Multidetector computed tomography scanning was conducted as previously reported (5,15,16). A calibration phantom (Image Analysis, Lexington, KY, USA) with a water equivalent compound (CT-Water, Light Speed Ultra, General Electric, Milwaukee, WI, USA) and calcium hydroxyapatite at 0, 75, and 150 mg/cm^3 was placed under each participant (16).

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were measured(5,15); briefly, 25 contiguous 5mm thick sections (120kVP, 400mA, gantry rotation time 500ms, table feed 3:1 were acquired covering 125mm above S1). Fat was identified using an image display window of −195 to −45 HU and a window center of −120 HU. After manually tracing the abdominal muscular wall separating the visceral from the subcutaneous compartment high resolution volumetric measures SAT and VAT were defined as the volumetric fat content outside and inside of this dividing line. The intra-class correlation coeficient was 0.992 for VAT and 0.997 for SAT.

Fatty liver was measured on Multidetector computed tomography scans of the abdomen and has been described elsewhere(16). Briefly, three areas from the liver, two from the spleen and one from the external phantom were measured. The average of the liver and spleen measures were then calculated and used to create liver/spleen ratios and liver/phantom ratios. The intra-class correlation coefficient was 0.99 (16). Given that the phantom but not the spleen was visualized on all scans, primary analyses were conducted with a liver phantom ratio as the indexed standard; secondary analyses were conducted on the liver-spleen ratio. Only participants with abdominal scans were used in the current analysis, since data from the abdominal scans had better reproducibility than chest scans (16).

Distribution of the fatty liver phenotype

The distributions of liver phantom ratio and liver spleen ratio were left skewed with a median [Lower–Upper Quartile] of 0.37[0.34–0.39] and 1.21[1.13–1.28] respectively (Supplemental Figure 1A). The 95th percentiles were 0.41 and 1.37 for the liver phantom ratio and liver spleen ratio, respectively. In the literature, an liver spleen ratio of 1.1 corresponds to the presence of 30% fatty liver (17). We found that a liver phantom ratio cutoff of 0.33 had a 98% sensitivity and 70% specificity using liver spleen ratio cutpoint of 1.1 as the gold standard (Supplemental Figure 1B).

Measurement of covariates

Risk factors used in analyses in this paper were measured at the seventh examination cycle of the Offspring cohort (1998–2001) or the first examination of the Third Generation cohort

(2002–2005). Body mass index (BMI) is defined by weight (kilograms)/height (meter)^2; waist circumference (WC) is measured at the level of the umbilicus; diabetes (DM) is defined as a fasting plasma glucose (FPG) of at least 126 mg/dL at examination or treatment with either insulin or a hypoglycemic agent; impaired fasting glucose (IFG) is defined as FPG of 100–125 mg/dL among those not treated for diabetes; hypertension (HTN) is defined as a systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg or on antihypertensive treatment. Triglycerides (TG) and high density lipoprotein (HDL) levels are measured on fasting morning samples. Participants are considered current smokers if they had smoked at least 1 cigarette per day in the year preceding the Framingham Heart Study examination. Alcohol use was assessed through a series of physician administered questions. Physical activity, assessed with a questionnaire, is a score based on the average daily number of hours of sleep and sedentary, slight, moderate, and heavy activity of the participant. Women are considered menopausal if their periods had stopped for at least 1 year. Metabolic syndrome (MetS) is defined from modified Adult Treatment Panel criteria. Obesity is defined as BMI ≥ 30 kg/m^2. Insulin resistance was determined as the top quartile of the homeostasis model (HOMA-IR: [fasting glucose × fasting insulin]/22.5] distribution among individuals without diabetes (18,19). Circulating adiponectin and resistin were measured by enzyme linked immunoassay after an 8 hour fast as previously described (20).

Determination of fatty liver phantom ratio dichotomous cutoff and continuous distribution

The distributions of liver phantom ratios and liver spleen ratios were characterized. Because the liver phantom ratio and liver spleen ratio are likely measures of more than just fat in the liver (i.e water content, iron, etc) the top 5% of points in liver phantom ratio were winsorized for analyses with fatty liver as a continuous variable.

Prior to winsorization, to determine the liver phantom ratio cut-off that mirrored a liver-spleen ratio of 1.1, the cutoff that best discriminates the presence of 30% fat in the liver (17), we minimized misclassification of subjects at various cutoffs for liver phantom ratio. From a Receiver Operating Curve analysis of liver phantom ratio compared to a gold standard of liver spleen ratio of 1.1 we determined the sensitivity and specificity of various cutoffs of liver phantom ratio and established a liver phantom ratio cutoff of 0.33 or lower as our working definition of fatty liver.

Statistical analyses

Differences in participant characteristics between those with (liver phantom ratio ≤ 0.33) and without fatty liver (liver phantom ratio > 0.33) were determined using a t-test for normally distributed traits, Wilcoxon rank sum test for non-normally distributed continuous variables or ordinal variables, and a chi squared test for dichotomous variables. As the liver phantom ratio was not normally distributed, Spearman correlation coefficients were used to determine age- and sex-adjusted correlations of continuous metabolic traits with liver phantom ratio.

Primary multivariable analyses focused on fatty liver (yes/no) as the exposure and individual metabolic risk factors and fat depot measures as the dependent (outcome) variables. For dichotomous outcomes, odds ratios (calculated fatty liver yes vs. fatty liver no) are reported; for continuous outcomes, the regression coefficients for the presence of fatty liver are reported. We also modeled continuous fatty liver as the exposure and odds ratios and regression coefficients for a 1 SD decrease in liver phantom ratio are reported for dichotomous and continuous outcomes, respectively. The following modeling structures were used. In Model 1, age, sex, alcohol consumption (after exclusions mentioned above), menopausal status, hormone replacement therapy, smoking (3-level variable: current/former/never smoker) were included as covariates. In addition, lipid treatment, hypertension

treatment, and diabetes treatment were included as covariates in models for HDL cholesterol, log triglycerides, systolic and diastolic blood pressure, and fasting plasma glucose, respectively. In Model 2, we additionally adjusted for body mass index, waist circumference, and VAT. SAT was not included in these multivariate models because it was highly collinear with BMI.

In secondary analyses, we additionally added physical activity and education to the models. Assessment of the significance of sex and age interactions with fatty liver on metabolic risk factors was also assessed. Analyses were performed using SAS version 9.1; a two-sided 0.05 alpha was used to declare statistical significance.

Results

Study Sample Characteristics

The characteristics of the participants are shown in Table 1. Fifty one percent of the sample were women, with an average age of 51 years and a BMI of 27.6 kg/m^2. Using liver phantom ratio ≤ 0.33 to define fatty liver, we determined the characteristics of the participants with and without fatty liver (Table 1). Individuals with fatty liver had a substantially more adverse cardiovascular disease risk factor profile (Table 1).

Prevalence

The overall prevalence of fatty liver was 17%. Age- and gender-specific prevalence was higher for men (19%) compared with women (15%), and peaked for men between ages 55–64 years and for women between ages 75–84 years (Table 2). There was little difference in prevalence using liver spleen ratio instead of liver phantom ratio as a measure of fatty liver (data not shown).

Correlations Between Fatty Liver and Metabolic/Anthropometric Traits

Fatty liver as measured using liver phantom ratio and liver spleen ratio was associated with all tested metabolic and fat-depot variables. Decreases in liver phantom ratio and liver spleen ratio (i.e. reflecting more fat in the liver) were associated with higher levels of VAT, WC, BMI, TG, weight, SAT, FPG, HOMA-IR, SBP, DBP, and lower adiponectin and HDL ($p<0.001$ for all; Table 3).

Multivariable-adjusted Correlations Between Fatty Liver and Metabolic/Anthropometric Traits

Fatty liver (as both continuous and dichotomous measures) was significantly associated with all glucose, lipid and blood pressure traits ($p <0.001$) except resistin levels in multivariable analyses (Table 4). Compared to participants without fatty liver, individuals with fatty liver had a higher adjusted odds ratio of prevalent DM (odds ratio [OR], 2.98; 95% confidence interval [CI] 2.12–4.21), insulin resistance (IR; OR, 6.16; 95% CI, 4.90 – 7.76), MetS (OR, 5.22; 95% CI 4.15–6.57), HTN (OR, 2.73; 95% CI 2.16–3.44) and IFG (OR, 2.95; 95% CI 2.32–3.75) than individuals without fatty liver ($p<0.001$ for all).

After further adjustment for BMI, WC, and VAT, there remained statistically significant associations of fatty liver with prevalent DM (OR, 1.64; 95% CI 1.11 – 2.41), IFG (OR, 1.58; 95% CI 1.21 – 2.07), insulin resistance (IR; OR, 2.79; 95% CI, 2.14 – 3.65), MetS (OR, 1.95; 95% CI 1.48 – 2.56), log HOMA-IR (beta 0.21 mg/dL 95% CI 0.17 – 0.25 mg/dL), adiponectin (beta −1.59 mg/dL, 95% CI −2.57 – −0.62), log TG (beta 0.22 mg/dL 95% CI 0.17 – 0.28 mg/dL), HDL (beta −2.5 mg/dL 95% CI −3.9 – −1.1 mg/dL) and HTN (OR, 1.52; 95% CI 1.17 – 1.97), whereas SBP and DBP were no longer associated with fatty liver ($p = 0.09$ and 0.19 respectively; Table 4).

Similar associations were observed when we examined decreasing liver phantom ratio as a continuous measure of fatty liver (Table 4). Similar results were also observed after additional adjustment for physical activity and education (data not shown). There was no evidence for an interaction by age or gender in the association of fatty liver with continuous or dichotomous metabolic risk factors except with adiponectin where women had a slightly higher effect than men, and in HOMA-IR where individuals >50 years of age had a higher HOMA-IR values than those <50 years of age but in all cases the effect in these classes was directionally consistent with the overall effect (data not shown).

The median glucose, TG, HDL, SBP and DBP values in participants above and below the 90^{th} percentile cut-point for VAT derived from a healthy referent sample(21) (Figure 1) show that lipid and glucose traits were associated with fatty liver ($p<0.0001$), while SBP and DBP were associated to a lesser extent ($p=0.0002$ and 0.004 respectively) with fatty liver high and low levels of VAT. When fatty liver and VAT were jointly considered in the multivariate models, VAT remained associated with all metabolic correlates (all $p<0.0001$; data not shown) whereas fatty liver was not associated with SBP and DBP ($p=0.06$ and 0.16 respectively. However, fatty liver remained associated with all other metabolic traits (p-values<0.004) (data not shown).

Conclusions

Fatty liver is observed in 17% of participants in an unselected community-based sample. Individuals with fatty liver are characterized by a high-risk metabolic profile. After adjustment for other fat depots including VAT, fatty liver remained associated with lipid and glucose traits.

The most compelling and unique finding in our study was the association of fatty liver with lipid and glucose traits independent of VAT. Not all obese individuals develop metabolic disease from their obesity. Understanding how individuals that develop metabolic sequelae from their obesity differ from those that do not may help target at-risk individuals and guide development of novel therapeutics to combat disease. In the present work, we extend previous studies (6,22–27) and illustrate how fatty liver associates with metabolic syndrome components in the largest study to date of Caucasian individuals that have not been selected for the presence of fatty liver, obesity, or metabolic disease. The association of liver fat with lipid, glucose and blood pressure traits may be indirect and due to generalized adiposity, or to the presence of fat in particular depots including VAT. The size of our cohort and the richness of the covariates and traits measured including VAT gave us the unique opportunity to assess the association of liver fat with these cardiometabolic traits above and beyond VAT. In particular, we found that VAT is the strongest correlate of fatty liver and after adjusting for VAT, fatty liver remains associated with dyslipidemia and dysglycemia. Given the cross sectional, observation nature of our measures, our findings must be considered in light of the fact that association does not prove causality.

The liver is the main source of lipid regulation in the body, plays an important role in glucose metabolism, and overall is known to play little known role in blood pressure regulation. Fat accumulation in the liver is predominantly in the form of triglycerides. Fifteen percent of this fat comes from dietary cholymicrons, 60% from non-esterified fatty acids that come from lipolysis from adipose tissue or from lipoproteins hydrolyzed above a rate that can be taken up by adipose tissue, and 25% from newly synthesized fatty acids (28). Delivery of non esterified fatty acids from visceral adipose tissue has been shown to be as high at 20% of the total delivery of fatty acids to the liver compared to just 5% in lean individuals without visceral fat (29). In our population-based study we show that even though VAT was the strongest correlate of fatty liver, the correlation is at best modest

(−0.34), suggesting that VAT is only one component in the pathogenesis of fatty liver. It has been shown that in the absence of peripheral fat stores or in insulin resistant states where peripheral tissues are impaired in their ability to accumulate energy stores, there can be an increase in non-esterified fatty acid delivery to the liver and increased fat accumulation in mice and humans (30–32).. Indeed we find that the second best correlate of fatty liver is insulin resistance. Delivery of excess fatty acids to the liver in energy excess states due to differences in fat storage ability and/or insulin resistance peripherally in the population may result in de novo lipogenesis, fatty acid esterification, and storage of esterified fatty acids as cytoplasmic triglycerides or to formation of VLDL particles (33,34).. These VLDL particles can be secreted and can lead to the formation of atherogenic small dense lipoprotein particles, cholesterol rich VLDL remnants, and triglyceride rich HDL particles which can be cleared by the kidney leading to lower levels of HDL (33).. In this way, fatty liver may be specifically related to hypertriglyceridemia, low HDL, and impaired glucose utilization above and beyond other fat depots consistent with what we find in our analyses. Further, the lack of peripheral fat storage capacity may be indirectly indicated by low levels of adipokines such as adiponectin, which is inversely corrected with fatty liver. Alternatively, low levels of adiponectin may be related directly to the excess storage of energy in the liver.

The conjoint associations of fatty liver and VAT in association with lipid and glucose traits highlights the independent roles of different metabolic fat depots. Further, our findings that fatty liver was mostly associated with lipid and glucose traits may help explain in part why these abnormalities are often seen together. In addition, understanding why some, but not all individuals, develop fatty liver can shed light into understanding why certain individuals develop metabolic complications of obesity while others do not. Finally, it will be of great interest to determine whether the presence of fat in the liver prospectively is an independent predictor of development of not only metabolic disease in the form of dysglycemia or dyslipidemia but also of cardiovascular disease.

The strength of the current study is the large, well characterized cohort of individuals with a wealth of metabolic traits and covariates measured. Further, our sample is unselected for obesity-related traits, reducing selection bias. Indeed we establish that fatty liver is prevalent at 17%, affects more men than women, and peaks in women at later ages than in men in the largest Caucasian population based study to date. Our study directly measured fatty liver on CT, which allowed us to quantify it more precisely as compared to indirect measures of fatty liver disease such as elevated liver function tests which have a low sensitivity to detect the presence of the condition. We also measured both liver phantom ratio and liver spleen ratio and found that our results were comparable between these two measures, suggesting that these results can be compared with studies that have just the liver spleen ratio. The distribution was skewed with most people having little or no fatty liver. The peak of the distribution may represent a point at which people have no fat in their liver or alternatively low levels of fat that can be considered “normal” for the population. Since high water, glycogen or iron concentrations in the liver increase the attenuation of the liver confounding by these deposits would if anything lead to underestimation of fatty liver; individuals to the left of the peak likely do have high liver fat. Our study was limited by including only individuals of European ancestry and thus cannot be generalized to other ethnicities. Also, these individuals were initially from one geographic area and were part of a health outcomes study which may not be generalizable. Further, covariates were measured at times separate from the CT scans and computed tomography can only indirectly measure fat in the liver; these effects may result in misclassification. However, misclassification would only serve to bias our results towards the null, and would not lead to a positive association, as we have observed. Further, a general limitation of the diagnosis of diabetes in population-based studies is that it is dependent on a one-time assessment of glucose and self-reported medication use, which may include metformin. In particular, metformin might be used for

both PCOS and impaired fasting glucose. The exposure and covariate data was measured from 1998–2005, and may not reflect current trends. Lastly, these data are cross sectional and derived from an observational study; therefore we can not draw conclusions

Fatty liver is a prevalent condition and is characterized by dysglycemia and dyslipidemia independent of VAT. These findings highlight the specificity of fat accumulation in particular depots and the presence of metabolic disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support:

EKS was supported by an NIH T32 DK07191-32 grant to Daniel K. Podolsky in the department of gastroenterology at Massachusetts General Hospital and NIH F32 DK079466-01 and NIH K23DK080145-01 grants to EKS. The Framingham Heart Study is supported by core contract N01-HC25195. Additional research support was provided by an American Diabetes Association Career Development Award (JBM), the General Clinical Research Centers Program (Grant No. M01-RR-01066); and National Institute of Diabetes and Digestive and Kidney Diseases K24 DK080140 (JBM). Dushyant V Sahani has a research agreement with General Electric and is on the Speakers' Bureau of Bracco Diagnostics. JBM currently has research grants from GlaxoSmithKline and sanofi-aventis, and has consulting agreements with Eli Lilly and Interleukin Genetics.

Abbreviations

FHS	Framingham Heart Study
BMI	Body mass index
WC	Waist circumference
VAT	Visceral adipose tissue
OR	Odds ratio
DM	Diabetes Mellitus
CI	Confidence Interval
MetS	Matabolic Syndrome
p	P value
HTN	Hypertension
IFG	Impaired fasting glucose
TG	Triglycerides
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HDL	High density lipoprotein
FPG	Fasting plasma glucose
Kg	Kilogram
KY	Kentucky
USA	United States of America

Mg	Miligrams
cm^3	Centimerters cubed
Mm	Milimeters
WI	Wisconcin
kVP	Kilovolt potential
mA	Miliamp
S1	Sacral spine 1
HU	Hounsefeld units
dL	Deciliter
m^2	Milimeter
SD	Standard Deviation
TNF	Tumor necrosis factor
VLDL	Very low density lipoprotein

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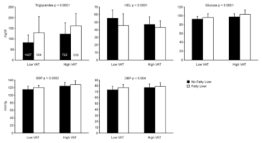

Figure 1.

Median and IQR (error bars) for triglycerides, high density lipoproteins (HDL), glucose, systolic blood pressure (SBP) and diastolic blood pressure (DBP) p: age, gender, and VAT corrected p value between fatty liver categories; histogram counts are shown in triglyceride panel apply to all panels. The high VAT category refers to those above the 90th percentile cut-point derived from a healthy referent sample.

Table 1

Characteristics of the participants

Category	All (2589)*	No Fatty Liver (2150)*	Fatty Liver (439)*	p-value#
Covariates				
Female (%)	51	44	53	0.0002
Age (years)	51.0(10.6)	50.8(10.6)	52.3(10.7)	0.0015
Drinks per week	3.0(3.5)	3.0(3.4)	3.1(3.9)	0.7619
Physical Activity	37.4(6.8)	37.5(6.9)	36.9(6.4)	0.0256
Smoking Category				0.1376
Smoke Never (%)	49.7 (1287)	50.6 (1088)	45.3 (199)	
Smoke Former (%)	38.7 (1002)	37.9 (815)	42.6 (137)	
Smoke Current (%)	11.6 (300)	11.5 (247)	12.1 (53)	
Education Category				0.0028
Education some High School (%)	1.6 (41)	1.5 (32)	2.5 (11)	
Education High School Graduate	21.3 (551)	20.7 (445)	24.3 (107)	
Education Some College (%)	29.7 (769)	29.0 (624)	32.9 (144)	
Education College Graduate (%)	47.4 (1227)	48.8 (1049)	40.3 (177)	
Menopause (women only) (%)	26.1 (676)	26.1 (561)	26.2 (115)	0.0623
HRT (%)	11.9 (308)	11.8 (254)	12.5 (55)	0.1872
Fat related				
BMI (kg/m2)	27.6(5.3)	26.8(4.8)	31.4(5.8)	<.0001
Waist Circumference (cm)	96.5(14.3)	94.4(13.4)	106.4(14.1)	<.0001
Subcutaneous Adipose Tissue (cm3)	2847.7(1399.0)	2697.5(1327.1)	3583.4(1506.4)	<.0001
Visceral Adipose Tissue (cm3)	1749.5(1021.4)	1568.1(912.9)	2638.1(1059.6)	<.0001
BMI Category				<.0001
Normal weight (BMI<25)	34.0 (882)	38.9 (837)	10.3 (45)	
Overweight (25<=BMI<30)	39.5 (1022)	40.4(869)	34.9 (153)	
Obese (BMI>=30)	26.5 (685)	20.7 (444)	54.9 (241)	
Glucose related				
Fasting Glucose (mg/dl)	99.1 (12.9)	97.1 (19.4)	108.7 (33.6)	<.0001
Diabetes Mellitus (%)	6.7 (173)	5.1 (110)	14.6 (64)	<.0001
IFG-Non-DM Only(%)	27.5 (712)	23.6 (507)	48.8 (214)	<.0001
HOMA-IR [Median (Q1–Q3)]	2.63 (2.11 – 3.54)	2.47 (2.05 – 3.21)	3.88 (2.95 – 5.39)	<.0001
log HOMA-IR	1.03 (0.47)	0.95 (0.43)	1.40 (0.51)	<.0001
Insulin resistance (%)	28.9(692)	21.6(425)	62.7(267)	<.0001
Adiponectin (μg/ml)**	9.8(6.0)	10.5(6.1)	7.0(4.8)	<.0001
Resistin [Median (Q1–Q3)]	13.40 (10.60 – 17.10)	13.25 (10.40 – 17.05)	14.20 (11.80 – 17.70)	0.0474
log Resistin (ng/ml)**	2.62 (0.41)	2.61 (0.41)	2.67 (0.39)	0.1199
Lipid related				
Triglycerides (mg/dL)	103[71–155]	95[67–139]	157[110–217]	<.0001
HDL Cholesterol (mg/dl)	52.5(15.8)	54.0(15.7)	45.2(14.1)	<.0001
Total Cholesterol (mg/dL)	195.2(35.4)	194.6(35.0)	197.9(37.1)	0.1065

Category	All (2589)*	No Fatty Liver (2150)*	Fatty Liver (439)*	p-value#
Blood pressure related				
SBP (mmHg)	121.1 (16.2)	120.0(16.1)	126.8(15.3)	<.0001
DBP (mmHg)	75.28(9.3)	74.7(9.1)	78.1 (9.5)	<.0001
Hypertension (%)	27.3 (707)	23.6 (507)	45.4 (199)	<.0001
Syndrome related				
Metabolic Syndrome (%)	31.4 (813)	25.0 (538)	62.9 (276)	<.0001

data in parentheses refers to the standard deviation for continuous traits and the number affected for dichotomous traits

*represents mean (SD) or median(inter quartile range) or percent (number of individuals)

#based on t-test or Wilcoxon Rank Sum Test or Chi squared

**based on 857 individuals in offspring only, 157 with fatty liver and 700 without fatty liver

HRT: hormone replacement therapy

BMI: Body mass index

IFG: impaired fasting glucose

HOMA-IR: Homeostasis model assessment of insulin resistance

HDL: high density lipoprotein

SBP: systolic blood pressure

Table 2

Prevalence of Fatty Liver

	Fatty Liver						
Age	**Total**	**(%)**	**Men**	**(%)**	**Women**	**(%)**	**p value***
<35	6/45	13.3	6/40	15.0	0/5	0.0	>0.9999
35–44	113/779	14.6	73/436	16.7	40/343	11.7	0.0514
45–54	154/926	16.6	79/420	18.8	75/506	14.8	0.1111
55–64	94/486	21.1	53/207	25.6	41/279	14.7	0.0036
65–74	60/290	20.7	30/134	22.4	30/156	19.2	0.5618
75–84	12/63	19.1	5/27	18.5	7/36	19.4	>0.9999
all	439/2589	17.0	246/1264	19.0	193/1325	15.0	0.0010

* p value for comparison between sexes from Fisher's Exact test

Table 3

Negative Spearman Correlations of LPR and LSR with continuous Traits

	LPR(n = 2589)		LSR(n = 1284)	
Trait	**Corr***	**p value**	**Corr***	**p value**
BMI (kg/m2)	0.25	<.0001	0.27	<.0001
Waist Circumference (cm)	0.26	<.0001	0.27	<.0001
SAT (cm3)	0.20	<.0001	0.21	<.0001
VAT (cm3)	0.34	<.0001	0.34	<.0001
WEIGHT (kg)	0.23	<.0001	0.26	<.0001
Glucose (mg/dL)	0.17	<.0001	0.17	<.0001
HOMA-IR	0.32	<.0001	0.32	<.0001
Adiponectin (μg/ml)**	−0.25	<.0001	−0.32	<.0001
Resistin (ng/ml)**	0.07	<.0001	0.08	0.08
TG (mg/dL)	0.23	<.0001	0.30	<.0001
HDL (mg/dL)	−0.19	<.0001	−0.23	<.0001
SBP (mmHg)	0.14	<.0001	0.11	<.0001
DBP (mmHg)	0.11	<.0001	0.10	0.0005
HEIGHT (cm)	−0.04	0.04	−0.02	0.51

* negative spearman correlation coeficient

** based on 857 individuals in offspring only; 157 with fatty liver and 700 without fatty liver

BMI: body mass index

SAT: subcutaneous adipose tissue

VAT: visceral adipose tissue

HOMA-IR: Homeostasis model assessment of insulin resistance

TG: triglycerides

HDL: high density lipoprotein

SBP: systolic blood pressure

DBP diastolic blood pressure

Table 4

Multivariate adjusted models for fatty liver

		FL +covariates*				FL + covariates' and obesity traits#		
	Dependent Trait	**N**	**effect$**	**95% CI**	**p value**	**effect$**	**95% CI**	**p value**
Dichotomous Fatty Liver	Glucose (mg/dL)	2588	7.7	[5.73–9.67]	<0.001	3.54	[1.43–5.64]	0.001
	IFG	2415	2.95	[2.32 – 3.75]	<0.001	1.58	[1.21 – 2.07]	<0.001
	DM	2588	2.98	[2.12 – 4.21]	<0.001	1.64	[1.11 – 2.41]	0.012
	log HOMA-IR	2395	0.44	[0.40 – 0.49]	<0.001	0.21	[0.17 – 0.25]	<0.001
	Insulin resistance	2395	6.16	[4.90 – 7.76]	<0.001	2.79	[2.19–3.65]	<0.001
	Adiponectin (mg/ml)	854	−3.17	[−4.09 – −2.24]	<0.001	−1.59	−2.57 — −0.62]	0.001
	log Resistin (ng/ml)	857	0.05	[−0.02 – 0.12]	0.147	0.00	[−0.07 – 0.08	0.924
	log TG (mg/dL)	2588	0.41	[0.35–0.46]	<0.001	0.22	[0.17 – 0.28]	<0.001
	HDL (mg/dL)	2588	−7.08	[−8.44 – −5.73]	<0.001	−2.48	[−3.89 – −1.06]	<0.001
	SBP (mmHg)	2589	4.61	[3.10–6.12]	<0.001	1.38	[−.22 – 2.97]	0.091
	DBP (mmHg)	2587	2.88	[1.96– 3.81]	<0.001	0.64	[−0.34 – 1.61]	0.2
	HTN	2586	2.73	[2.16–3.44]	<0.001	1.52	[1.17 – 1.97]	0.002
	MetS	2587	5.22	[4.15 – 6.57]	<0.001	1.95	[1.48–2.56]	<0.001
	BMI (kg/m2)	2589	4.35	[3.39–5.30]	<0.001			
	WC (cm)	2589	4.14	[3.41–4.86]	<0.001			
	SAT (cm3)	2589	810	[636–984	<0.001			
	VAT (cm3)	2589	989.2	865.5–1113.0]	<0.001			

	FL +covariates*				FL + covariates' and obesity traits#		
Dependent Trait	**N**	**effect&**	**95% CI**	**p value**	**effect**	**95% CI**	**p value**
Glucose (mg/dL)	2588	2.91	[2.17–3.65]	<0.001	1.36	[0.56–2.15]	<0.001
IFG	2415	1.43	[1.30 – 1.56]	<0.001	1.10	[1 – 1.22]	0.047
DM	2588	1.56	[1.39 – 1.75]	<0.001	1.29	[1.12 – 1.47]	<0.001

		FL +covariates*				FL + covariates' and obesity traits#		
	Dependent Trait	**N**	**effect&**	**95% CI**	**p value**	**effect**	**95% CI**	**p value**
Continuous Fatty Liver	log HOMA-IR	2395	0.17	[0.16 – 0.19]	<0.001	0.08	[0.07 –0.10]	<0.001
	Insulin resistance	2395	0.44	[0.39–0.49]	<0.001	0.64	[0.57–0.72]	<0.001
	Adiponectin (mg/ml)	854	−1.26	[−1.61 – −0.90]	<0.001	−0.62	[−1.00 – −0.24]	0.001
	log Resistm (ng/ml)	857	0.03	[0.00 – 0.06]	0.032	0.01	[−0.02 – 0.04]	0.452
	log TG (mg/dL)	2588	0.14	[0.12–0.16]	<0.001	0.07	[0.05– 0.09]	<0.001
	HDL (mg/dL)	2588	−2.5	[−3.01–−1.99]	<0.001	−0.69	[−1.23–−0.16]	0.011
	SBP (mmHg)	2589	1.72	[1.15 – 2.29]	<0.001	0.52	[−0.08–1.12]	0.092
	DBP (mmHg)	2587	1.09	[.75 – 1.44]	<0.001	0.25	[−0.12 – 0.61]	0.19
	HTN	2586	1.52	[1.28 – 1.64]	<0.001	1.22	[1.10–1.35]	<0.001
	MetS	2587	1.96	[1.79 – 2.17]	<0.001	1.27	[1.12 – 1.41]	<0.001
	BMI (kg/m2)	2589	1.6	[1.41–1.79]	<0.001			
	WC (cm)	2589	1.62	[1.42 – 1.81]	<0.001			
	SAT(cm3)	2589	336.4	[285.7–397.0]	<0.001			
	VAT (cm3)	2589	365.5	[335.1–395.9]	<0.001			

*covariates= age, sex, alcoholic drinks per week, menopausal status, hormone replacement therapy, smoking

#obesity traits= BMI, waist circumference, VAT

$effect= the change in the continuous dependent trait or in the Odds Ratio of having the dependent trait in individuals with fatty liver compared to those without fatty liver.

&effect= the change in the continuous dependent trait or in the Odds Ratio of having the dependent trait in individuals per standard deviation DECREASE in LPR.

FL: Fatty Liver

IFG: impaired fasting glucose

DM: diabetes mellitus

HOMA-IR: Homeostasis model assessment of insulin resistance

TG: triglycerides

HDL: high density lipoprotein

SEP: systolic blood pressure

DBP diastolic blood pressure

HTN: hypertension

MS: metabolic syndrome

BMI: body mass index

WC: waist circumference

SAT: subcutaneous adipose tissue

VAT: visceral adipose tissue