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

Elizabeth K. Speliotes,1,5 Joseph M. Massaro,6,7 Udo Hoffmann,2 Ramachandran S. Vasan,6,8 James B. Meigs,4 Dushyant V. Sahani,2 Joel N. Hirschhorn,5,10,11 Christopher J. O’Donnell,3,6 and Caroline S. Fox6,9

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. In this study, 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 way of multidetector computed tomography of the abdomen in 2,589 individuals from the community-based Framingham Heart Study. 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, waist circumference, and visceral adipose tissue). The prevalence of fatty liver was 17%. Compared with participants without fatty liver, individuals with fatty liver had a higher adjusted odds ratio (OR) of diabetes (OR 2.98, 95% confidence interval [CI] 2.12-4.21), metabolic syndrome (OR 5.22, 95% CI 4.15-6.57), hypertension (OR 2.73, 95% CI 2.16-3.44), impaired fasting glucose (OR 2.95, 95% CI 2.32-3.75), insulin resistance (OR 6.16, 95% CI 4.90-7.76); higher triglycerides, systolic blood pressure (SBP), and diastolic blood pressure (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 diabetes, hypertension, impaired fasting glucose, metabolic syndrome, HDL, triglycerides, and adiponectin levels (all \(P<0.001\)), whereas associations with SBP and DBP were attenuated (\(P>0.05\)). Conclusion: Fatty liver is a prevalent condition and is characterized by dysglycemia and dyslipidemia independent of visceral adipose tissue and other obesity measures. This work begins to dissect the specific links between fat depots and metabolic disease. (HEPATOLOGY 2010;51:1979-1987)
Obesity is a global epidemic. In the United States, more than 66% of individuals are overweight or obese and more than 33% are obese. Obesity affects more than 1 billion people worldwide and is expected to increase to 1.5 billion by 2115. Obesity is associated with metabolic complications, although not all obese individuals develop medical sequelae. 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 the metabolic syndrome, insulin resistance, and cardiovascular complications. Subcutaneous and visceral adipose tissue as well as fat in liver are all correlated with waist circumference, 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, whereas resistin may promote steatosis and insulin resistance. Furthermore, 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. Alternatively, fat in the liver may confer independent metabolic consequences above and beyond the effects of visceral fat.

The goal of this study was 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. We report the measurement, prevalence, and metabolic and anthropometric correlates of fatty liver in The Framingham Heart Study.

Subjects and Methods

Subjects. Subjects 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 have been reported. The study was initiated in 1948, enrolling 5,209 residents of Framingham, Massachusetts. These individuals have been followed since then with multiple serial examinations and collection of risk factor data. In 1971, 5,124 offspring and their spouses were recruited into the Offspring Study and have been followed every 4-8 years since then. In 2002, 4,095 Third Generation members and their spouses were enrolled. Between 2002 and 2005, multidetector computed tomography (CT) examinations of the chest and abdomen were performed in 3,529 individuals drawn from families including both Offspring and Third Generation participants.

Multidetector CT Scan Cohort. A total of 3,529 individuals underwent multidetector CT scanning, 1,418 from the Offspring Study and 2,111 from the Third Generation. Inclusion criteria for the study favored individuals who still resided in the greater New England area and included 755 families. The 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 weighing >160 kg were excluded from examination. Individuals undergoing scans were excluded from this analysis if their multidetector CT scans were not interpretable for fatty liver (n = 323), did not attend Offspring Examination 7 (n = 23) or if individuals reported greater than seven 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 2,589.

Multidetector CT Scan Protocol and Measurement of Fatty Liver, Visceral Adipose Tissue, and Subcutaneous Adipose Tissue. Multidetector CT scanning was conducted as reported. A calibration phantom (Image Analysis, Lexington, KY) with a water equivalent compound (CT-Water, Light Speed Ultra; General Electric, Milwaukee, WI) and calcium hydroxyapatite at 0, 75, and 150 mg/cm³ was placed under each scan to measure CT numbers. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were measured; briefly, 25 contiguous 5-mm-thick sections (120 kVp, 400 mA, gantry rotation time 500 ms, table feed 3:1 were acquired covering 125 mm 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 measurements of SAT and VAT were defined as the volumetric fat content outside and inside of this dividing line. The intraclass correlation coefficient was 0.992 for VAT and 0.997 for SAT.

Fatty liver was measured on multidetector CT scans of the abdomen and has been described elsewhere.
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 measurements were then calculated and used to create liver spleen ratios and liver phantom ratios. The intraclass correlation coefficient was 0.99. 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, because data from the abdominal scans had better reproducibility than chest scans.

**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 (Supporting Fig. 1A). The 95th percentiles were 0.41 and 1.37 for the liver phantom ratio and liver spleen ratio, respectively. In the literature, a liver spleen ratio of 1.1 corresponds to the presence of 30% fatty liver. We found that a liver phantom ratio cutoff of 0.33 had a 98% sensitivity and 70% specificity using liver spleen ratio cut-point of 1.1 as the gold standard (Supporting Fig. 1B).

**Measurement of Covariates.** Risk factors used in analyses in this study were measured at the seventh examination cycle of the Offspring Study cohort (1998-2001) or the first examination of the Third Generation cohort (2002-2005). Body mass index (BMI) was defined as weight (kg)/height (m)²; waist circumference was measured at the level of the umbilicus; diabetes was defined as a fasting plasma glucose of at least 126 mg/dL at examination or treatment with either insulin or a hypoglycemic agent; impaired fasting glucose was defined as fasting plasma glucose of 100-125 mg/dL among those not treated for diabetes; and hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg or on antihypertensive treatment. Triglycerides and high-density lipoprotein (HDL) levels are measured on fasting morning samples. Participants are considered current smokers if they had smoked at least one 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 were considered menopausal if their periods had stopped for at least 1 year. Metabolic syndrome is defined from modified Adult Treatment Panel criteria. Obesity is defined as BMI ≥30 kg/m². Insulin resistance was determined as the top quartile of the homeostasis model homeostasis model assessment of insulin resistance (HOMA-IR) (fasting glucose × fasting insulin/22.5) distribution among individuals without diabetes. Circulating adiponectin and resistin were measured by way of enzyme-linked immunoassay after an 8-hour fast as described.

**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 (water content, iron, and so forth), the top 5% of points in the liver phantom ratio were winsorized for analyses with fatty liver as a continuous variable.

Prior to winsorization, to determine the liver phantom ratio cutoff that mirrored a liver spleen ratio of 1:1, the cutoff that best discriminates the presence of 30% fat in the liver, we minimized misclassification of subjects at various cutoffs for liver phantom ratio. From a receiver operating curve analysis of liver phantom ratio compared with 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 nonnormally distributed continuous variables or ordinal variables, and a chi-square test for dichotomous variables. Because the liver phantom ratio was not normally distributed, Spearman correlation coefficients were used to determine age-adjusted 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 versus 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 standard deviation 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 (three-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, SBP and DBP, and fasting plasma glucose, respectively. In model 2, we additionally adjusted for BMI, waist circumference, and VAT. SAT was not included in these multivariate models because it was highly collinear with BMI.

In secondary analyses, we 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 study subjects 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/m². Using a 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-specific and sex-specific prevalence was higher for men (19%) compared with women (15%), and peaked for men between ages 55 and 64 and for women between ages 75 and 84 (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 (reflecting more fat in the liver) were associated with higher levels of VAT, waist circumference, BMI, triglycerides, weight, SAT, fasting plasma glucose, 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 diabetes (odds ratio [OR] 2.98, 95% confidence interval [CI] 2.12-4.21), insulin resistance (OR 6.16, 95% CI 4.90-7.76), metabolic syndrome (OR 5.22, 95% CI 4.15-6.57), hypertension (OR 2.73, 95% CI 2.16-3.44), and impaired fasting glucose (OR 2.95, 95% CI 2.32-3.75) than individuals without fatty liver (P < 0.001 for all).

After further adjustment for BMI, waist circumference, and VAT, there remained statistically significant associations of fatty liver with prevalent diabetes (OR 1.64, 95% CI 1.11-2.41), impaired fasting glucose (OR 1.58, 95% CI 1.21-2.07), insulin resistance (OR 2.79, 95% CI 2.14-3.65), metabolic syndrome (OR 1.95, 95% CI 1.48-2.56), log HOMA-IR (beta 0.14, 95% CI 0.17-0.2), adiponectin (beta −1.59 mg/dL, 95% CI −2.57 to −0.62), log triglycerides (beta 0.22 mg/dL, 95% CI 0.17-0.28 mg/dL), HDL (beta −2.48, 95% CI −3.89 to −1.06), and hypertension (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 sex 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. However, in all cases, the effect in these classes was directionally consistent with the overall effect (data not shown).

The median glucose, triglycerides, HDL, SBP, and DBP values in participants above and below the 90th percentile cut-point for VAT derived from a healthy referent sample21 (Fig. 1) show that lipid and glucose traits were associated with fatty liver (P < 0.0001), whereas 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...
Table 1. Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Covariates</th>
<th>All (2,589)</th>
<th>No Fatty Liver (2,150)</th>
<th>Fatty Liver (439)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>51</td>
<td>44</td>
<td>63</td>
<td>0.0002</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.0 (10.6)</td>
<td>50.8 (10.6)</td>
<td>52.3 (10.7)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Drinks per week</td>
<td>3.0 (3.5)</td>
<td>3.0 (3.4)</td>
<td>3.1 (3.9)</td>
<td>0.7619</td>
</tr>
<tr>
<td>Physical activity</td>
<td>37.4 (6.8)</td>
<td>37.5 (6.9)</td>
<td>36.9 (6.4)</td>
<td>0.0256</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td>0.1376</td>
</tr>
<tr>
<td>Never (%)</td>
<td>49.7 (1,287)</td>
<td>50.6 (1,088)</td>
<td>45.3 (199)</td>
<td></td>
</tr>
<tr>
<td>Former (%)</td>
<td>38.7 (1,002)</td>
<td>37.9 (815)</td>
<td>42.6 (187)</td>
<td></td>
</tr>
<tr>
<td>Current (%)</td>
<td>11.6 (300)</td>
<td>11.5 (247)</td>
<td>121 (53)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>0.0028</td>
</tr>
<tr>
<td>Some high school (%)</td>
<td>1.6 (41)</td>
<td>1.5 (32)</td>
<td>2.5 (11)</td>
<td></td>
</tr>
<tr>
<td>High school graduate (%)</td>
<td>21.3 (551)</td>
<td>20.7 (445)</td>
<td>24.3 (107)</td>
<td></td>
</tr>
<tr>
<td>Some college (%)</td>
<td>29.7 (769)</td>
<td>29.0 (624)</td>
<td>32.9 (144)</td>
<td></td>
</tr>
<tr>
<td>College graduate (%)</td>
<td>47.4 (1,227)</td>
<td>48.6 (1,049)</td>
<td>40.3 (177)</td>
<td></td>
</tr>
<tr>
<td>Menopause (women only) (%)</td>
<td>26.1 (676)</td>
<td>26.1 (561)</td>
<td>26.2 (115)</td>
<td>0.0623</td>
</tr>
<tr>
<td>Hormone replacement therapy (%)</td>
<td>11.9 (308)</td>
<td>11.8 (254)</td>
<td>12.5 (55)</td>
<td>0.1872</td>
</tr>
<tr>
<td>Fat-related</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6 (5.3)</td>
<td>26.8 (4.8)</td>
<td>31.4 (6.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.5 (14.3)</td>
<td>94.4 (13.4)</td>
<td>106.4 (14.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAT (cm³)</td>
<td>2,847.7 (1,399.0)</td>
<td>2,697.5 (1,327.1)</td>
<td>3,583.4 (1,506.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>VAT (cm³)</td>
<td>1,749.5 (1,021.4)</td>
<td>1,568.1 (912.9)</td>
<td>2,638.1 (1,059.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normal weight (BMI &lt;25)</td>
<td>34.0 (882)</td>
<td>38.9 (837)</td>
<td>10.3 (45)</td>
<td></td>
</tr>
<tr>
<td>Overweight (25 ≤ BMI &lt; 30)</td>
<td>39.5 (1,022)</td>
<td>40.4 (869)</td>
<td>34.9 (153)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI ≥ 30)</td>
<td>26.5 (685)</td>
<td>20.7 (444)</td>
<td>54.9 (241)</td>
<td></td>
</tr>
<tr>
<td>Glucose-related</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>99.1 (12.9)</td>
<td>97.1 (19.4)</td>
<td>108.7 (33.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>6.7 (173)</td>
<td>5.1 (110)</td>
<td>14.6 (64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Impaired fasting glucose: non diabetes only (%)</td>
<td>27.5 (712)</td>
<td>23.6 (507)</td>
<td>48.8 (214)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA-IR [median (Q1-Q3)]</td>
<td>2.63 (2.11-3.64)</td>
<td>2.47 (2.05-3.21)</td>
<td>3.88 (2.95-5.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>log HOMA-IR</td>
<td>1.03 (0.47)</td>
<td>0.95 (0.43)</td>
<td>1.40 (0.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin resistance (%)</td>
<td>28.9 (692)</td>
<td>21.6 (425)</td>
<td>62.7 (267)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)†</td>
<td>9.6 (4.0)</td>
<td>10.6 (6.1)</td>
<td>7.0 (4.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resistin [median (Q1-Q3)]</td>
<td>13.40 (10.60-17.10)</td>
<td>13.26 (10.40-17.05)</td>
<td>14.20 (11.80-17.70)</td>
<td>0.0474</td>
</tr>
<tr>
<td>log Resistin (ng/mL)†</td>
<td>2.06 (0.41)</td>
<td>2.61 (0.41)</td>
<td>2.67 (0.39)</td>
<td>0.1199</td>
</tr>
<tr>
<td>Lipid-related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>103 (71-155)</td>
<td>95 (67-139)</td>
<td>157 (110-217)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>52.5 (15.8)</td>
<td>54.0 (15.7)</td>
<td>46.2 (14.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>195.2 (35.4)</td>
<td>194.8 (35.0)</td>
<td>197.9 (37.1)</td>
<td>0.1065</td>
</tr>
<tr>
<td>Blood pressure-related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>121.1 (16.2)</td>
<td>120.0 (16.1)</td>
<td>126.8 (16.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>75.28 (9.3)</td>
<td>74.7 (9.1)</td>
<td>78.1 (9.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>27.3 (707)</td>
<td>23.6 (507)</td>
<td>45.4 (199)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Syndrome-related</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>31.4 (813)</td>
<td>25.0 (538)</td>
<td>62.9 (276)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are presented as the mean (standard deviation) or median (interquartile range) or percentage (number of individuals). Data in parentheses refer to the standard deviation for continuous traits and the number affected for dichotomous traits.

*Based on t test or Wilcoxon rank sum test or chi-square test.
†Based on 857 individuals in offspring only, 157 with fatty liver and 700 without fatty liver.

Table 2. Prevalence of Fatty Liver

<table>
<thead>
<tr>
<th>Age</th>
<th>Total (%)</th>
<th>Men (%)</th>
<th>Women (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>6/45 (13.3)</td>
<td>6/40 (15.0)</td>
<td>0/5 (0.0)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>35-44</td>
<td>113/779 (14.6)</td>
<td>73/436 (16.7)</td>
<td>40/343 (11.7)</td>
<td>0.0514</td>
</tr>
<tr>
<td>45-54</td>
<td>154/926 (16.6)</td>
<td>79/420 (18.8)</td>
<td>75/506 (14.8)</td>
<td>0.1111</td>
</tr>
<tr>
<td>55-64</td>
<td>94/486 (21.1)</td>
<td>53/207 (25.6)</td>
<td>41/279 (14.7)</td>
<td>0.0036</td>
</tr>
<tr>
<td>65-74</td>
<td>60/290 (20.7)</td>
<td>30/134 (22.4)</td>
<td>30/156 (19.2)</td>
<td>0.5618</td>
</tr>
<tr>
<td>75-84</td>
<td>12/63 (19.1)</td>
<td>5/27 (18.5)</td>
<td>7/36 (19.4)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>All</td>
<td>439/2,589 (17.0)</td>
<td>246/1,264 (19.0)</td>
<td>193/1,325 (15.0)</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

*Comparison between sexes from Fisher’s exact test.
and 0.16, respectively). However, fatty liver remained associated with all other metabolic traits ($P < 0.004$) (data not shown).

**Discussion**

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 study, we extend previous reports and illustrate how fatty liver associates with the 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, observational 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 a 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 chylomicrons, 60% from nonesterified 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 nonesterified fatty acids from VAT has been shown to be as high at 20% of the total delivery of fatty acids to the liver compared with 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 nonesterified fatty acid delivery to the liver and increased fat accumulation in mice and humans.$^{30-32}$ Indeed, we found 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 very low-density lipoprotein (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 that can be cleared by the kidney, leading to lower levels of HDL.$^{35}$ In this way, fatty liver may be specifically related to hypertriglyceridemia, low HDL, and impaired glucose use above and beyond other fat depots, consistent with what we found in our analyses. Furthermore, 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.

**Table 3. Negative Spearman Correlations of Liver/Phantom Ratio and Liver/Spleen Ratio With Continuous Traits**

<table>
<thead>
<tr>
<th>Trait</th>
<th>Liver/Phantom Ratio ($n = 2,589$)</th>
<th>Liver/Spleen Ratio ($n = 1,284$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>0.25 $&lt;0.0001$</td>
<td>0.27 $&lt;0.0001$</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.26 $&lt;0.0001$</td>
<td>0.27 $&lt;0.0001$</td>
</tr>
<tr>
<td>SAT (cm$^3$)</td>
<td>0.20 $&lt;0.0001$</td>
<td>0.21 $&lt;0.0001$</td>
</tr>
<tr>
<td>VAT (cm$^3$)</td>
<td>0.34 $&lt;0.0001$</td>
<td>0.34 $&lt;0.0001$</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.23 $&lt;0.0001$</td>
<td>0.26 $&lt;0.0001$</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>0.17 $&lt;0.0001$</td>
<td>0.17 $&lt;0.0001$</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.32 $&lt;0.0001$</td>
<td>0.32 $&lt;0.0001$</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)†</td>
<td>$-0.25 &lt;0.0001$</td>
<td>$-0.32 &lt;0.0001$</td>
</tr>
<tr>
<td>Resistin (ng/mL)†</td>
<td>0.07 $&lt;0.0001$</td>
<td>0.08 $&lt;0.0001$</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>0.23 $&lt;0.0001$</td>
<td>0.30 $&lt;0.0001$</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>$-0.19 &lt;0.0001$</td>
<td>$-0.23 &lt;0.0001$</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>0.14 $&lt;0.0001$</td>
<td>0.11 $&lt;0.0001$</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>0.11 $&lt;0.0001$</td>
<td>0.10 $&lt;0.00005$</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>$-0.04$ 0.04</td>
<td>$-0.02$ 0.51</td>
</tr>
</tbody>
</table>

* Negative Spearman correlation coefficient.
† Based on 857 individuals in offspring only, 157 with fatty liver, and 700 without 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. Furthermore, 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 offer insight into 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 the development not only of metabolic disease in the form of dysglycemia or dyslipidemia but also of cardiovascular disease.

The strength of the present study is the large, well-characterized cohort of individuals with a wealth of metabolic traits and covariates measured. Furthermore, 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 scans, which allowed us to quantify it more precisely compared with 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. Because 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 that may not be generalizable. Furthermore, covariates were measured at times separate from the CT scans, and CT can only indirectly measure fat in the liver; these effects may result in misclassification. However, misclassification would only serve to bias our results toward the null, and would not lead to a positive association, as we have observed. Furthermore, 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 polycystic ovary syndrome and impaired fasting glucose. The exposure and covariate data were measured from 1998 to 2005, and may not reflect current trends. Lastly, these data are cross-sectional and derived from an observational study; therefore, we cannot 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.

References
4. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation,