

## Abdominal Obesity and Fatty Liver

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It has been hypothesized that visceral fat releases free fatty acids and adipokines and thereby exposes the liver to fat accumulation. The authors aimed to evaluate current epidemiologic evidence for an association between abdominal fat and liver fat content. Clinical and epidemiologic studies with data on abdominal fat and liver fat content were reviewed. Studies using waist circumference to estimate abdominal fat mass suggested a direct association between abdominal fat and liver fat content. Studies using imaging methods suggested a direct association between intraabdominal fat and liver fat content, but not between subcutaneous abdominal fat and liver fat content. In conclusion, clinical and epidemiologic studies of abdominal fat and liver fat content suggest a direct association between abdominal fat and liver fat content which is probably accounted for by visceral fat. However, results from the included studies do not allow strong conclusions regarding the temporal sequence of events. Future longitudinal studies are recommended to obtain additional information on associations and mechanisms. Both abdominal fat depots and other body compartments of interest should be included to further investigate the association between specific fat depots and liver fat content. Biomarkers may provide insight into underlying mechanisms.

abdominal fat; adiposity; fatty liver; intra-abdominal fat; obesity; subcutaneous fat, abdominal

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

### INTRODUCTION

The reason for differences in fat accumulation in the liver among persons who do not abuse alcohol is unknown (1). However, adipose tissue releases adipokines, which may be an important factor that increases liver fat content (1). Exposure of the liver to free fatty acids may be another important factor (1). Exposure to fatty acids could be due to dietary fat intake and/or release of free fatty acids from adipose tissue, especially from abdominal adipose tissue (1, 2).

Abdominal adipose tissue includes distinct anatomic depots, a subcutaneous fat depot and an intraabdominal fat depot, which can be divided into intraperitoneal and retroperitoneal depots (3). The intraperitoneal fat depot, also known as visceral fat, can be divided into mesenteric and omental depots (3). Subcutaneous fat differs from visceral fat in that venous drainage from subcutaneous fat is directed

into the systemic circulation, whereas venous drainage from visceral fat is directed into the portal vein. The metabolic products thus reach the liver directly and exercise a first-pass effect on liver metabolism (4, 5). It has been hypothesized that visceral fat releases free fatty acids and adipokines and thereby exposes the liver to fat accumulation (4, 5). Release from visceral fat of free fatty acids transported through the portal vein to the liver is supported by an investigation conducted by Nielsen et al. (6). Using tracer methods, they found a direct association between the amount of visceral fat and the delivery of free fatty acids to the liver (in the postabsorptive state). This association was stronger in women than in men (6). However, even in viscerally obese persons, more than 50–60 percent of the delivery of free fatty acids to the liver comes from the systemic circulation (6).

Our aim in this review was to evaluate the current epidemiologic evidence of an association between abdominal fat

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and liver fat content. In this paper, we discuss the choice of epidemiologic study design and statistical models for evaluating the association. We reviewed clinical and epidemiologic studies with data on abdominal fat and liver fat content that had been published between January 1966 and February 2007.

## METHODS

The inclusion criteria for the clinical and epidemiologic studies were that they had to include data on abdominal fat and nonalcoholic fatty liver disease (NAFLD) in adults. NAFLD is an umbrella diagnosis describing fat accumulation in the liver identified either by imaging methods (e.g., ultrasonography, computed tomography, or magnetic resonance spectroscopy) or by liver biopsy (7–9). Nonalcoholic steatohepatitis is found in a subset of NAFLD patients who have, in addition to fat accumulation, evidence of characteristic hepatocellular injury and necroinflammatory changes (7–9). NAFLD is histologically indistinguishable from the liver disease resulting from alcohol abuse (7–9). The diagnosis of NAFLD requires the exclusion of alcohol abuse as the cause of the liver disease; daily alcohol consumption as low as 30 g for men and 20 g for women may be sufficient to cause alcohol-induced liver disease (7–9). The methods used for assessment of abdominal fat mass range from anthropometric measurements to multiple-slice computed tomography or magnetic resonance imaging (10).

Only studies excluding persons with an alcohol consumption of  $\geq 30$  g/day for men and  $\geq 20$  g/day for women were included in the present review. Moreover, no study population was allowed to be solely composed of persons with type 2 diabetes mellitus, children, adolescents, or women with previous gestational diabetes. Studies using ratios as measures of abdominal obesity were not included, since adding further body compartments introduces additional complexity in addressing the relation between abdominal obesity and liver fat content. Furthermore, statistical arguments have been raised against the use of ratios (11).

A PubMed search of papers published from January 1966 onwards was performed in February 2007 using the following keywords: (abdominal obesity or abdominal fat or abdominal adipose tissue or visceral fat or visceral adipose tissue or subcutaneous fat or subcutaneous adipose tissue or subcutaneous abdominal fat or subcutaneous abdominal adipose tissue or body fat distribution or waist) and (fatty liver or liver fat or steatosis). The full texts of papers were searched. The retrieved papers were also searched for relevant references. Only papers published in English were considered.

## RESULTS

In total, 24 studies (12–35) met the inclusion criteria. For one study, results were reported in two separate papers (22, 36). The 2005 paper by Targher et al. (22) was selected for this review because in that paper the investigators reported results on both waist circumference and visceral fat area and fatty liver, whereas in their 2004 paper (36), they reported results on only waist circumference and fatty liver. In three

studies (12, 13, 20), some of the participants were included in more than one of the studies; therefore, those studies cannot be considered independent. Characteristics of the studies included are shown in tables 1 and 2. Among the included studies, eight (12–14, 19, 20, 29, 32, 34) were case-control studies and 16 (15–18, 21–28, 30, 31, 33, 35) were cross-sectional studies. In all of the studies, information on abdominal fat and liver fat content was collected at the same point in time.

Table 1 shows the results from studies using waist circumference as an estimate of abdominal fat mass, and table 2 shows the results from studies using imaging methods to estimate abdominal fat mass. Imaging methods, except for dual-photon and dual-energy x-ray absorptiometry scanning, allow distinction between the different abdominal fat depots (10). In the present review, results on subcutaneous abdominal and intraabdominal fat depots are shown. Six studies (14, 22, 24–27) reported results on abdominal fat mass estimated by both waist circumference and imaging methods. Results from those studies are included in both table 1 and table 2.

Table 3 shows the methods used to estimate abdominal fat mass and liver fat content, ordered with regard to assumed validity. Two studies (14, 35) used ultrasonography to estimate subcutaneous abdominal and intraabdominal fat, four studies used computed tomography (22, 24, 25, 32), and five studies (26, 27, 31, 33, 34) used magnetic resonance imaging (table 3). Levels of liver enzymes (aspartate aminotransferase, alanine aminotransferase, and  $\gamma$ -glutamyltransferase) were used to indicate liver fat content in one study (15). Liver fat content was estimated by ultrasonography in 15 studies (12, 14, 16–23, 25, 27, 28, 30, 35), computed tomography in one study (24), magnetic resonance spectroscopy in four studies (26, 31, 33, 34), and liver biopsy in three studies (13, 29, 32) (table 3). In the studies by Rocha et al. (21) and Oh et al. (28), the participants were diagnosed with fatty liver by ultrasonography, but results for the association between waist circumference and liver enzyme levels were reported. In the study by Targher et al. (22), fatty liver was confirmed by computed tomography.

### Studies using waist circumference to estimate abdominal fat mass

Among the studies that used waist circumference as an estimate of abdominal fat mass, 16 studies (13–17, 19–26, 28–30) found a significant direct association between waist circumference and NAFLD, whereas three studies (12, 18, 27) did not find an association (table 1). In the study by Rocha et al. (21), however, waist circumference was significantly directly correlated with alanine aminotransferase but not with aspartate aminotransferase or  $\gamma$ -glutamyltransferase (table 1).

Three studies (17, 23, 30) included body mass index (weight (kg)/height (m)<sup>2</sup>) in the analysis of waist circumference and NAFLD; those studies also found a direct association after inclusion of body mass index in the multivariate model (table 1).

Church et al. (24) found that adjustment for visceral fat area attenuated the direct association between waist circumference and NAFLD, whereas adjustment for subcutaneous abdominal fat area did not change the association (table 1).

In five studies (12, 17, 18, 23, 30) reporting results from multivariate logistic regression analyses, the analyses included adjustment for potential metabolic effects of fat accumulation in the liver (e.g., fasting triglyceride levels) (table 1). Three (17, 23, 30) of these studies found a significant direct association between waist circumference and NAFLD, whereas two (12, 18) found no association. Two (23, 30) of the three studies reporting significant results also reported significant direct associations between waist circumference and NAFLD in crude analyses (i.e., analyses without any adjustments). Marchesini et al. (12) and Ardigo et al. (18) reported significant direct associations in crude analyses. In the article by Hsiao et al. (17), crude results were not reported.

Fourteen studies (12, 13, 15–21, 23, 25, 28–30) were carried out both among men and women, four (22, 24, 26, 27) were carried out among men only, and one (14) was carried out among women only (table 1). Sex-specific results did not suggest sex differences in the association between waist circumference and liver fat content (table 1).

#### Studies using imaging methods to estimate abdominal fat mass

Among the studies that used imaging methods to estimate abdominal fat mass, three studies (14, 24, 34) found a significant direct association between subcutaneous abdominal fat and NAFLD, whereas eight studies (22, 25–27, 31–33, 35) did not find an association (table 2). In contrast, nine studies (14, 22, 24–26, 32–35) found a significant direct association between intraabdominal fat and NAFLD (table 2). Two studies (27, 31) did not find an association between intraabdominal fat and fatty liver (table 2).

In the case-control study by Sabir et al. (14), results were reported separately among cases (obese persons, defined as mean body mass index = 36 (standard deviation, 6)) and controls (nonobese persons, defined as mean body mass index = 26 (standard deviation, 5)) (table 2). In that study, subcutaneous and visceral fat thickness were significantly directly associated with liver fat content among both obese and nonobese persons. Westerbacka et al. (33) found that intraabdominal fat volume was significantly directly associated with liver fat content independently of subcutaneous abdominal fat volume among obese persons, whereas subcutaneous abdominal fat volume was not associated with liver fat content independently of intraabdominal fat volume among obese persons (table 2). Moreover, four studies (24, 27, 32, 34) reported results on subcutaneous abdominal fat and intraabdominal fat among overweight and obese persons (mean body mass index = 26–33) (table 2). In two of those studies (24, 34), subcutaneous abdominal and intraabdominal fat was directly associated with NAFLD. In contrast, in the study by Holt et al. (27), neither subcutaneous abdominal fat nor visceral fat was associated with fatty liver. In the case-control study by Chalasani et al. (32), persons with nonalcoholic steatohepatitis had a significantly higher visceral fat area than controls; there was no difference in subcutaneous fat area between persons with nonalcoholic steatohepatitis and controls. In four studies, results on subcutaneous abdominal fat (25, 26, 31, 35) and liver fat content

among nonobese persons (mean body mass index = 23–26) were reported, and in five studies results on intraabdominal fat (22, 25, 26, 31, 35) and liver fat content among nonobese persons were reported (table 2). In those studies, subcutaneous abdominal fat was not associated with liver fat content, whereas visceral fat was significantly directly associated with liver fat content in four (22, 25, 26, 35) of the five studies (22, 25, 26, 31, 35). In the study by Seppala-Lindroos (31), intraabdominal fat was not associated with liver fat content. In the study by Liu et al. (35), mesenteric fat thickness was significantly directly associated with fatty liver independently of subcutaneous abdominal and preperitoneal fat thickness, whereas subcutaneous abdominal fat thickness was not associated with fatty liver independently of mesenteric and preperitoneal fat thickness. The significant direct association between mesenteric fat thickness and fatty liver remained significant after inclusion of body mass index in the multivariate model.

In the study by Liu et al. (35), multivariate logistic regression analysis included adjustment for potential metabolic effects of fat accumulation in the liver (e.g., fasting triglyceride levels). However, Liu et al. (35) also reported significant direct associations between subcutaneous abdominal and mesenteric fat thickness and fatty liver in crude analyses.

Five studies (25, 32–35) were carried out among both men and women, five (22, 24, 26, 27, 31) were carried out among men only, and one (14) was carried out among women only (table 2). Sex-specific results did not suggest sex differences in the association between abdominal fat depots and liver fat content (table 2). However, the two studies (27, 31) not finding an association between intraabdominal fat and fatty liver were conducted among men (table 2).

#### DISCUSSION

In total, 24 studies (12–35) met the inclusion criteria. Studies using waist circumference as an estimate of abdominal fat mass suggested a direct association between abdominal fat mass and liver fat content. However, use of waist circumference does not allow distinction between the different abdominal fat depots. Studies using imaging methods (except for dual-photon and dual-energy x-ray absorptiometry scanning), in contrast, allow distinction between the different abdominal fat depots. These studies suggested a direct association between intraabdominal fat and liver fat content but not between subcutaneous abdominal fat and liver fat content. In all of the studies, information on abdominal fat content and liver fat content was collected at the same point in time; therefore, results from these studies do not allow strong conclusions regarding the temporal sequence of events and hence about putative cause-and-effect relations. At present, we have limited insight into the mechanisms and temporal sequences of events underlying the associations. The optimal epidemiologic approach for obtaining further insight into the relation between abdominal fat and liver fat content would probably be longitudinal studies with repeated concurrent measurements of abdominal fat, liver fat, and potential confounders, as well as collection of

**TABLE 1. Clinical and epidemiologic studies of the association between abdominal fat level (using waist circumference to estimate abdominal fat mass) and nonalcoholic fatty liver disease**

First author and year of publication (ref.)	Study design	Characteristics of participants			Results	
		No. of subjects (% female) and mean BMI*,†	Mean age (years)	Ethnicity or country of residence	Description	Schematic‡
Marchesini, 1999 (12)§	Case-control	46 persons with NAFLD* (35% female); mean BMI = 28 (SD,* 4) 92 controls matched for sex and age (35% female); mean BMI = 24 (SD, 2)	45 (SD, 13) 43 (SD, 10)	Italy	In multivariate logistic regression analysis (variables considered were weight, BMI, WC,* waist:hip ratio, HOMA,* insulin, triglyceride, and insulin levels and 180-minute glucose levels during oral glucose tolerance testing), WC was not associated with NAFLD.	NS* (both sexes)
Marchesini, 2001 (13)§	Case-control	30 persons with NAFLD (30% female); mean BMI = 27 (SD, 2) 10 controls (20% female); mean BMI = 24 (SD, 2)	41 (SD, 11) 48 (SD, 14)	Italy	Persons with NAFLD had significantly higher WC than controls ( $p < 0.005$ ).	↑ (both sexes)
Sabir, 2001 (14)¶	Case-control	68 obese females; mean BMI = 36 (SD, 6) 40 nonobese female controls; mean BMI = 26 (SD, 5)	44 (SD, 9) 34 (SD, 9)	Turkey	Significant direct correlation between WC and liver fat content (obese persons: $r = 0.45$ , $p < 0.0001$ ; nonobese persons: $r = 0.58$ , $p < 0.0001$ ).	Obese persons: ↑ Nonobese persons: ↑ (females)
Ruhl, 2003 (15)	Cross-sectional	5,538 persons with normal ALT* concentration (32% female); mean BMI = 26 (SD, 7) 186 persons with elevated ALT concentration (46% female); mean BMI = 30 (SD, 11)	45 (SD, 45) 39 (SD, 23)	United States	Persons with an elevated ALT concentration had significantly higher WC than persons with a normal ALT concentration ( $p < 0.001$ ).	↑ (both sexes)
Shen, 2003 (16)	Cross-sectional	4,009 persons (36% female); among males, mean BMI = 24; among females, mean BMI = 22	46 (SE*/SD not given)	China	WC was significantly directly associated with NAFLD ( $p = 0.0000$ ).	↑ (both sexes)
Hsiao, 2004 (17)	Cross-sectional	210 obese persons (78% female); among males, mean BMI = 32 (SD, 3); among females, mean BMI = 32 (SD, 4)	36 (SD, 10)	Taiwan	In multivariate logistic regression analysis (including sex, age, BMI, serum ferritin level, and HOMA), WC was significantly directly associated with fatty liver (per 1-cm increase in WC, OR* = 1.10, 95% CI*: 1.04, 1.16).	↑ (both sexes)
Ardigo, 2005 (18)	Cross-sectional	38 persons without fatty liver (66% female); mean BMI = 26 (SD, 2) 19 persons with mild fatty liver (73% female); mean BMI = 29 (SD, 3) 12 persons with moderate-to-severe fatty liver (50% female); mean BMI = 30 (SD, 5)	60 (SD, 6) 64 (SD, 4) 59 (SD, 7)	Italy	In multivariate logistic regression analysis (including age, insulin, glucose, triglycerides, and high density lipoprotein cholesterol), WC was not associated with categories of fatty liver ( $\beta$ coefficient not given, $p$ value not given).	NS (both sexes)
Brea, 2005 (19)	Case-control	40 persons with NAFLD (50% female); mean BMI = 32 (SD, 5) 40 controls matched for sex and age (50% female); mean BMI = 26 (SD, 4)	53 (SD, 13) 52 (SD, 11)	Spain	Persons with NAFLD had significantly higher WC than controls ( $p < 0.001$ ).	↑ (both sexes)
Bugianesi, 2005 (20)§	Case-control	174 persons with NAFLD (10% female); mean BMI = 27 (SD, 3) 42 controls matched for BMI (20% female); mean BMI = 28 (SD, 4)	41 (SD, 11) 43 (SD, 11)	Italy	Persons with NAFLD had significantly higher WC than controls ( $p < 0.0001$ ).	↑ (both sexes)
Rocha, 2005 (21)	Cross-sectional	81 persons with NAFLD (40% female) (40% had BMI $\geq 30$ )	45 (SD, 11)	Brazil	WC was significantly directly correlated with ALT concentration ( $r = 0.24$ , $p = 0.04$ ) but not with AST* ( $r = 0.16$ , $p$ value not given) or $\gamma$ -GT* ( $r = 0.01$ , $p$ value not given) concentrations.	ALT: ↑ AST: NS $\gamma$ -GT: NS (both sexes)

Targher, 2005 (22)¶	Cross-sectional	65 males without fatty liver; mean BMI = 24 (SD, 2) 35 males with fatty liver; mean BMI = 26 (SD, 1)	43 (SD, 4) 41 (SD, 4)	Italy	Men with fatty liver had significantly higher WC than men without fatty liver ( $p < 0.01$ ).	↑ (males)
Yoon, 2005 (23)	Cross-sectional	91 persons (71% female); mean BMI = 25 (SD, 3)	51 (SD, 9)	South Korea	In multivariate logistic regression analysis (including sex, age, BMI, plasma adiponectin level, and HOMA), WC was significantly directly associated with NAFLD (per 1-cm increase in WC, OR = 1.13, 95% CI: 1.04, 1.22).	↑ (both sexes)
Church, 2006 (24)¶	Cross-sectional	194 males without NAFLD; mean BMI = 28 (SD, 4) 24 males with NAFLD; mean BMI = 32 (SD, 4)	52 (SD, 7) 51 (SD, 5)	Non-Hispanic Caucasian	In multivariate logistic regression analysis (including age and alcohol consumption), WC was significantly directly associated with NAFLD (per 1-cm increase in WC, OR = 1.11, 95% CI: 1.06, 1.17). Additional adjustment for visceral fat area attenuated the association (OR = 1.05, 95% CI: 0.97, 1.10), whereas additional adjustment for subcutaneous abdominal fat area did not change the association (OR = 1.10, 95% CI: 1.02, 1.17).	↑ (males)
Eguchi, 2006 (25)¶	Cross-sectional	129 persons with NAFLD (49% female); mean BMI = 26 (SD, 3)	59 (SD, 12)	Japan	WC increased with severity of fatty liver (mild, moderate, or severe) ( $p < 0.0001$ ).	↑ (both sexes)
Chan, 2006 (26)¶	Cross-sectional	17 males; mean BMI = 25 (SD, 5)	49 (SD, 12)	Caucasian	Significant direct correlation between WC and liver fat content ( $r = 0.66$ , $p < 0.001$ ).	↑ (males)
Holt, 2006 (27)¶	Cross-sectional	7 males without fatty liver; mean BMI = 26 (SD, 2) 9 males with mild-to-moderate fatty liver; mean BMI = 29 (SD, 3) 6 males with severe fatty liver; mean BMI = 30 (SD, 5)	54 (SD, 8) 64 (SD, 6) 51 (SD, 7)	United Kingdom	No difference in WC between the three categories of fatty liver ( $p = 0.17$ ).	NS (males)
Oh, 2006 (28)	Cross-sectional	3,091 persons with NAFLD (33% female) (8% had BMI $\geq 30$ )	48 (SD, 11)	South Korea	Persons with an elevated ALT concentration had significantly higher WC than persons with a normal ALT concentration ( $p < 0.001$ ).	↑ (both sexes)
Targher, 2006 (29)	Case-control	50 persons with NAFLD (40% female); mean BMI = 27 (SD, 2) 40 controls matched for sex, age, and BMI (35% female); mean BMI = 26 (SD, 2)	46 (SD, 4) 46 (SD, 3)	Italy	Persons with NAFLD had significantly higher WC than controls ( $p < 0.05$ ).	↑ (both sexes)
Zelber-Sagi, 2006 (30)	Cross-sectional	326 persons (53% female); mean BMI = 27 (SD, 4)	51 (SD, 10)	Israel	In multivariate logistic regression analysis (including sex, age, BMI, HOMA, and triglycerides), WC was significantly directly associated with NAFLD (for WC $>102$ cm in males and WC $>88$ cm in females, OR = 2.9, 95% CI: 1.3, 6.4).	↑ (both sexes)

\* BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation; WC, waist circumference; HOMA, homeostasis model assessment; NS, not significant; ALT, alanine aminotransferase; SE, standard error; OR, odds ratio; CI, confidence interval; AST, aspartate aminotransferase;  $\gamma$ -GT,  $\gamma$ -glutamyltransferase.

† Weight (kg)/height (m)<sup>2</sup>.

‡ † = statistically significant direct association or statistically significant difference.

§ In the studies by Marchesini et al. (12), Marchesini et al. (13), and Bugianesi et al. (20), some of the participants were included in more than one of the studies. Therefore, these studies cannot be considered independent.

¶ Results from this study are also included in table 2.

**TABLE 2. Clinical and epidemiologic studies of the association between abdominal fat level (using imaging methods to estimate abdominal fat mass) and nonalcoholic fatty liver disease**

First author and year of publication (ref.)	Study design	Characteristics of participants			Results			
		No. and sex of subjects and mean BMI*, †	Mean age (years)	Ethnicity or country of residence	Subcutaneous abdominal fat		Visceral fat	
					Description	Schematic‡	Description	Schematic‡
Sabir, 2001 (14)§	Case-control	68 obese females; mean BMI = 36 (SD,* 6)	44 (SD, 9)	Turkey	Significant direct correlation between subcutaneous fat thickness and liver fat content (obese persons: $r = 0.37, p < 0.05$ ; nonobese persons: $r = 0.54, p < 0.0001$ ).	Obese persons: ↑  Nonobese persons: ↑ (females)	Significant direct correlation between visceral fat thickness and liver fat content (obese persons: $r = 0.57, p < 0.0001$ ; nonobese persons: $r = 0.42, p < 0.05$ ).	Obese persons: ↑  Nonobese persons: ↑ (females)
		40 nonobese female controls; mean BMI = 26 (SD, 5)	34 (SD, 9)					
Seppala-Lindroos, 2002 (31)	Cross-sectional	15 males with liver fat content below the median; mean BMI = 25 (SD, 4)	44 (SD, 8)	Finland	No difference in subcutaneous fat volume between the groups of liver fat content ( $p = 0.32$ ).	NS* (males)	No difference in intraabdominal fat volume between the groups of liver fat content ( $p = 0.76$ ).	NS (males)
		15 males with liver fat content above the median; mean BMI = 26 (SD, 4)	42 (SD, 8)					
Chalasanani, 2003 (32)	Case-control	18 persons with NASH* (50% female); mean BMI = 33 (SD, 5)	40 (SD, 1)	United States	No difference in subcutaneous fat area between persons with NASH and controls ( $p = 0.7$ ).	NS (both sexes)	Persons with NASH had significantly higher visceral fat area than controls ( $p = 0.01$ ).	↑ (both sexes)
		18 controls matched for race, sex, age, and BMI (50% female); mean BMI = 32 (SD, 4)	42 (SD, 2)					
Westerbacka, 2004 (33)	Cross-sectional	66 males; mean BMI = 27 (SD, 4)	41 (SD, 8)	Caucasian	In multivariate linear regression analysis (including intraabdominal fat volume and serum adiponectin level), subcutaneous fat volume was not associated with liver fat content after adjustment for sex and age (per 1-cm <sup>3</sup> increase in fat volume, $\beta = 3.127 \times 10^{-5}, p = 0.197$ ).	NS (both sexes)	In multivariate linear regression analysis (including subcutaneous abdominal fat volume and serum adiponectin level), intraabdominal fat volume was significantly directly associated with liver fat content after adjustment for sex and age (per 1-cm <sup>3</sup> increase in fat volume, $\beta = 2.157 \times 10^{-4}, p < 0.001$ ).	↑ (both sexes)
		66 females; mean BMI = 30 (SD, 4)	42 (SD, 8)					
Targher, 2005 (22)§	Cross-sectional	65 males without fatty liver; mean BMI = 24 (SD, 2)	43 (SD, 4)	Italy	—¶	—	Men with fatty liver had significantly higher visceral fat area than men without fatty liver ( $p < 0.001$ ).	↑ (males)
		35 males with fatty liver; mean BMI = 26 (SD, 1)	41 (SD, 4)					
Thomas, 2005 (34)	Case-control	11 persons with NASH (36% female); mean BMI = 29 (SD, 5)	52 (SD, 12)	United Kingdom	In multivariate linear regression analysis (including sex and age), subcutaneous fat volume was significantly directly associated with liver fat content (liver fat content increased by 72% (95% CI*: 27, 133) per 1% increase in subcutaneous volume).	↑ (both sexes)	In multivariate linear regression analysis (including sex and age), intraabdominal fat volume was significantly directly associated with liver fat content (liver fat content increased by 104% (95% CI: 37, 205) per 1% increase in visceral fat volume).	↑ (both sexes)
		23 controls (26% female); mean BMI = 27 (SD, 4)	43 (SD, 12)					

Chan, 2006 (26)§	Cross-sectional	17 males; mean BMI = 25 (SD, 5)	49 (SD, 12)	Caucasian	In multivariate linear regression analysis (including age and plasma adiponectin level), subcutaneous fat mass was not associated with liver fat content ( $\beta$ coefficient not given, $p > 0.05$ ).	NS (males)	In multivariate linear regression analysis (including age and plasma adiponectin level), visceral fat mass was significantly directly associated with liver fat content ( $\beta$ coefficient not given, $p$ value not given).	↑ (males)
Church, 2006 (24)§	Cross-sectional	194 males without NAFLD*; mean BMI = 28 (SD, 4) 24 males with NAFLD; mean BMI = 32 (SD, 4)	52 (SD, 7) 51 (SD, 5)	Non-Hispanic Caucasian	Men with NAFLD had significantly higher subcutaneous fat area than men without NAFLD ( $p < 0.001$ ).	↑ (males)	Men with NAFLD had significantly higher visceral fat area than men without NAFLD ( $p < 0.001$ ).	↑ (males)
Eguchi, 2006 (25)§	Cross-sectional	129 persons with NAFLD (49% female); mean BMI = 25 (SD, 3)	59 (SD, 12)	Japan	Subcutaneous fat area was not correlated with severity of fatty liver (mild, moderate, or severe) (correlation coefficient not given, $p$ value not given). Subcutaneous fat area was not correlated with severity of fatty liver among nonobese persons (BMI < 25) (correlation coefficient not given, $p$ value not given).	All persons: NS Nonobese persons: NS (both sexes)	Visceral fat area was significantly directly correlated with severity of fatty liver (mild, moderate, or severe) (correlation coefficient not given, $p < 0.01$ ). Visceral fat area was significantly directly correlated with severity of fatty liver among nonobese persons (BMI < 25) (correlation coefficient not given, $p < 0.01$ ).	All persons: ↑ Nonobese persons: ↑ (both sexes)
Holt, 2006 (27)§	Cross-sectional	7 males without fatty liver; mean BMI = 26 (SD, 2) 9 males with mild-to-moderate fatty liver; mean BMI = 29 (SD, 3) 6 males with severe fatty liver; mean BMI = 30 (SD, 5)	54 (SD, 8) 64 (SD, 6) 51 (SD, 7)	United Kingdom	No difference in subcutaneous fat volume between the three categories of fatty liver ( $p = 0.63$ )	NS (males)	No difference in visceral fat volume between the three categories of fatty liver ( $p = 0.63$ ).	NS (males)
Liu, 2006 (35)	Cross-sectional	134 males; mean BMI = 25 (SD, 3) 157 females; mean BMI = 23 (SD, 3)	43 (SD, 8) 41 (SD, 7)	China	In multivariate logistic regression analysis (including sex, age, mesenteric and preperitoneal fat thickness, blood pressure, HOMA,* glucose, triglycerides, LDL* cholesterol, HDL* cholesterol, alkaline phosphatase, and ALT*), subcutaneous fat thickness was not associated with fatty liver (per 1-mm increase in subcutaneous fat thickness, OR* = 1.04, 95% CI: 0.98, 1.10); after additional adjustment for BMI, the OR was 0.99 (95% CI: 0.93, 1.06).	NS (both sexes)	In multivariate logistic regression analysis (including sex, age, subcutaneous abdominal and preperitoneal fat thickness, blood pressure, HOMA, glucose, triglycerides, LDL cholesterol, HDL cholesterol, alkaline phosphatase, and ALT), mesenteric fat thickness was significantly directly associated with fatty liver (per 1-mm increase in visceral fat thickness, OR = 1.50, 95% CI: 1.27, 1.77); after additional adjustment for BMI, the OR was 1.34 (95% CI: 1.12, 1.60).	↑ (both sexes)

\* BMI, body mass index; SD, standard deviation; NS, not significant; NASH, nonalcoholic steatohepatitis; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; HOMA, homeostasis model assessment; LDL, low density lipoprotein; HDL, high density lipoprotein; ALT, alanine aminotransferase; OR, odds ratio.

† Weight (kg)/height (m)<sup>2</sup>.

‡ ↑ = statistically significant direct association or statistically significant difference.

§ Results from this study are also included in table 1.

¶ No data available.

**TABLE 3. Techniques for estimating abdominal fat mass and liver fat content used in the studies included in the present review**

Technique (in ascending order of assumed validity)	No. of studies	Reference(s)*
Aim of measurement: to estimate abdominal fat mass		
Waist circumference	19	12–30
Ultrasonography	2	14, 35
Computerized tomography or magnetic resonance imaging		
Computerized tomography	4	22, 24, 25, 32
Magnetic resonance imaging	5	26, 27, 31, 33, 34
Aim of measurement: to estimate liver fat content		
Liver enzyme levels	1	15
Ultrasonography	15	12, 14, 16–23, 25, 27, 28, 30, 35
Computerized tomography or magnetic resonance spectroscopy		
Computerized tomography	1	24
Magnetic resonance spectroscopy	4	26, 31, 33, 34
Liver biopsy	3	13, 29, 32

\* Studies which used that method to estimate abdominal fat level/liver fat content (see reference list).

biologic material for examining markers of the signals from abdominal fat to the liver and from the liver to abdominal fat, possibly indirectly via the brain and other organs.

### Selection problems

The study populations in this review included different ethnic groups, both men and women, and a broad age range. The selection of the study populations may have affected the external validity of the studies, but selection bias seems unlikely, since the participants, at least, were not aware of their liver fat content.

### Information problems

Different methods have been used to estimate abdominal fat mass and liver fat content. In this review, the studies were ordered according to the methods employed.

*Methods for estimating abdominal fat mass.* Anthropometric measurements are useful for classifying people according to their body fat distribution (10). However, using waist circumference, no distinction between visceral organs, subcutaneous abdominal fat, and intraabdominal fat is made. Computed tomography and magnetic resonance imaging are considered the best techniques available for valid assessment of the size of the different abdominal fat depots (10). Both methods are expensive, however, and computed tomography exposes the participant to ionizing radiation. As table 3 shows, computed tomography or magnetic resonance imaging was used to estimate abdominal fat mass in most of the included studies using imaging methods.

Studies using ratios as measures of abdominal fat mass were not included, because adding further body compartments introduces additional complexity in addressing the relation between abdominal obesity and liver fat content. The biologic interactions between the different body compartments and accumulation of fat in the liver are not yet clear. The functions of the different fat depots are complex and include, for example, release of both free fatty acids and biologically active compounds like adipokines into the circulation/portal vein. Furthermore, statistical arguments have been raised against the use of ratios (11). At present, the most relevant analytical strategy seems to be inclusion of measures of the different abdominal fat depots and other body compartments as potential confounders simultaneously (see below).

*Methods for diagnosing NAFLD.* Laboratory testing can provide some clues to the presence of NAFLD. Serum liver enzyme concentrations have been used in screening for NAFLD, but these are not considered sufficiently sensitive or specific for diagnosing NAFLD (7–9). Imaging studies can identify the presence of fat in the liver (7–9). Ultrasonographic examination lacks both sensitivity and specificity for detecting NAFLD. Computed tomography imaging of the liver is more sensitive for detecting NAFLD, and magnetic resonance imaging and magnetic resonance spectroscopy are the most sensitive (7–9). Identifying nonalcoholic steatohepatitis, however, requires a liver biopsy (7–9). As table 3 shows, ultrasonographic examination was used to estimate liver fat content in most of the included studies.

In the study by Rocha et al. (21), waist circumference was significantly directly correlated with alanine aminotransferase but not with aspartate aminotransferase or  $\gamma$ -glutamyltransferase among persons with NAFLD. In a study evaluating the validity of liver enzymes in detecting persons with fatty liver, the sensitivity of alanine aminotransferase was higher than that of aspartate aminotransferase and  $\gamma$ -glutamyltransferase (37). This may explain the lack of an association between waist circumference and levels of aspartate aminotransferase and  $\gamma$ -glutamyltransferase.

### Information bias

Information bias is unlikely to have affected the results of the included studies, since liver fat content was estimated independently of abdominal fat level.

### Potential effect modification

No clear effect modification by sex was observed. The rationale behind the examination of effect modification by sex was Nielsen et al.'s (6) observation of a direct association between visceral fat and the delivery of free fatty acids to the liver. This association was stronger in women than in men. Among the included studies, only two studies (27, 31) did not find an association between intraabdominal fat and fatty liver. These two studies were conducted among men. Thus, the findings by Nielsen et al. (6) might provide a biologic explanation for the lack of an association between intraabdominal fat and fatty liver in these two studies (27, 31). However, in the study by Seppala-Lindroos et al. (31),



only 15 persons were included in each group, raising the possibility of a false-negative result (type 2 error).

In the studies included in this review, direct associations between intraabdominal fat and liver fat content were reported within a wide range of body mass index, suggesting an association across categories of body mass index. Thus, body mass index may be considered a potential confounder, and not a potential effect modifier.

Potential effect modification by ethnicity could not be evaluated because of the limited information on ethnicity; in most studies, only the country of residence was indicated. Moreover, potential effect modification by age could not be evaluated because of the similar age ranges in the studies, and no age-specific results were reported.

### Potential confounding

In most of the included studies, several variables were included in the multivariate analyses. Generally, investigators should carefully consider which variables to include in multivariate analysis of the association between abdominal fat and liver fat content. Because of the biologic complexities involved, there may be a risk of including variables that are either causes of abdominal fat accumulation or consequences of fat accumulation in the liver. Analyses including potential causes or consequences have no clear interpretation and probably do not answer relevant questions.

*Adjustment for other body compartments.* Three studies (17, 23, 30) included body mass index in the analysis of waist circumference and NAFLD; those studies found a direct association between waist circumference and NAFLD. Liu et al. (35) reported results with and without adjustment for body mass index in analysis of mesenteric and subcutaneous abdominal fat thickness and fatty liver. They found a significant direct association between mesenteric fat thickness and fatty liver that was independent of subcutaneous abdominal and preperitoneal fat thickness; they also found this association after additional adjustment for body mass index in the multivariate analysis. There was no association between subcutaneous abdominal fat thickness and fatty liver. Note that adjustment for body mass index in analysis of specific body fat depots and a given outcome introduces a substitution aspect (redistribution of the size of the different body compartments). Consequently, adjustment for body mass index excludes the possibility of addressing isolated hypotheses on selected body compartments. The effect of one body compartment can only be assessed in relation to another; in a substitution model, differences in one body compartment are always followed by concomitant opposite differences in other body compartments. Thus, results from these studies may provide evidence that abdominal/mesenteric obesity increases fat accumulation in the liver more than another body compartment does, but results from these studies cannot provide evidence of whether abdominal/mesenteric obesity promotes fat accumulation in the liver or another body compartment prevents fat accumulation in the liver.

An alternative approach for investigating the association between a specific fat depot and fat accumulation in the liver could be to enter separate terms for other body compart-

ments, whether fat or lean body mass. This model implies that more fat would simply be added to one body fat depot, keeping the other body compartments constant. This approach may provide more valuable information on the role of specific fat depots. This approach has been partly used in the studies by Westerbacka et al. (33) and Liu et al. (35), who included intraabdominal fat and subcutaneous abdominal fat/mesenteric fat, subcutaneous abdominal fat, and preperitoneal fat simultaneously in analysis of these fat depots. In those studies, intraabdominal/mesenteric fat was significantly directly associated with fatty liver independently of subcutaneous abdominal fat/subcutaneous abdominal and preperitoneal fat, whereas subcutaneous abdominal fat was not associated with fatty liver independently of intraabdominal/mesenteric and preperitoneal fat. Church et al. (24) found that adjustment for visceral fat area attenuated the direct association between waist circumference and NAFLD, whereas adjustment for subcutaneous abdominal fat did not change the association; this suggests that the direct association between waist circumference and liver fat content was primarily accounted for by visceral fat. However, neither peripheral subcutaneous fat nor lean body mass was included in these analyses, raising the possibility of confounding from other body compartments.

An alternative explanation for the direct association between intraabdominal fat and liver fat content could be confounding from another factor, such as subcutaneous abdominal fat, since visceral fat and subcutaneous fat are highly correlated (3). However, two studies (33, 35) included intraabdominal and subcutaneous abdominal fat/mesenteric fat and subcutaneous abdominal fat simultaneously in analysis of these fat depots. Those studies found an independent significant direct association between intraabdominal/mesenteric fat and fatty liver. Moreover, subcutaneous abdominal fat was found to be significantly directly associated with NAFLD in only three (14, 24, 34) out of 11 (14, 22, 24–27, 31–35) studies, and in those three studies, intraabdominal fat was also found to be directly associated with NAFLD. Since none of those three studies included intraabdominal fat and subcutaneous abdominal fat simultaneously in the analyses of these fat depots, it cannot be excluded that the observed direct association between subcutaneous abdominal fat and NAFLD may be due to the strong correlation with visceral fat.

*Adjustment for potential consequences of fat accumulation in the liver.* In six studies (12, 17, 18, 23, 30, 35) reporting results from multivariate logistic regression analyses, the analyses included adjustment for potential metabolic effects of fat accumulation in the liver (e.g., fasting triglyceride levels). Therefore, in those analyses, the variation in liver fat content studied was limited to the variation that did not lead to subsequent changes in, for example, triglyceride levels. Crude and multivariate analyses from those studies thus reflect two different biologic scenarios, and the results cannot be compared directly.

### Conclusions and perspectives

In conclusion, clinical and epidemiologic studies of the association between abdominal fat and liver fat content

suggest a direct association between abdominal fat and liver fat content which is probably accounted for by visceral fat. Thus, these findings provide additional evidence of a detrimental health effect of abdominal obesity. Insight into the mechanisms underlying the relation between abdominal fat, especially visceral fat, and liver fat content is warranted. In the long term, this insight may identify specific targets for the prevention and treatment of fat accumulation in the liver. However, the results from the included studies do not allow strong conclusions regarding the temporal sequence of events and hence about putative cause-and-effect relations. We recommend that in future epidemiologic studies, a longitudinal approach be pursued and potential effect modification by ethnicity, sex, and age be considered in order to obtain further insight into the relation between abdominal fat and liver fat content. We also recommend considering entering both abdominal fat depots and other body compartments of interest into the analysis as an alternative approach for investigating the association between specific fat depots and liver fat content. Finally, inclusion of variables in multivariate analysis should be considered carefully to avoid adjustment for potential causes of abdominal fat accumulation and/or consequences of fat accumulation in the liver, leading to results with no clear interpretation.

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