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Journal

Journal of the American Heart Association, 12(18)

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Publication Date

2023-09-19

DOI

10.1161/JAHA.123.030470

Peer reviewed

Journal of the American Heart Association

ORIGINAL RESEARCH

Association Between Alcohol Consumption and Ectopic Fat in the Multi-Ethnic Study of Atherosclerosis

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BACKGROUND: The relationship between alcohol consumption and ectopic fat distribution, both known factors for cardiovascular disease, remains understudied. Therefore, we aimed to examine the association between alcohol consumption and ectopic adiposity in adults at risk for cardiovascular disease.

METHODS AND RESULTS: In this cross-sectional analysis, we categorized alcohol intake among participants in MESA (Multi-Ethnic Study of Atherosclerosis) as follows (drinks/day): <1 (light drinking), 1 to 2 (moderate drinking), >2 (heavy drinking), former drinking, and lifetime abstention. Binge drinking was defined as consuming ≥5 drinks on 1 occasion in the past month. Visceral, subcutaneous, and intermuscular fat area, pericardial fat volume, and hepatic fat attenuation were measured using noncontrast computed tomography. Using multivariable linear regression, we examined the associations between categories of alcohol consumption and natural log-transformed fat in ectopic depots. We included 6756 MESA participants (62.1±10.2 years; 47.2% women), of whom 6734 and 1934 had chest computed tomography (pericardial and hepatic fat) and abdominal computed tomography (subcutaneous, intermuscular, and visceral fat), respectively. In adjusted analysis, heavy drinking, relative to lifetime abstention, was associated with a higher (relative percent difference) pericardial 15.1 [95% CI, 7.1–27.7], hepatic 3.4 [95% CI, 0.1–6.8], visceral 2.5 [95% CI, –10.4 to 17.2], and intermuscular 5.2 [95% CI, –6.6 to 18.4] fat but lower subcutaneous fat –3.5 [95% CI, –15.5 to 10.2]). The associations between alcohol consumption and ectopic adiposity exhibited a J-shaped pattern. Binge drinking, relative to light-to-moderate drinking, was also associated with higher ectopic fat.

CONCLUSIONS: Alcohol consumption had a J-shaped association with ectopic adiposity. Both heavy alcohol intake and binge alcohol drinking were associated with higher ectopic fat.

Key Words: alcohol consumption ■ cardiovascular disease ■ ectopic fat

Worldwide, excessive alcohol consumption is a leading cause of morbidity and premature mortality.[1] Although the effect of light-to-moderate alcohol intake on cardiovascular health is still controversial,[2–4] excessive alcohol consumption significantly increases the risk of cardiovascular disease (CVD).[5–7] The potential mechanisms by which excessive alcohol may raise CVD risk include its association with higher body mass index (BMI), blood pressure (BP), blood glucose, and atherogenic dyslipidemia.[8–10]

Another possible mechanism may involve the effect of alcohol on ectopic fat deposition,[11–14] which is defined as the accumulation of adipocytes in and around organs such as the liver, skeletal muscle, intestines, and heart.[15] Furthermore, ectopic fat deposition is associated with CVD independent of other risk factors, including obesity

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This article was sent to Tiffany M. Powell-Wiley, MD MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.030470

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Relative to lifetime abstention, excessive alcohol intake was associated with higher ectopic adiposity measured by computed tomography, with the strongest association in pericardial and hepatic fat depots, followed by intermuscular, visceral, and subcutaneous fat depots.
- The relationship between alcohol consumption and ectopic adiposity exhibited a J-shaped pattern, with the lowest levels being seen in the light and moderate drinking categories.

What Are the Clinical Implications?

- The risk of cardiovascular disease related to excessive alcohol consumption may be mediated through ectopic fat distribution.

Nonstandard Abbreviations and Acronyms

MESA	Multi-Ethnic Study of Atherosclerosis

using BMI criteria.[15,16] It has even been suggested that ectopic fat deposition explains the heterogeneity in CVD risk among individuals with similar BMI.[17] Other than a distinct sexual dimorphism, the causal mechanisms that determine differing body fat composition have not yet been fully investigated.[15,16] A J-shaped association between alcohol consumption and excess adiposity that mirrors that for CVD risk[18,19] could provide new insight into the mechanisms of cardiovascular risk development.

In the analysis presented here, we examined the relationship between self-reported alcohol intake and computed tomography (CT)-derived ectopic fat depots among participants of MESA (Multi-Ethnic Study of Atherosclerosis). We hypothesized the following: (1) heavy drinking would be associated with higher fat compared with lifetime abstention in each ectopic fat depot except for subcutaneous fat; (2) binge drinking would also have a strong relationship with fat distribution; (3) based on prior literature and the J-shaped relationship of alcohol consumption with CVD risk, those with low and moderate alcohol consumption would have the lowest levels of ectopic fat; and (4) there would be no significant heterogeneity by age, sex, and race or ethnicity.

METHODS

Study Design and Population

The data and materials used in this cross-sectional analysis are available and can be requested at http://www.mesa-nhlbi.org. The study design, eligibility, and methods for the MESA have been previously published.[20] In brief, the MESA commenced in July 2000 to investigate the prevalence, correlates, and progression of subclinical CVD in a community-based sample of men and women aged 45 to 84 years. From 2000 to 2002 (Exam 1), a total of 6814 participants were recruited from 6 field centers in the United States (New York, NY; Baltimore, MD; Chicago, IL; Los Angeles, CA; St. Paul, MN; and Forsyth County, NC). The study population was free of clinical CVD at baseline and included 4 self-reported racial or ethnic groups of White, Black, Hispanic, and 803 Chinese American participants. In this study we included participants with available data on alcohol consumption and CT-derived ectopic fat measurement. All MESA participants provided written informed consent, and the institutional review boards approved the study at each center.[20]

Assessment of Alcohol Consumption

Trained personnel of the MESA study collected data on alcohol consumption by asking the participants to complete a personal-history questionnaire. Each participant was asked, "Have you ever consumed alcoholic beverages?" If yes, the following question was, "Do you presently drink alcoholic beverages?" The answers to these 2 questions categorized each participant into 3 categories: (1) lifetime abstention, (2) former, or (3) current drinking. Those who reported current and former drinking were asked, "For how many years did you drink alcoholic beverages?" Additionally, they were asked about the usual number of drinks consumed per week (before they stopped drinking if they reported former drinking). Those who reported current drinking also were asked about the number of drinks consumed during the past 24 hours and the largest number of drinks consumed in 1 day in the past month.

Each participant also completed a 120-item food-frequency questionnaire (FFQ). Using the FFQ, each participant was asked to consider their usual eating habits over the past year and to record the usual serving size (small, medium, or large) and average consumption of specific beverages and foods. For beverages, 9 options were given: rare or never, 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day," 2 to 3 per day, 4 to 5 per day, and ≥6 per day. The percentages of alcohol in wine, beer, and liquor were assumed to be 9.3%, 3.6%, and 14.2%, respectively. The MESA FFQ is a modification of a previously validated questionnaire originally designed for the Insulin Resistance and Atherosclerosis Study.[21,22] The FFQ also collected data on the type of alcohol consumed (wine, beer, and liquor). Liquor has also been referred to as "hard alcohol" or "spirits" as documented in a previous MESA study.[23]

The following alcohol consumption categories, using similar cutoffs for both men and women, were computed and used in the analyses: (1) lifetime abstention (participants who reported never consuming alcohol); (2) former drinking (participants who reported previous but not current alcohol consumption); (3) light drinking (participants who reported currently consuming, on average, <1 alcoholic drink per day); (4) moderate drinking (participants who reported currently consuming 1 to 2 alcoholic drinks per day); and (5) heavy drinking (participants who reported currently consuming >2 alcoholic drinks per day).

In order to examine the potential association with binge drinking, which is another distinct pattern of excessive alcohol consumption, a separate categorization of alcohol intake was computed as follows: (1) binge drinking (participants who reported consuming ≥5 alcohol drinks in a single day in the past month without concurrent light, moderate, or heavy alcohol drinking, ie, exclusively binge drinking behavior, using an abbreviated definition of binge drinking given the low levels of binge drinking in this study); (2) nonbinge heavy drinking (participants who reported habitual heavy drinking without binge drinking; and (3) a comparison group, light-to-moderate drinking (a joint category of participants who reported light [<1 drink/day] and moderate [1–2 drinks/day] drinking).

Assessment of Ectopic Fat

Pericardial fat volume and hepatic fat was derived from cardiac CT scans that were performed at baseline (2000–2002) in a subset of MESA participants either with an ECG-triggered electron-beam scanner (Chicago, Los Angeles, and New York field centers; Imatron C-150; GE Imatron, Milwaukee, WI) or with prospectively ECG-triggered scan acquisition with a multidetector system that acquired 4 simultaneous 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (Baltimore, Forsyth Country, and St. Paul field centers; Lightspeed [GE Medical Systems, Milwaukee, WI] or Volume Zoom [Siemens, Erlangen, Germany]). Three experienced CT analysts measured pericardial fat volume on the previously obtained images of the heart.

For pericardial fat volume, slices within 15 mm above and 30 mm below the superior extent of the left main coronary artery were included. This region of the heart was selected because it includes the pericardial fat located around the proximal coronary arteries (left main coronary, left anterior descending, right coronary, and circumflex arteries). The anterior border of the volume was defined by the chest wall and the posterior border by the aorta and the bronchus. Volume analysis software (GE Health Care, Waukesha, WI) was used to discern fat from other tissues with a threshold of –190 to –30 Hounsfield units. The final pericardial fat volume was the sum of all voxels containing fat.[24] This technique for measuring pericardial fat volume has been found to be highly correlated with total volume of pericardial fat volume.[25]

Hepatic fat was measured based on liver attenuation, which has been previously described.[26] Briefly, liver attenuation was measured as the average density of 3 regions (~1 cm^2 each) on a cardiac CT scan. Trained analysts placed the 3 regions consistently in the parenchyma of the right lobe of the liver while avoiding vascular structures and hepatic cysts.[26] Liver attenuation has been shown to be inversely correlated with fatty change assessed by liver biopsy (correlation coefficient: –0.90; $P<0.0001$).[27]

Abdominal fat area measurements, including subcutaneous, visceral, and intermuscular, were measured from Exam 2 (2002–2004) and Exam 3 (2004–2005) by abdominal CT in a random subset of 1970 MESA participants. Electron-beam CT scanners were used at Northwestern University and the University of California, Los Angeles (Imatron C-150), with settings collimation 3 mm, slice thickness 6 mm, reconstruction using 25 6-mm slices with 35-cm field of view and normal kernel. Multidetector CT scanners were used at Columbia University, Wake Forest University, and University of Minnesota field centers (Sensation 64, GE Lightspeed; Siemens S4 Volume Zoom; and Siemens Sensation 16). Image interpretation was blinded to clinical information.[28] Using the MIPAV 4.1.2 software (National Institutes of Health, Bethesda, MD), 2 5-mm noncontrast slices between the L-4 and L-5 vertebral levels were interrogated for subcutaneous, visceral, and total intermuscular abdominal fat areas (in cm^2).[28] Subcutaneous fat was defined as the fat outside of the visceral cavity but did not include that located within the muscular fascia. Visceral fat was defined as tissue within the contour of the visceral cavity. Fat tissue was identified as being between –190 and –30 Hounsfield units. We calculated the total intermuscular fat area by combining fat within the fascia for the oblique, rectus abdominus, paraspinal, and psoas muscle groups.[29] Inter-rater and intrarater reliabilities for total abdominal, subcutaneous, and visceral cavity areas were 0.99 for all measures.[28]

Covariates

During the MESA baseline examination, standardized questionnaires were used to obtain self-reported demographic information and level of education, annual household income, smoking history, medical history, and medication usage for high BP, high cholesterol, or diabetes. Cigarette smoking was calculated in pack-years and defined as current, former, or never. Total dietary calories (kilocalories per day) were estimated

from the MESA FFQ, which has comparable validity in White, Black, and Hispanic individuals,[21,22] and with additional modification to include foods typically eaten by Chinese American individuals.[20] Physical activity was measured by using a detailed, semiquantitative questionnaire adapted from the Cross-Cultural Activity Participation Study.[30] Sedentary behavior was assessed by self-reported time spent watching television as hours per week. BMI was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic resting BPs were measured in seated participants. Total and high-density lipoprotein cholesterol, triglycerides, and glucose levels were measured from blood samples obtained after a 12-hour fast. Low-density lipoprotein cholesterol was calculated with the Friedewald equation.[31] Diabetes was defined as fasting glucose >6.99 mmol/L (126 mg/dL) or use of hypoglycemic medication.[20] Diagnosis of hypertension was defined as self-reported treatment for hypertension with medications or a systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg. Dyslipidemia was defined as total cholesterol level of ≥200 mg/dL, or triglycerides level of ≥150 mg/dL, or low-density lipoprotein cholesterol ≥130 mg/dL, or high-density lipoprotein cholesterol <40 mg/dL (for men) and <50 mg/dL (for women), or self-reported current use of lipid-lowering medications.

Inclusion and Exclusion

For the final analysis, we included participants with CT data on pericardial fat and hepatic fat (n=6734) measured at enrollment, and visceral, subcutaneous, and intermuscular fat (n=1934), measured at Exam 2 or Exam 3. Among these participants, we excluded individuals with missing information on alcohol consumption (n=58) or missing key covariates for Model 1 (n=246) and Model 2 (n=523). The final sample size for each ectopic fat category for analysis was as follows: pericardial fat (n=6727), hepatic fat (n=6678), subcutaneous fat (n=1613), visceral fat (n=1889), and intermuscular fat (n=1934).

Statistical Analysis

The study population's baseline characteristics were compared across the categories of alcohol consumption. We reported categorical variables as counts (percentages) and continuous variables as mean (SD) or median (interquartile range), depending on the normality of the data. To compare the baseline characteristics, we used analysis of variance for continuous variables and the chi-square test for categorical variables. Because the ectopic fat variables were not normally distributed, they were log transformed, as was BMI. The values for hepatic attenuation ranged from –28 to 110, with lower values indicating more hepatic fat. For ease of interpretation, before log-transformation, we subtracted each hepatic attenuation value from 120, yielding values of 10 to 148.

We used a multivariable linear regression model to examine the association between alcohol consumption categories and natural log-transformed fat volume from each depot separately. Two separate regression models were fitted. Model 1 was adjusted for age, sex, race or ethnicity, education, and income. Model 2 was adjusted for all variables in Model 1 plus cigarette smoking, total energy intake, and physical activity. Finally, we back transformed the beta coefficient into a percent difference to improve the interpretability and comparability of the results. Relative percent differences were calculated using the following formula: 100*(exp (estimate)-1).

Similarly, we examined the association of current binge drinking (ie, without heavy drinking) and non-binge heavy drinking, relative to light-to-moderate drinking, with the ectopic fat distribution and BMI using a multivariable linear regression model. We chose this approach in order to examine the potential impact of exclusive binge drinking behavior versus heavy drinking but without binge drinking on ectopic fat depots.

Sensitivity Analysis

We also performed subgroup analyses stratified by sex and race or ethnicity and formally tested for heterogeneity by group. We examined the association of alcohol consumption and ectopic fat distribution among participants by baseline CVD risk factors including diabetes, hypertension, and dyslipidemia. Finally, in additional sensitivity analysis, we also adjusted for marital status, depression, and sedentary lifestyle.

A 2-sided P value ≤0.05 was considered statistically significant, and all statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Our analysis included 6756 MESA participants with a mean age of 62.1±10.2 years (52.8% female) who had available data on alcohol consumption and CT-derived fat measurement. The distribution of self-reported alcohol consumption categories was as follows: 1390 (20.6%) lifetime abstention, 1625 (24.0%) former drinking, 2925 (43.3%) light drinking, 597 (8.8%) moderate drinking, and 220 (3.3%) heavy drinking. Participants who reported heavy drinking had higher rates of current smoking, diastolic BP, total cholesterol level, triglycerides level, and total energy intake. Lower levels of physical exercise were reported among those in lifetime abstention and heavy drinking categories. The group with lifetime abstention or former drinking were on average older and more likely to have CVD risk factors like diagnosed diabetes, use of antihypertensive

Table 1. Baseline Characteristics of the Study Participants

Characteristics	Overall (n=6756)	Lifetime abstention (n=1390)	Former drinking (n=1624)	Light drinking (n=2925)	Moderate drinking (n=597)	Heavy drinking (n=220)	*P* value
Age, y	62.1±10.2	63.9±10.23	62.9±10.22	61.0±10.14	62.6±10.13	59.4±9.56	<0.0001
Women, n (%)	3566 (47.2)	1065 (76.6)	764 (47.0)	1504 (51.4)	206 (34.5)	27 (12.3)	<0.0001
Race or ethnicity, n (%)							<0.0001
White	2595 (38.4)	245 (17.6)	484 (29.8)	1361 (46.5)	357 (59.8)	148 (67.3)	
Chinese American	800 (11.8)	432 (31.1)	118 (7.3)	223 (7.6)	22 (3.7)	5 (2.3)	
Black	1867 (27.6)	325 (23.4)	620 (38.2)	766 (26.2)	126 (21.1)	30 (13.6)	
Hispanic	1494 (22.1)	388 (27.9)	402 (24.8)	575 (19.7)	92 (15.4)	37 (16.8)	
Body mass index, kg/m^2	28.3±5.5	27.9±5.65	29.2±5.78	28.3±5.36	27.2±4.72	28.1±4.33	<0.0001
Education ≥bachelor's degree, n (%)	35.3	321 (12.1)	438 (27.0)	1247 (42.6)	287 (48.1)	201 (48.8)	<0.0001
Married, n (%)	4097 (60.6)	846 (60.9)	912 (56.2)	1803 (61.6)	387 (64.8)	149 (67.7)	<0.0001
Family income ≥$75 000 per year, n (%)	1469 (22.6)	128 (9.7)	215 (14.0)	834 (29.3)	213 (36.7)	79 (36.4)	<0.0001
Systolic blood pressure, mm Hg	126.5±21.5	129.6±22.95	128.1±21.82	124.4±20.66	126.2±21.07	125.7±17.87	<0.0001
Diastolic blood pressure, mm Hg	71.9±10.3	70.9±10.28	72.1±10.39	71.7±10.13	73.4±10.14	76.1±9.74	<0.0001
Taking antihypertensive medication, n (%)	2508 (37.1)	553 (39.8)	690 (42.5)	983 (33.6)	208 (34.8)	74 (33.6)	<0.001
Diabetes diagnosis, n (%)	675 (10.0)	182 (13.1)	252 (15.5)	213 (6.9)	28 (4.7)	10 (4.5)	<0.0001
Fasting glucose, mg/dL	97.4±30.2	100.3±32.98	100.2±33.56	94.9±27.60	94.8±25.87	97.8±27.75	<0.0001
High-density lipoprotein-cholesterol, mg/dL	50.9±14.8	51.1±14.17	48.2±13.44	51.2±14.76	55.4±17.94	54.0±16.55	<0.0001
Low-density lipoprotein-cholesterol, mg/dL	117.2±31.4	118.0±32.00	115.9±31.37	118.0±30.96	114.8±32.00	117.8±31.69	0.072
Total cholesterol, mg/dL	194.2±35.7	196.8±35.78	189.9±35.68	194.6±35.55	195.0±35.41	200.6±35.41	<0.0001
Triglycerides, mg/dL	131.7±89.0	141.7±99.49	130.7±82.33	127.5±86.46	127.6±89.43	144.4±92.05	<0.0001
Current smoker, n (%)	886 (13.1)	80 (5.8)	204 (12.6)	414 (14.2)	119 (19.9)	69 (31.4)	<0.0001
Binge drinker, n (%)	536 (14.3)			219 (7.5)	158 (26.5)	159 (72.3)	<0.0001
Total energy intake, kcal	1621.6±871.4	1389.9±812.26	1653.0±903.18	1636.5±828.04	1803.3±904.64	2160.9±1042.5	<0.0001
Total intentional exercise, metabolic equivalents/wk	1553.5±2342.6	1250.4±2083.0	1410.7±2249.7	1728.9±2473.5	1783.3±2360.0	1566.8±2469.8	<0.0001
Reported total physical activity, h/d	12.6±5.9	11.4±5.92	12.7±6.03	13.2±5.83	12.6±5.29	12.1±5.28	<0.0001

Continued

Table 1. Continued

Characteristics	Overall (n=6756)	Lifetime abstention (n=1390)	Former drinking (n=1624)	Light drinking (n=2925)	Moderate drinking (n=597)	Heavy drinking (n=220)	*P* value
Pericardial fat volume, cm^3*	79.6±42.1	75.0±35.51	83.2±44.68	77.3±41.28	84.1±45.83	102.4±49.02	<0.0001
Hepatic fat liver attenuation, HU*	61.5±12.6	61.1±13.80	61.3±11.97	62.2±12.22	61.6±12.50	57.6±13.31	<0.0001
Subcutaneous total area, cm^2	267.4±119.1	275.4±121.46	283.7±133.61	263.4±114.77	239.2±97.89	241.5±95.07	<0.001
Visceral total area, cm^2†	223.4±74.6	202.3±66.98	234.2±79.25	224.1±73.31	227.9±72.04	254.4±80.01	<0.0001
Intermuscular fat area, cm^2†	24.5±11.8	23.9±11.09	25.0±13.82	23.8±10.79	26.6±12.25	26.8±12.93	0.011

Light drinking, <1 drink/day; moderate drinking, 1 to 2 drinks/day; heavy drinking, >2 drinks/day. Data are given as mean±SD or n (%). *P* value by analysis of variance for continuous variables or chi-square for categorical variables.

*Pericardial and hepatic fat measured by computed tomography at enrollment (n=6734).

†Subcutaneous, visceral, and intermuscular fat measured by abdominal computed tomography on selected sample at visit 2 and visit 3 (n=1934).

medications, and lower total intentional exercise (Table 1). Few participants reported heavy drinking without binge drinking (n=54), and this was especially the case for women where nonbinge heavy drinking was basically nonexistent (n=<5). The distribution of pericardial fat volume, hepatic fat attenuation, and subcutaneous, visceral, and intermuscular total fat area by category of alcohol consumption is also shown in Table 1.

In Model 1, which adjusted for age, sex, and race or ethnicity, relative to lifetime abstention, light and moderate drinking category has lower adiposity all fat depots whereas heavy drinking was associated with a higher adiposity. In the heavy drinking category, the relative percent difference for pericardial and hepatic fat was 17.0 (95% CI, 9.1–25.5; *P*<0.0001) and 3.8 (95% CI, 0.5–7.1; *P*=0.022), respectively. A similar pattern of higher adiposity in heavy drinking category and lower adiposity in light (or moderate) drinking categories was observed in visceral, subcutaneous, and intermuscular locations, but with weaker and varying strengths (Table 2).

In our full model (Model 2), which adjusted for Model 1 plus cigarette smoking, total energy intake, and physical activity, compared with lifetime abstention, heavy drinking was associated with higher adiposity in all 5 fat depots. This association was strongest for pericardial 15.1 (95% CI, 7.1–23.7; *P*<0.0001) and hepatic 3.4 (95% CI, 0.1–6.8; *P*=0.045) fat and was not significant for subcutaneous 3.5 (95% CI, –15.5 to 10.2; *P*=0.599), visceral 2.5 (95% CI, –10.4 to 17.2; *P*=0.724), and intermuscular 5.2 (95% CI, –6.6 to 18.4; *P*=0.405) fat (Table 2).

Additionally, in all fat depots there was an apparent J-shaped pattern of percent difference in the association with alcohol intake with the lowest estimates found in light and moderate drinking categories (Table 2 and Figure 1). Exclusive binge drinking (ie, without habitual heavy drinking), compared with light-to-moderate drinking, was associated with higher adiposity in all fat depots. These estimates were particularly strong for pericardial, hepatic, and intermuscular fat with a significant association, whereas those in subcutaneous and visceral fat were weaker and nonsignificant. Compared with light-to-moderate drinking, associations for heavy drinking without concurrent binge drinking were similar to those for binge drinking but were not significant for any fat depot (Table 3 and Figure 2). In contrast, alcohol consumption was associated with BMI among both men and women in a U-shaped pattern. Notably, participants in the moderate alcohol drinking category had the lowest BMI relative to those with lifetime abstention from alcohol (Table 2). When compared with light-to-moderate drinking, both nonbinge heavy drinking and binge drinking were not significantly associated with BMI (Table 3).

Table 2. Relative Percent Difference in Body Fat Distribution and Body Mass Index by Alcohol Consumption Categories

Body fat subtype and body mass index	Alcohol consumption category*,†	Model 1‡		Model 2§	
		Relative percent difference (95% CI)	*P* value	Relative percent difference (95% CI)	*P* value
Pericardial	Former drinking	1.3 (–2.2 to 5.1)	0.4535	–1.4 (–5.1 to 2.4)	0.453
	Light drinking	–2.2 (–5.4 to 1.1)	0.1946	–3.9 (–7.2 to –0.5)	0.024‖
	Moderate drinking	2.1 (–6.7 to 2.8)	0.4010	–4.9 (–9.6 to 0.01)	0.051
	Heavy drinking	17.0 (9.1 to 25.5)	<0.0001‖	15.1 (7.1 to 23.7)	<0.0001‖
Hepatic	Former drinking	–0.5 (–2.1 to 1.2)	0.5646	–0.7 (–2.3 to 1.0)	0.425
	Light drinking	–2.3 (–3.8 to –0.9)	0.0018‖	–2.5 (–4.0 to –1.0)	0.002‖
	Moderate drinking	–1.4 (–3.4 to 0.8)	0.2025	–1.5 (–2.7 to 0.8)	0.203
	Heavy drinking	3.8 (0.5 to 7.1)	0.0220‖	3.4 (0.1 to 6.8)	0.045‖
Subcutaneous	Former drinking	–0.3 (–6.8 to 6.8)	0.9414	–0.1 (–7.0 to 7.2)	0.973
	Light drinking	–5.4 (–10.4 to 0.5)	0.0708	–5.5 (–11.2 to 0.6)	0.078
	Moderate drinking	–10.4 (–18.0 to –2.0)	0.0166‖	–10.5 (–18.5 to –1.9)	0.019‖
	Heavy drinking	–3.3 (–15.0 to 10.0)	0.6082	–3.5 (–15.5 to 10.2)	0.599
Visceral	Former drinking	0.8 (–6.1 to 8.1)	0.8267	–0.5 (–7.6 to 7.1)	0.890
	Light drinking	–2.7 (–8.6 to 3.7)	0.4053	–3.3 (–9.4 to 3.3)	0.319
	Moderate drinking	–8.7 (–16.8 to 0.2)	0.0561	–10.3 (–18.5 to –1.3)	0.026‖
	Heavy drinking	5.4 (–7.5 to 20.0)	0.4304	2.5 (–10.4 to 17.2)	0.724
Intermuscular	Former drinking	0.2 (–5.9 to 6.7)	0.9433	–1.2 (–7.5 to 5.5)	0.719
	Light drinking	–3.1 (–8.4 to 2.6)	0.2810	–4.7 (–10.1 to 1.1)	0.110
	Moderate drinking	2.9 (–5.3 to 11.8)	0.5009	–0.1 (–8.3 to 8.8)	0.975
	Heavy drinking	9.6 (–2.2 to 22.8)	0.1162	5.2 (–6.6 to 18.4)	0.405
Body mass index	Former drinking	0.7 (–0.6 to 2.1)	0.3030	0.2 (–1.2 to 1.6)	0.740
	Light drinking	–0.9 (–2.1 to 0.3)	0.1529	–1.0 (–2.2 to 0.3)	0.137
	Moderate drinking	–4.2 (–5.9 to –2.5)	<0.0001‖	–4.3 (–6.2 to –2.6)	<0.0001‖
	Heavy drinking	–0.8 (–3.3 to 1.9)	0.5668	–0.5 (–3.1 to 2.2)	0.703

*Light drinking, <1 drink/day; moderate drinking, 1 to 2 drinks/day; heavy drinking, >2 drinks/day.
†Reference group for each fat depot: lifetime abstention.
‡Model 1 adjusted for age, sex, race or ethnicity, education, and income.
§Model 2 adjusted for Model 1 plus cigarette smoking, total energy intake, and physical activity.
‖*P* values <0.05.

Heavy drinking of liquor, relative to lifetime abstention, had the strongest association with higher (relative percent difference amount of pericardial fat 20.5 [95% CI, 9.4–32.8]; *P*<0.001 and hepatic fat 4.7 [95% CI, 0.2–9.4]; *P*=0.041), whereas light and moderate consumption of wine had the opposite association (–6.2 [95% CI, –9.7 to –2.6]; *P*<0.0001) and –12.1 [95% CI, –17.7 to –6.0]; *P*<0.0001, respectively). Similarly, light and moderate wine consumption, and to a lesser extent beer, were associated with lower BMI. Light but not moderate, beer consumption was associated with lower adiposity in pericardial, –5.3 (95% CI, –9.0 to –1.4; *P*=0.008) and hepatic –2.0 (95% CI, –3.7 to –0.2; *P*=0.033) locations (Table 4).

Sensitivity Analysis

Current alcohol drinking was reported more frequently among White participants and least frequently among Chinese American participants. Moderate and heavy alcohol consumption was more frequent among men than women (Figure S1). Additionally, the prevalence of heavy alcohol consumption was highest among White participants, followed by Hispanic and Black participants, and lowest among Chinese American participants (Figure S2).

There was significant heterogeneity in the association between alcohol consumption and BMI by sex, with a stronger and more U-shaped association for women compared with men (interaction *P*-value <0.0001). In subgroup analysis, significant heterogeneity by sex was found only between drinking categories for pericardial (interaction *P* value <0.0001) and hepatic fat (interaction *P*-value <0.002). Notably, the estimates for heavy drinking and ectopic fat tended to be higher for women compared with men across the board (Table S1). There were no significant interactions by age or race or ethnicity (Table S2). Table S3 shows results from analysis by baseline CVD risk factors (diabetes, hypertension, and dyslipidemia). The

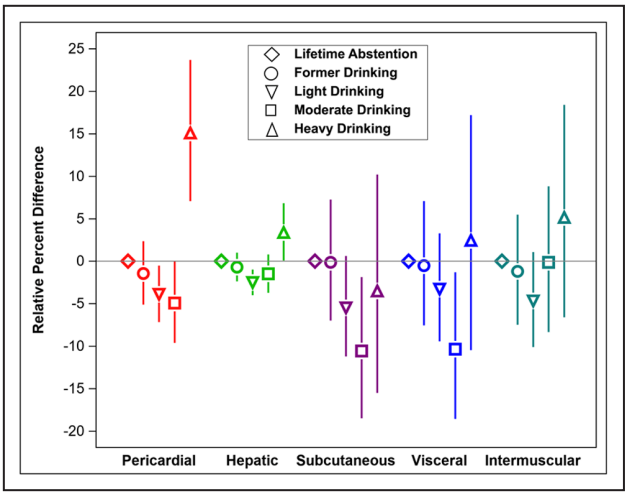

Figure 1. Association of alcohol consumption with body fat distribution (relative percent difference and 95% CI) among MESA participants.*†‡

*Light drinking, <1 drink/day; moderate drinking, 1–2 drinks/day; heavy drinking, >2 drinks/day. †Pericardial and intrahepatic fat measured by CT at enrollment (n=6734). Subcutaneous, visceral, and intermuscular fat measured by abdominal CT on selected sample at visit 2 and visit 3 (n=1934). Subcutaneous, visceral, pericardial, and intermuscular fat in cm^2. Hepatic fat is defined as the inverse hepatic fat attenuation in HU. ‡Model adjusted for age, sex, race or ethnicity, education, income, cigarette smoking, total energy intake, and physical activity. CT indicates computed tomography; HU, Hounsfield unit; and MESA, Multi-Ethnic Study of Atherosclerosis.

results were robust after additional adjustment for depression, marital status, and sedentary behavior (Table S4).

DISCUSSION

The main objective of this study was to examine the association between alcohol consumption and distribution of ectopic adiposity in a multiethnic cohort of adults at risk for CVD. This study revealed several findings. First, heavy alcohol consumption, relative to lifetime abstention from alcohol, was associated with significantly higher pericardial fat. Second, binge drinking, relative to other patterns of alcohol consumption, was similarly associated with higher levels of pericardial fat. Results were similar for adiposity in other locations, with the strongest associations for pericardial and hepatic fat depots followed by intermuscular fat, visceral, and subcutaneous fat, respectively. Third, the association between alcohol consumption and adiposity in various depots exhibited a J-shaped pattern, with the lowest levels being seen in the moderate or more rarely light drinking category. There was no significant heterogeneity in the relationship between categories of alcohol intake and levels of adiposity or BMI by race or ethnicity or age.

Both excessive alcohol intake and excess ectopic fat accumulation are known risk factors for CVD.[15,32] Multiple studies have reported a J-shaped relationship with low-moderate alcohol consumption tied to the lowest cardiovascular risks, whereas excessive alcohol intake is linked with a higher risk[32–34]; however, the true relationship between alcohol consumption and CVD risk remains controversial.[3] Multiple mechanisms involving CVD risk factors have been suggested for these findings,[8,9,35,36] but methodological bias and confounding by social determinants of health have not been sufficiently eliminated. Attempts to answer this question through investigation of the association of alcohol intake with anthropometric measures, particularly BMI, have yielded inconsistent results.[10] For example, some studies have found alcohol intake to be associated with increased BMI in men,[37,38] whereas in women they found a negative to null association.[39] Others have also reported a positive relationship between alcohol intake and higher BMI in both men and women but with some sexual dysmorphism in fat distribution.[40] Previous studies using waist circumference and waist-to-hip ratio have found significant associations between alcohol intake and abdominal adiposity.[41–43] Yet, anthropometric measurements for adiposity have some limitations. BMI, in particular, has long been criticized as an indirect measurement of total body fat that fails to exclude other tissue types.[15,17] Our analysis revealed a more U-shaped association of alcohol consumption with BMI, with the lowest BMI for moderate drinking. Counterintuitively, we found a lower level of BMI for heavy drinking compared with lifetime abstention. Comparing our results for directly measured fat from different depots provides insight into how the estimates for BMI may provide a distorted view of how alcohol consumption may influence the excess adiposity most tied to cardiometabolic risk. Finally, despite differing alcohol consumption patterns and known differences in distribution of ectopic fat in men compared with women, heterogeneity by sex was significant only in pericardial and hepatic depots and BMI.

Advanced imaging techniques, such as CT or magnetic resonance imaging, can directly and more accurately quantify ectopic fat, including differentiating between fat stored in different depots.[44] Differing body fat distributions have been associated with variable cardiometabolic outcomes and are increasingly theorized to have distinct functions.[15,45] Previous studies that used CT-derived measurements have generally linked heavy alcohol intake with higher visceral fat or visceral-to-subcutaneous fat ratio,[11–14] but few studies have investigated this relationship with fat stored in other locations. For instance, it is well known that higher pericardial fat volume is associated with cardiovascular risk,[24,46–49] but literature on how alcohol consumption may affect pericardial fat accumulation is

Table 3. Relative Percent Difference in Body Fat Distribution and Body Mass Index Among 3742 MESA Participants Who Reported Nonbinge Heavy Drinking and Binge Drinking Compared With Light and Moderate Alcohol Drinking

Body fat subtype, body mass index, and alcohol consumption categories†	Relative percent difference (95% CI)‡	*P* value
Pericardial		
Light-to-moderate drinking (n=3020)	Ref.	…
Nonbinge heavy drinking (n=54)	8.3 (−4.5 to 22.8)	0.214
Binge drinking (n=654)	7.5 (3.0 to 12.2)	<0.001*
Hepatic		
Light-to-moderate drinking (n=2987)	Ref.	…
Nonbinge heavy drinking (n=54)	3.3 (−2.3 to 9.2)	0.251
Binge drinking (n=651)	2.2 (0.2 to 4.1)	0.028*
Subcutaneous		
Light-to-moderate drinking (n=744)	Ref.	…
Nonbinge heavy drinking (n=16)	2.4 (−16.6 to 25.8)	0.818
Binge drinking (n=154)	2.0 (−5.7 to 10.2)	0.622
Visceral		
Light-to-moderate drinking (n=871)	Ref.	…
Nonbinge heavy drinking (n=20)	−1.6 (−20.2 to 21.5)	0.884
Binge drinking (n=186)	1.2 (−6.6 to 9.7)	0.774
Intermuscular		
Light-to-moderate drinking (n=892)	Ref.	…
Nonbinge hHeavy drinking (n=21)	2.0 (−15.3 to 22.8)	0.835
Binge drinking (n=190)	11.0 (3.3 to 19.3)	0.005*
Body mass index		
Light-to-moderate drinking (n=3033)	Ref.	…
Nonbinge heavy drinking (n=54)	0.4 (−4.1 to 5.1)	0.197
Binge drinking (n=655)	1.2 (−0.4 to 2.7)	0.146

**P* values <0.05.
†Defined as follows: light-to-moderate drinking=1 to 2/day; heavy drinking=>2 drinks/day; binge drinking=≥5 drinks in the past month.
‡Model adjusted for age, sex, race or ethnicity, education, income, cigarette smoking, total energy intake, and physical activity.

almost nonexistent. Similarly, studies examining alcohol drinking patterns and intramuscular fat are lacking. On the other hand, more evidence exists to show that heavy alcohol intake is associated with higher hepatic fat[50–52]—a condition that is associated with dyslipidemia and dysglycemia.[53] Further, previous reports of a J-shaped association with hepatic fat exist with a lower prevalence of hepatic fat among those who consumed low and moderate amount of alcohol.[52] Our results are generally consistent with the extant literature. Of all the fat depots that we examined, pericardial fat had the strongest association with excessive alcohol intake, and relationships were J-shaped for all fat measures in MESA. We note that the differences in the uncertainty around the estimates for excessive alcohol intake and adiposity in various depots may be explained by a difference in the sample sizes available for our analysis (n=6734 for pericardial and hepatic fat compared with n=1934 for other fat depots). Nonetheless, the consistent J-shaped pattern we observed is striking in its comparison to the J-shaped association between alcohol consumption and CVD risk,[5,18] offering novel speculations about the mediating role of fat distribution in this important but unresolved relationship. Through poorly understood and interrelated mechanisms, alcohol intake affects lipids and glucose metabolism, coagulation, endothelial function, and inflammation.[54] For example, alcohol consumption is associated with higher levels of high-density lipoprotein-cholesterol, but its effect on the level of low-density lipoprotein-cholesterol is inconsistent. Furthermore, alcohol has also been reported to affect the level of adiponectin, a hormone that influences both glucose metabolism and fatty acid oxidation.[54] However, it is unclear whether alcohol through such mechanisms may also influence adipogenesis and the pattern of body fat distribution.

The finding that light and moderate alcohol consumption is associated with the lowest levels of ectopic fat is unintuitive but consistent with prior evidence showing the lowest CVD risk in this group—a subject with significant controversy.[3–5] Both relationships may be explained by residual confounding from more general behavior patterns, especially those involving overall patterns of energy consumption and those driven

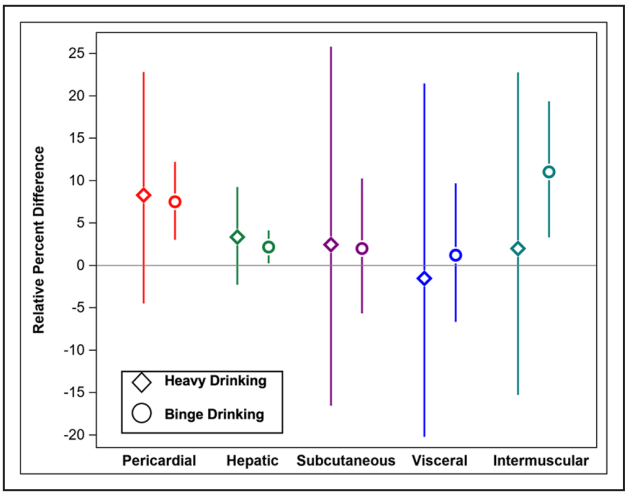

Figure 2. Association of heavy and binge compared with light-moderate alcohol drinking with body fat distribution (relative percent difference and 95% CI) Among MESA participants.*†‡

*Light-to-moderate drinking, current drinking <1 drink/day; heavy drinking, 2 drinks/day; binge drinking ≥5 drinks in the past month. †Pericardial and intrahepatic fat measured by CT at enrollment (n=6734). Subcutaneous, visceral, and intermuscular fat measured by abdominal CT on selected sample at visit 2 and visit 3 (n=1934). Subcutaneous, visceral, pericardial, and intermuscular fat in cm^2. Hepatic fat is defined as the inverse hepatic fat attenuation in HU. ‡Model adjusted for age, sex, race or ethnicity, education, income, cigarette smoking, total energy intake, and physical activity.

by comorbidities that are influenced by alcohol consumption or family history. Another possible explanation for these observations may well be related to the reasons for nondrinkers to self-select into that category. Moreover, comparing with those in the lifetime abstention and former drinking groups is particularly challenging as there are many reasons why an individual might both avoid alcohol consumption and have higher levels of adiposity and other CVD risk factors. In our study, participants in the light-to-moderate drinking group had lower rates of current smoking, diastolic BP, total cholesterol level, total glycerides level, and lower total energy intake but reported higher physical activity compared with heavy drinking. Due to the well-documented negative consequences resulting from alcohol consumption, it is important that clinicians emphasize to patients the potential risks related to excessive alcohol intake.

Binge alcohol drinking (consuming ≥5 alcoholic drinks on 1 occasion) is another common alcohol consumption behavior that is rarely studied directly and is challenging to characterize separately from more consistent patterns alcohol drinking.[55] Binge drinking is associated with numerous adverse health consequences, particularly unintentional injuries,[55] but its effect on adiposity has not been studied. We found that binge drinking, even in the absence of more generalized heavy drinking, may also be detrimental by encouraging higher ectopic adiposity.

We observed lower pericardial and hepatic fat among individuals who reported light and moderate consumption of wine. In contrast, heavy consumption of liquor was associated with higher pericardial fat while the results for beer consumption were less consistent. These apparent differential effects of alcohol type on cardiovascular health have been previously reported in MESA and may be due to the salutary effect of polyphenols found in wine.[23,56] However, other studies have attributed these differences to lifestyle characteristics, drinking patterns, and access to health care between wine and nonwine drinkers.[57,58]

Given known sexual dimorphism in body fat distribution and differences in both alcohol consumption patterns and body fat distribution by age, sex, and race or ethnicity, heterogeneity in the relationship between drinking and fat accumulation might be expected. Supporting heterogeneity by sex, a previous study based on the Framingham cohort revealed that men who consumed higher amounts of alcohol had higher visceral fat, whereas women who consumed higher amounts of alcohol had lower subcutaneous fat.[14] Our findings are consistent with this as we found generally stronger estimates for women compared with men, although interaction was significant only for pericardial and hepatic fat. As previously noted, however, this may be the result of differing sample sizes for the fat depots and the higher sample sizes required to assess heterogeneity. In either case, this pattern of fat distribution may contribute to higher cardiovascular risk in both men and women. Due to very few women that reported binge drinking, we could not assess its possible differential impact by sex on the fat variables. Despite obesity remaining a major public health concern particularly among racial and ethnic minority groups,[59] there is limited literature on effect modification attributable to alcohol consumption. One study reported that, in Black women, even light to moderate drinking can lead to weight gain.[39] In our study, the prevalence of heavy alcohol intake was unevenly distributed among the various racial and ethnic groups; nevertheless, we did not find significant heterogeneity by race or ethnicity. The aging process is known to affect body fat distribution by increased loss of muscle mass, sarcopenia, and adiposity,[60] but we did not find significant heterogeneity by age.

Study Strengths

Our study has several strengths as the data are from a large cohort composed of multiple racial and ethnic groups in the United States. The MESA study personnel collected data on alcohol consumption using

Table 4. Relative Percent Difference in Body Fat Distribution and Body Mass Index by Alcohol Consumption Among MESA Participants Stratified by Alcohol Type

Body fat subtype and body mass index	Alcohol consumption category	Wine		Beer		Liquor	
		Relative percent difference (95% CI)	*P* value	Relative percent difference (95% CI)	*P* value	Relative percent difference (95% CI)	*P* value
Pericardial	Former drinking	−2.0 (−5.6 to 1.8)	0.299	−1.8 (−5.4 to 2.0)	0.347	−1.0 (−4.7 to 2.8)	0.596
	Light drinking	−6.2 (−9.7 to −2.6)	<0.001	−5.3 (−9.0 to −1.4)	0.008	−1.6 (−5.5 to 2.4)	0.433
	Moderate drinking	−12.1 (−17.7 to −6.0)	<0.001	−1.7 (−9.4 to 6.7)	0.688	8.7 (−0.1 to 18.2)	0.052
	Heavy drinking	1.7 (−8.1 to 12.6)	0.745	0.9 (−7.9 to 10.6)	0.839	20.5 (9.4 to 32.8)	<0.001
Hepatic	Former drinking	−0.89 (−2.6 to 0.8)	0.300	−0.7 (−2.4 to 1.0)	0.437	−0.6 (−2.3 to 1.1)	0.462
	Light drinking	−3.4 (−5.0 to −1.7)	<0.0001	−2.0 (−3.7 to −0.2)	0.033	−2.3 (−4.1 to −0.5)	0.013
	Moderate drinking	−5.2 (−8.0 to −2.3)	0.001	0.0 (−3.6 to 4.0)	0.996	2.3 (−1.6 to 6.3)	0.247
	Heavy drinking	−1.1 (−5.5 to 3.6)	0.645	0.8 (−3.2 to 5.1)	0.693	4.7 (0.2 to 9.4)	0.041
Subcutaneous	Former drinking	−0.1 (−6.9 to 7.2)	0.985	−0.2 (−7.0 to 7.2)	0.963	0.4 (−6.5 to 7.8)	0.916
	Light drinking	−5.1 (−11.4 to 1.7)	0.138	−6.0 (−12.7 to 1.1)	0.097	−4.1 (−11.2 to 3.5)	0.278
	Moderate drinking	−12.5 (−22.5 to −1.2)	0.032	−14.2 (−27.4 to 1.5)	0.075	−2.5 (−18.4 to 16.5)	0.779
	Heavy drinking	−10.4 (−25.8 to 8.2)	0.252	−7.2 (−21.1 to 9.0)	0.361	−0.2 (−15.8 to 18.3)	0.982
Visceral	Former drinking	−0.6 (−7.6 to 6.9)	0.875	−0.8 (−7.8 to 6.7)	0.831	−0.01 (−7.1 to 7.5)	0.989
	Light drinking	−6.1 (−12.6 to 0.9)	0.089	−4.6 (−11.6 to 3.0)	0.229	−2.2 (−9.6 to 5.8)	0.581
	Moderate drinking	−11.6 (−22.2 to 0.5)	0.059	−11.0 (−24.2 to 4.5)	0.156	−0.5 (−16.6 to 18.7)	0.957
	Heavy drinking	−1.8 (−18.6 to 18.3)	0.845	−9.3 (−23.7 to 7.7)	0.265	6.2 (−10.8 to 26.5)	0.499
Intermuscular	Former drinking	−1.8 (−8.0 to 4.8)	0.592	−1.5 (−7.7 to 5.1)	0.650	−1.4 (−7.6 to 5.3)	0.675
	Light drinking	−6.0 (−11.9 to 0.3)	0.060	−2.9 (−9.2 to 4.0)	0.401	−2.4 (−9.0 to 4.7)	0.497
	Moderate drinking	−0.4 (−11.1 to 11.6)	0.941	−11.8 (−23.6 to 2.0)	0.090	−8.0 (−21.2 to 7.5)	0.294
	Heavy drinking	−1.5 (−16.6 to 16.3)	0.858	8.4 (−6.8 to 26.2)	0.296	12.9 (−3.2 to 31.6)	0.122
Body mass index	Former drinking	0.2 (−1.2 to 1.6)	0.751	0.2 (−1.2 to 1.6)	0.740	0.5 (−0.9 to 1.9)	0.508
	Light drinking	−2.0 (−3.4 to −0.6)	0.005	−1.9 (−3.3 to −0.4)	0.013	−0.9 (−2.4 to 0.6)	0.245
	Moderate drinking	−6.5 (−8.8 to −4.2)	<0.0001	−2.8 (−5.7 to 0.2)	0.068	1.0 (−2.1 to 4.2)	0.530
	Heavy drinking	−3.4 (−6.9 to 0.3)	0.075	−2.8 (−6.0 to 0.5)	0.101	1.1 (−2.5 to 4.8)	0.552

Reference: lifetime abstention in each alcohol type group. Light drinking, <1 drink/day; moderate drinking, 1 to 2 drinks/day; heavy drinking, >2 drinks/day. Pericardial and hepatic fat measured by computed tomography at enrollment (n=6734). Subcutaneous, visceral, and intermuscular fat measured by abdominal computed tomography on selected sample at visit 2 and visit 3 (n=1934). Model adjusted for age, sex, race or ethnicity, education, income, cigarette smoking, total energy intake, and physical activity.

standardized methods and procedures. We leveraged available CT imaging data to directly measure ectopic adiposity. This enabled our study to have more accurate detection of differences in ectopic fat distribution among various categories of alcohol consumption compared with anthropometric measures. We also adjusted for total energy intake, investigated the associations of heavy drinking and binge drinking separately, and evaluated the shape of the relationship between alcohol consumption and excess adiposity from multiple ectopic depots.

Study Limitations

Our study has several limitations. First, the amount of alcohol consumption was self-reported and, therefore, is susceptible to recall bias. There is also a potential for selection bias based on who was excluded and or those who had missing data for ectopic fat measurement. Second, we did not take into account other patterns of alcohol consumption, such as changes in the drinking patterns over time, which may be important contributors to body fat deposition.[40,41,43] Third, few Chinese American participants reported moderate or heavy drinking, limiting our ability to assess whether the associations in this group were similar to those in the other racial and ethnic groups. Similarly, few participants reported heavy drinking without binge drinking, limiting our ability to determine these associations separately. This is particularly the case for women who reported lower rates of binge drinking than men, further limiting our ability to assess heterogeneity by sex for estimates of binge drinking. Although the levels of alcohol drinking may be lower in this study than in the general population and we used alternate definition for binge drinking, our estimate reflects an underestimate of the relationship with fully defined binge drinking.[61] We could not fully account for why individuals might

choose to drink or not. These reasons are overly complex and may also be strongly related to patterns of fat accumulation. Additionally, alcohol consumption was measured at baseline, but abdominal fat was measured at Exam 2 and Exam 3. Finally, this study was a secondary analysis of cross-sectional data, so we cannot assess the temporality of the associations between alcohol consumption and body composition, and the potential for misclassification of drinking patterns cannot be excluded.

The generalizability of the results for this study is limited because the MESA cohort comprised participants from 6 communities, all in the United States. Second, although MESA recruited a multiethnic cohort of men and women, there were very few Chinese American and women participants who reported moderate or heavy drinking. Therefore, our results may have limited generalizability to those demographic groups.

CONCLUSIONS

Alcohol consumption had a J-shaped association with ectopic adiposity consistent across different fat depots, with both heavy alcohol intake and binge alcohol drinking associated with higher fat levels. Future studies are needed to investigate the role that ectopic fat distribution plays in mediating the relationship between alcohol consumption and CVD.

ARTICLE INFORMATION

Received April 10, 2023; accepted August 11, 2023.

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Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. Dr Chevli and Dr Mongraw-Chaffin conceived and designed the study, as well as reviewing and editing the original article draft. Dr Kazibwe prepared the original article draft. Ms. Evans performed statistical analysis and assisted in reviewing and editing the article. All authors were involved in writing the paper and had final approval of the submitted and published versions.

Sources of Funding

This research was supported by contracts R01HL088451, 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences. This paper has been reviewed and approved by the MESA Publications and Presentations Committee. This analysis was not funded.

Disclosures

A.C. Wood has received funding from Hass Avocado Board, The National Cattleman's Beef Association, and Ionis Pharmaceuticals for studies unrelated to the current article. M.D. Shapiro is on the Scientific Advisory Boards of Amgen, Ionis, Novartis, and Precision BioScience and is a consultant for Ionis, Novartis, Regeneron, EmendoBio, and Aidoc for studies unrelated to the current article. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S4
Figures S1-S4

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