CHEST Online Supplement

Adiposity and Interstitial Lung Abnormalities in Community-Dwelling Adults

The MESA Cohort Study

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e-Appendix 1: IRB Approval numbers by site

Columbia University: IRB-AAAA7791

University of California Los Angeles: 99-11-057-23B

Johns Hopkins University: NA_00030361_AM00004951

University of Minnesota: 9805M00034

Wake Forest University: BG00-035

Northwestern University: STU00021057

University of Vermont: 09-971

e-Table 1: Timeline for MESA study visits and procedures perform which are included in this analysis

Exam Number	Years	Procedures performed and included in this analysis
1	2000-2002	Cardiac CT: High Attenuation Areas and PAT volume
2	2002-2003	Abdominal CT: abdominal VAT and abdominal SAT
3	2004-2005	Spirometry, Biomarkers, Abdominal CT: abdominal VAT and SAT
4	2005-2007	Spirometry
5	2010-2012	Full Lung CT: Interstitial Lung Abnormalities
6	2016-2018	No procedures included in this analysis

Definition of abbreviations: CT: computed tomography scan; PAT: pericardial adipose tissue VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue

e-Table 2: Characteristics of subjects included in the full, abdominal VAT, ILA, and FVC cohorts.

	PAT Cohort (N=6784)	VAT Cohort (N=1923)	ILA Measured (N=2423)	FVC Measured (N=1415)
Age	62 (53-70)	65 (57-73)	59 (52-67)	64 (56-72)
Male	3192 (47)	964 (50)	1140 (47)	730 (52)
Race				
Caucasian	2615 (39)	771 (40)	951 (39)	580 (41)
Asian	797 (12)	251 (13)	333 (14)	215 (15)
African-American	1884 (28)	404 (21)	636 (26)	268 (19)
Hispanic	1488 (22)	497 (26)	503 (21)	352 (25)
Weight (kg)	77 (66-89)	77 (66-90)	77 (66-90)	77 (66-89)
Height (cm)	166 (159-174)	167 (159-174.)	166 (159-174)	167 (160-175)
BMI (kg/m2)	27.6 (24.5-31.2)	27.4 (24.5-30.8)	27.5 (24.5-31.0)	27.2 (24.3-30.7)
BMI category				
<18.5	58 (1)	13 (1)	14 (1)	12 (1)
18.5-25.0	1886 (28)	528 (38)	690 (28)	418 (30)
25.0-30.0	2654 (39)	757 (39)	956 (39)	577 (41)
30-35	1424 (21)	381 (20)	509 (21)	285 (20)
>35	762 (11)	244 (13)	10 (254)	123 (9)
Smoking Status				
Never Smoker	3401 (50)	843 (46)	1337 (55)	653 (46)
Former Smoker	2475 (36)	800 (43)	819 (34)	588 (42)
Current Smoker	886 (13)	202 (11)	263 (11)	164 (12)
Pack-years	15 (5-32)	16 (6-32)	13 (3-29)	14 (3-29)
Pericardial adipose volume (cm^3)	71 (49-100)	72 (51-101)	68 (48-95)	71 (50-99)
Abdominal VAT area (cm^2)	137 (97-193)	137 (97-193)	135 (97-186)	136 (96-188)
Abdominal SAT area (cm^2)	236 (170-310)	236 (170-309)	242 (174-319)	235 (170-309)

Continuous variables reported as median (interquartile range)
Categorical variables reported as N (%)
Missing: Full PAT cohort is missing smoking status on 22 subjects, and pack-years on 94 subjects.

Definition of abbreviations: BMI: body mass index; PAT: pericardial adipose tissue; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; ILA: interstitial lung abnormalities; FVC: forced vital capacity.

e-Table 3: Spearman correlations between adipose tissue depots and traditional measures of body composition

	Pericardial AT	**Abdominal VAT**	**Abdominal SAT**
Abdominal VAT	0.67*	1	
Abdominal SAT	0.20*	0.33*	1
Body Mass Index	0.51*	0.57*	0.69*
Height	0.16*	0.17*	-0.14*
Weight	0.48*	0.54*	0.46*

*indicates p<0.0001

e-Table 4: Associations between abdominal subcutaneous adipose tissue area and high attenuation areas, interstitial lung abnormalities, and forced vital capacity in subjects in whom abdominal SAT was completely imaged.

SAT	N	Change in HAA per doubling in SAT area	95% CI	p-value	N	Odds of ILA per doubling in SAT area	95% CI	p-value	N	Change in FVC per doubling in SAT area	95% CI	p-value
Model 1	1006	13.0	-9.7 to 35.6	0.26	523	1.1	0.7 to 1.6	0.66	847	-4.9	-6.4 to -3.4	<0.001
Model 2	865	54.2	33.4 to 75.0	<0.001	487	0.9	0.6 to 1.4	0.65	840	-5.3	-6.9 to -3.6	<0.001
Model 3	865	42.2	19.3 to 65.0	<0.001	487	0.7	0.4 to 1.3	0.27	840	-2.7	-4.5 to -0.8	0.004

Definition of abbreviations: SAT: subcutaneous adipose tissue; HAA: high attenuation areas operationalized as (-1/percent HAA^2); ILA: interstitial lung abnormalities; SD: standard deviation; CI: confidence interval
Model 1: HAA analyses adjusted for study site, imaged lung volume, and radiation dose; ILA and FVC analyses are unadjusted
Model 2: Model 1 + age, sex, race, height, smoking status, percent emphysema, and cigarette pack-years
Model 3: Model 2 + visceral adipose tissue area

e-Table 5: Associations of abdominal visceral and subcutaneous adipose tissue area as measured at L3/L4 with high attenuation areas, interstitial lung abnormalities, and forced vital capacity.

VAT	N	Change in HAA per doubling in VAT area	95% CI	p-value	N	Odds of ILA per doubling in VAT area	95% CI	p-value	N	Change in FVC (percent predicted) per doubling in VAT area	95% CI	p-value
Model 1	1895	70.8	58.4 to 83.2	<0.001	848	1.1	0.9 to 1.4	0.43	1403	-3.2	-4.1 to -2.2	<0.001
Model 2	1812	45.5	33.9 to 57.1	<0.001	832	1.0	0.7 to 1.3	0.93	1388	-4.5	-5.5 to -3.5	<0.001
Model 3	1552	32.6	17.5 to 47.7	<0.001	723	1.2	0.8 to 1.8	0.39	1217	-3.2	-4.6 to -1.9	<0.001

SAT	N	Change in HAA per doubling in SAT area	95% CI	p-value	N	Odds of ILA per doubling in SAT area	95% CI	p-value	N	Change in FVC per doubling in SAT area	95% CI	p-value
Model 1	1613	26.3	8.7 to 43.9	0.003	738	0.9	0.7 to 1.3	0.70	1229	-4.6	-5.8 to -3.9	<0.001
Model 2	1552	49.3	34.0 to 64.5	<0.001	723	0.9	0.6 to 1.3	0.49	1217	-4.5	-5.8 to -3.2	<0.001
Model 3	1552	36.2	19.4 to 53.0	<0.001	723	0.8	0.5 to 1.2	0.29	1217	-2.2	-3.8 to -0.7	0.005

Definition of abbreviations: BMI: body mass index; SAT: subcutaneous adipose tissue; CI: confidence interval; HAA: high attenuation areas; ILA: interstitial lung abnormalities; FVC: forced vital capacity

Model 1: HAA analyses adjusted for study site, imaged lung volume, and radiation dose; ILA and FVC analyses are unadjusted
Model 2: Model 1 + age, sex, race, smoking status, percent emphysema, cigarette pack-years, and site
Model 3: Model 2 + visceral adipose tissue area

e-Table 6: Associations between subcutaneous adipose tissue area and high attenuation areas and interstitial lung abnormalities within pre-specified subgroups

	N	Change in HAA per doubling in SAT area	95% CI	P for interaction	N	Change in ILA per doubling in SAT area	95% CI	P for interaction	N	Change in percent predicted FVC per doubling in SAT area	95% CI	P for interaction
Sex				0.56				0.16				0.051
Male	786	61.0	38.2 to 83.7		361	0.9	0.5 to 1.6		635	-6.0	-7.9 to -4.2	
Female	776	47.1	21.2 to 72.9		365	1.2	0.6 to 2.4		594	-4.3	-6.4 to -2.2	
Age				0.74				0.41				0.07
<65	923	52.2	30.7 to 73.6		508	0.8	0.5 to 1.3		764	-6.0	-7.5 to -4.5	
≥65	639	63.7	34.0 to 93.5		218	1.8	0.9 to 3.6		465	-4.1	-7.0 to -1.2	
BMI (kg/m²)*				<0.001				0.59				0.07
<18.5	13	33.2	-148 to 214.4						12	3.2	-10.5 to 16.9	
18.5-25	508	6.9	-26.7 to 40.4		218	1.4	0.5 to 3.7		410	-4.8	-7.9 to -1.8	
25-30	670	-26.5	-70.5 to 17.6		327	1.5	0.5 to 4.4		524	-3.9	-7.9 to 0.04	
30-35	266	-5.9	-72.5 to 60.8		117	1.0	0.1 to 7.7		208	-4.9	-11.3 to 1.4	
>35	105	-98.6	-214 to 16.7						75	-4.7	-14.6 to 5.1	
Smoking Status				0.047				0.19				0.005
Ever Smoker	842	28.8	11.8 to 45.9		361	0.8	0.5 to 1.4		637	-6.8	-8.8 to -4.8	
Never Smoker	780	47.4	30.4 to 64.4		379	1.3	0.7 to 2.5		604	-3.9	-5.8 to -1.9	

Definition of abbreviations: BMI: body mass index; SAT: subcutaneous adipose tissue; CI: confidence interval; HAA: high attenuation areas; ILA: interstitial lung abnormalities; FVC: forced vital capacity
*Subgroup analysis not performed in subjects with BMI <18.5 for ILA and FVC (N=4 for ILA, N=12 for FVC), and BMI >35 for ILA (N=43) due to small sample size.

Models are adjusted for age, sex, race, height, smoking status, percent emphysema, and cigarette pack-years. HAA models are additionally adjusted for study site, imaged lung volume, and radiation dose;

e-Table 7: Associations of pericardial adipose tissue volume with high attenuation areas, interstitial lung abnormalities, and forced vital capacity within pre-specified subgroups by age and smoking status.

	N	Change in HAA per doubling in PAT volume	95% CI	P for interaction	N	Change in ILA per doubling in PAT volume	95% CI	P for interaction	N	Change in percent predicted FVC per doubling in PAT volume	95% CI	P for interaction
Age				0.48				0.66				0.55
<65	3756	64.4	54.6 to 74.3		1592	1.5	1.1 to 2.0		861	-5.3	-6.7 to -3.9	
≥65	2934	66.2	53.7 to 78.6		802	1.2	0.9 to 1.5		539	-5.8	-8.1 to -3.5	
BMI*				0.25				0.24				0.08
18.5-25	1866	34,5	16.1 to 53.0		685	1.3	0.8 to 2.2		418	-3.5	-6.4 to -0.5	
25-30	2616	19.4	5.6 to 33.2		943	1.4	0.97 to 2.1		575	-4.4	-6.8 to -2.0	
30-35	1401	20.5	2.4 to 38.7		484	1.3	0.8 to 2.3		289	-6.5	-10.2 to -2.9	
>35	750	59.3	37.1 to 81.5		250	0.4	0.2 to 0.9		109	-5.7	-10.8 to -0.5	
Smoking Status				0.61				0.46				0.03
Ever Smoker	3449	66.7	55.8 to 77.5		1130	1.2	0.9 to 1.6		752	-7	-8.7 to -5.4	
Never Smoker	3315	66.9	55.6 to 78.1		1289	1.1	0.8 to 1.5		663	-3.7	-5.6 to -1.8	

Definition of abbreviations: BMI: body mass index
*Subgroup analysis not performed in subjects with BMI less than 18.5 due to small sample size (N=57 for HAA, N=5 for ILA, N=9 for FVC) and exclude radiation dose due to collinearity

e-Table 8: Associations of visceral adipose tissue area with high attenuation areas, interstitial lung abnormalities, and forced vital capacity within pre-specified subgroups by age and smoking status

	N	Change in HAA per doubling in VAT area	95% CI	P for interaction	N	Change in ILA per doubling in VAT area	95% CI	P for interaction	N	Change in percent predicted FVC per doubling in VAT area	95% CI	P for interaction
Age				0.73				0.62				0.48
<65	1070	36.5	19.2 to 53.8		582	1.0	0.7 to 1.7		863	-5.6	-6.9 to -4.2	
≥65	768	50.0	29.1 to 71.0		262	2.0	1.1 to 3.5		541	-5.3	-7.4 to -3.2	
BMI*				0.09				0.04				0.04
18.5-25	525	7.4	-18.9 to 33.7		226	0.9	0.4 to 1.9		418	-4.5	-6.8 to -2.2	
25-30	747	-17.5	-44.9 to 9.9		357	2.4	1.1 to 5.0		572	-6.0	-8.5 to -3.5	
30-35	376	4.3	-33.5 to 42.1		164	2.9	0.9 to 9.1		281	-5.9	-9.9 to -1.8	
>35	177	39.1	-16.2 to 94.4		77	0.3	0.01 to 5.3		121	-2.3	-8.9 to 4.3	
Smoking Status				0.42				0.88				<0.001
Ever Smoker	1035	31.6	13.7 to 49.5		432	1.1	0.7 to 1.8		739	-7.6	-9.2 to -6.0	
Never Smoker	888	50.5	31.7 to 69.4		429	1.4	0.8 to 2.5		665	-3.1	-4.8 to -1.4	

Definition of abbreviations: BMI: body mass index; VAT: visceral adipose tissue; CI: confidence interval; HAA: high attenuation areas; ILA: interstitial lung abnormalities; FVC: forced vital capacity

Models are adjusted for age, sex, race, smoking status, percent emphysema, and cigarette pack-years. HAA models are additionally adjusted for study site, imaged lung volume, and radiation dose.
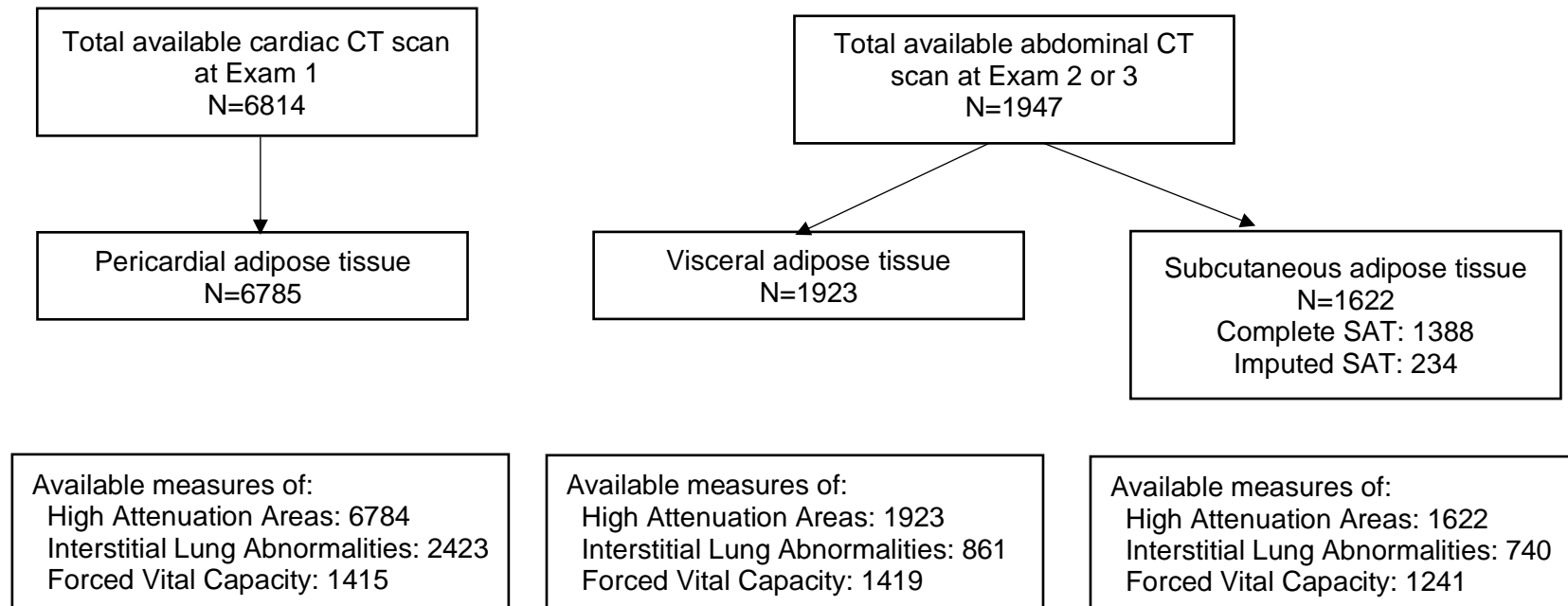
*Subgroup analysis not performed in subjects with BMI less than 18.5 due to small sample size (N=13 for HAA, N=5 for ILA, N=12 for FVC) and exclude radiation dose due to collinearity

e-Table 9: The proportion of the total effect of pericardial adipose tissue volume or visceral adipose tissue on HAA that is explained by each biomarker in fully adjusted models

	Pericardial Adipose Tissue and HAA	Visceral Adipose Tissue and HAA
Interleukin-6	0.08	0.17
Leptin	NA	0.18
Adiponectin	NA	0.04
C-reactive protein	NA	0.11

*Fully adjusted models including age, sex, race, smoking status, percent emphysema, cigarette pack-years, study site, imaged lung volume, and radiation dose.

e-Figure 1: Flow diagram of study inclusion


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┌─────────────────────────┐              ┌─────────────────────────┐
│ Total available cardiac  │              │ Total available abdominal│
│      CT scan             │              │   CT scan at Exam 2 or 3 │
│     at Exam 1            │              │        N=1947            │
│      N=6814             │              │                          │
└─────────────────────────┘              └─────────────────────────┘

┌─────────────────────────┐    ┌─────────────────────┐    ┌─────────────────────────┐
│ Pericardial adipose      │    │ Visceral adipose    │    │ Subcutaneous adipose     │
│     tissue               │    │     tissue          │    │     tissue               │
│     N=6785               │    │     N=1923          │    │     N=1622               │
│                          │    │                     │    │  Complete SAT: 1388      │
│                          │    │                     │    │  Imputed SAT: 234        │
└─────────────────────────┘    └─────────────────────┘    └─────────────────────────┘
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Available measures of:
High Attenuation Areas: 6784
Interstitial Lung Abnormalities: 2423
Forced Vital Capacity: 1415

Available measures of:
High Attenuation Areas: 1923
Interstitial Lung Abnormalities: 861
Forced Vital Capacity: 1419

Available measures of:
High Attenuation Areas: 1622
Interstitial Lung Abnormalities: 740
Forced Vital Capacity: 1241

e-Figure 2: Association between abdominal subcutaneous adipose tissue area and (A) high attenuation areas, (B) interstitial lung abnormalities, and (C) forced vital capacity. Models are adjusted for age, sex, smoking status, and visceral adipose tissue area.
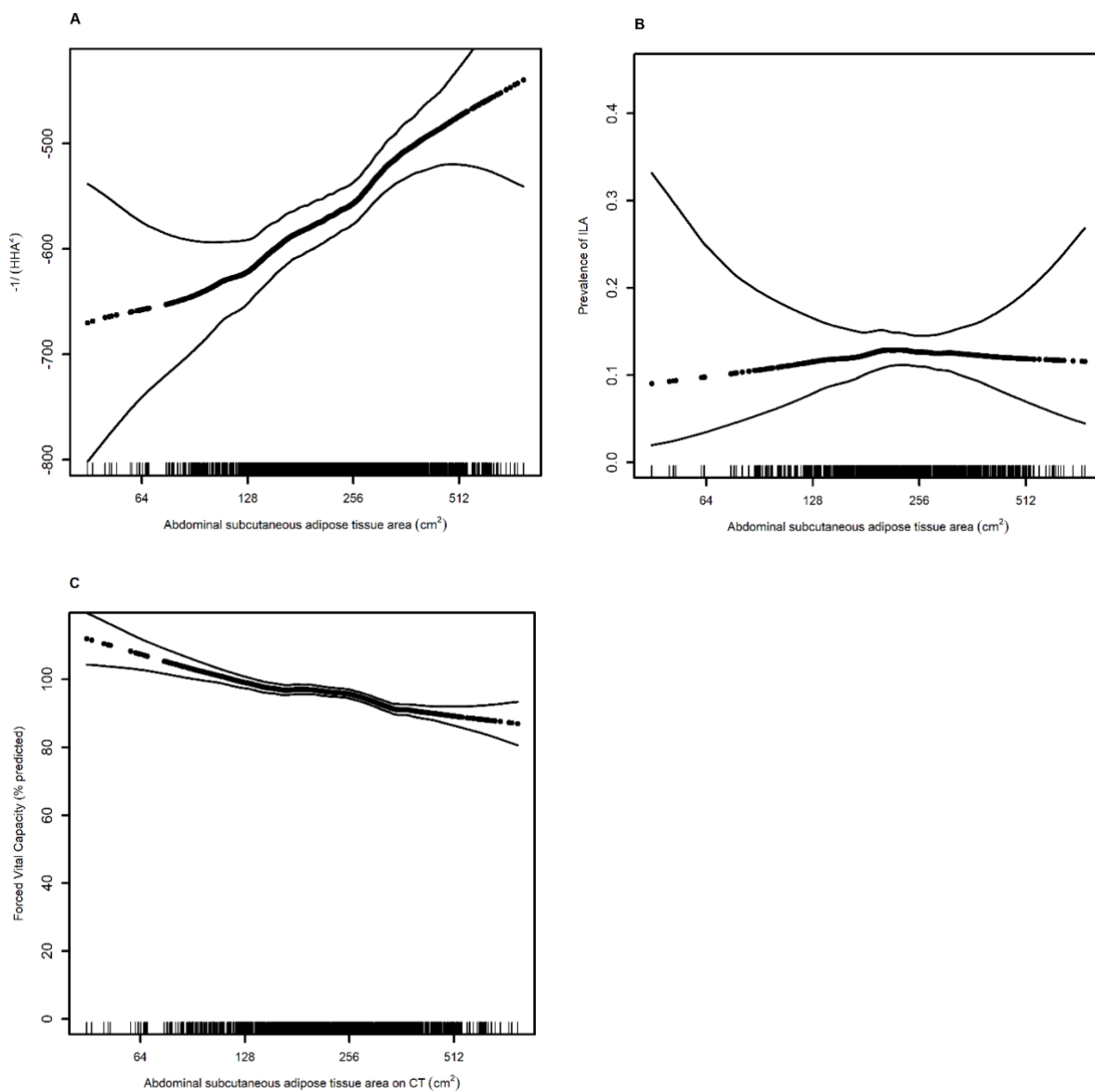
e-Figure 3: Scatter plots for the correlation of pericardial adipose tissue volume with plasma (A) interleukin-6 (ρ = 0.25, p<0.0001), (B) leptin (ρ = 0.13, p<0.001), (C) adiponectin (ρ = -0.16, p<0.0001), (D) c-reactive protein (ρ = 0.14, p<0.0001), (E) resistin (ρ = 0.08, p=0.002), and (F) tumor necrosis factor alpha (ρ = 0.14, p<0.0001).
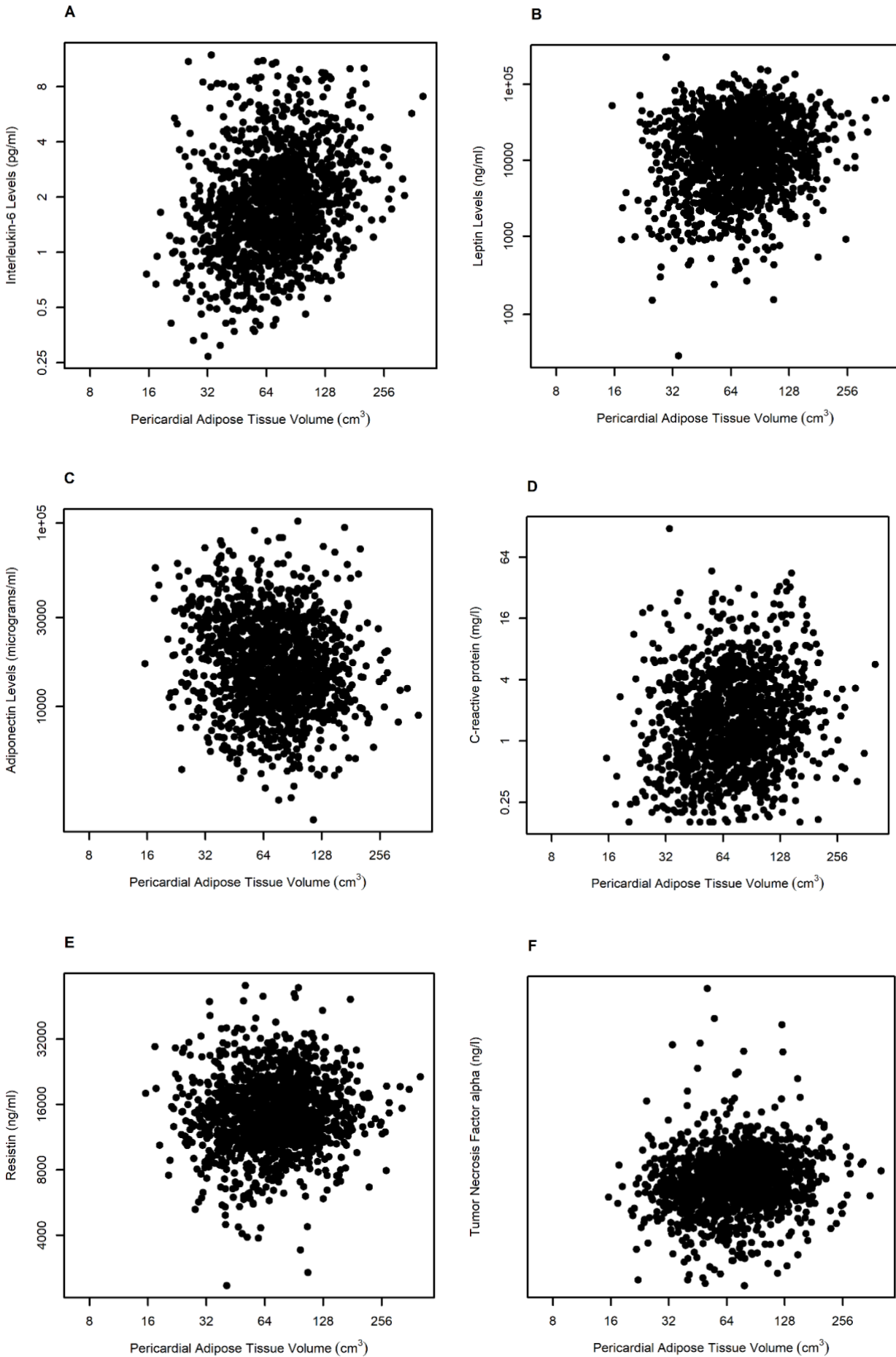
e-Figure 4: Scatter plots for the association between abdominal visceral adipose tissue area and plasma (A) interleukin-6 (r= 0.32, p<0.001), (B) leptin (r= 0.28, p<0.001), (C) adiponectin (r= -0.31, p<0.001), (D) c-reactive protein (r= 0.25, p<0.001), (E) resistin (r= 0.07, p=0.01), and (F) tumor necrosis factor alpha (r= 0.12, p=0.001).

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