ONLINE DATA SUPPLEMENT

Title: Rapid decline in lung function is temporally associated with greater metabolically active adiposity in a longitudinal study of healthy adults

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Supplemental methods

Spirometry

As part of a strict quality control program, each center sent 10% sample of spirograms and microprocessor strips to a selected consultant for quality testing. At CARDIA year 10 examination visit, spirometry was performed using the Collins Survey 8-liter water-sealed spirometer and the Eagle II microprocessor (Warren E. Collins, Inc., Braintree, MA) in a sitting position with nose clips, as per the 1979 American Thoracic Society criteria [E1]. If, at the end of the three trials, there were at least three acceptable tracings, and with the maximum FVC and FEV_1 reproduced to within 5% or 100 mL, whichever is greater, no more trials were performed. At CARDIA year 20 examination visit, a dry rolling-seal SensorMedics model 1022 spirometer fitted by OMI (Viasys Corp, Loma Linda, CA) was used for spirometry testing in a standing position with nose clips. The criteria for reproducibility were changed at the year 20 visit - the two largest FVC values were to agree within 150 ml, and the two largest FEV_1 values were also to agree within 150 ml, consistent with the 1994 update by the American Thoracic Society [E2]. A comparability study performed on 25 volunteers at the LDS Hospital (Salt Lake City, UT) demonstrated excellent consistency between the old and new machines; the average difference between the Collins Survey and OMI spirometer was 6 ml for FVC and 21 ml for FEV_1 [E3].

CT-assessed regional fat depots

Chest CT scan was performed from the posterior lung recess to the lung apex and including the upper part of the abdomen. The protocol was ECG-gated and weight-based, with slice thickness ranging from 2.5 to 3 mm. Limited abdominal CT scan included coverage of 15 cms. above the

superior end-plate of the sacrum (i.e., S1 level), as determined based on the technologist identification of the lumbosacral joint, with 2.5 mm helical slice thickness and a pitch of 6.5 mm/rotation. CT scan centers were provided with dedicated computers with software to handle sending the data in an encrypted and secure manner to one center for standardized analysis of images to provide quantitative information. The scanner was phantom calibrated. Quality control was done twice each month by the technologists to monitor the temporal variation in radiation exposure. The core CT exam had an estimated effective dose of 3.7 mSv (1.8-7.4 mSv) and the additional cardiac CT scan added 2 mSv (1-4 mSv), resulting in a combined total exposure of 5.7 mSv (3-11 mSv). The exposures were well below the commonly used threshold of "low exposure"; women who had the potential to be pregnant were required to have a pregnancy test prior to being eligible for the CT exam.

Intra-thoracic visceral adiposity was represented by measuring the pericardial adipose tissue and this was done by encompassing the entire heart with the chest CT and then analyzing data originating from the 45 mm of adipose tissue encasing the proximal coronary arteries. The key anatomic landmark was the origin of the left main coronary artery from the aorta. The volume extended 15 mm superiorly and 30 mm inferiorly. Intrathoracic visceral adipose tissue was defined by the volume of pericardial adipose tissue in the range -190 to -30 HU.

Abdominal adiposity was represented by data recovered from images tacked from mid-liver and another 60 images of the lower abdomen. This data was subcategorized to three major compartments: total abdominal, subcutaneous abdominal, and intra-abdominal visceral adipose tissue compartments. Because the optimal single level to measure intra-abdominal visceral

adipose tissue, as a proxy for total intra-abdominal visceral adipose tissue is not clear, and may vary by race and gender, the protocol used a volumetric acquisition and analysis centered at L4-L5 level. Abdominal subcutaneous adiposity was defined by the adipose tissue volume for 10 mm slice of abdomen centered at L4 - L5 disk space (limited to fat pixels in the range -190 to -30 HU). Abdominal intramuscular adiposity was defined by the intramuscular adipose tissue for 10 mm slice of abdomen centered at L2 – L3 disk space (limited to fat pixels in the range -190 to -30 HU). Intra-abdominal visceral adiposity was calculated as following: Visceral fat volume = Abdomen fat volume - Intramuscular adipose tissue for 10 mm slice of abdominal centered at L4-L5 disk space (limited to fat pixels in the range -190 to -30 HU).

Power calculations

Power for our logistic regression analyses is more than adequate since we are powered to detect an odds ratio for incident metabolic syndrome due to rapid decline in FEV1 or FVC of as little as 1.16, with 80% power and α=0.05. Our observed odds ratio was $\geq$ 1.58, as noted in Table 4 in the main text.

Supplemental Results

One possible explanation for rapid decline predicting metabolically active adiposity was that individuals with rapid decline in lung function between CARDIA Y10 and Y20 (mean age of 35 and 45 years) gained more weight between Y20 and Y25 (mean age of 45 and 50 years) than those without rapid decline. We did not find that to be the case. Individuals in the rapid FEV_1

decline group gained *less* weight compared with the non-rapid decline group (p=0.04. Similarly, the rapid FVC decline group gained less weight compared with the non-rapid decline group (p=0.005; Table E-VII). Similarly, rapid decline was not associated with subsequent increase in waist circumference or in waist to hip ratio (Table E-VII) Thus, rapid decline in lung function was temporally associated with metabolically active adiposity (i.e. metabolic syndrome/intrathoracic visceral adiposity); and this association was not explained by an increase in general adiposity.

One may be interested in understanding the strength of rapid decline in lung function in predicting incident metabolic syndrome. The ROC curve for the prediction of incident metabolic syndrome at CARDIA Y20 and/or Y25 by decline in lung function between Y10 and Y20 (as continuous variables) demonstrated an area under the curve (AUC) of 0.65. The strength of this prediction compares with that by a traditional risk factor such as BMI at Y10 (AUC of 0.76). Addition of BMI to decline in lung function in this study further increased the AUC to 0.78.

Supplemental Tables

Table E-I: Absence of interaction between sex and rapid FEV_1 decline between CARDIA Y10 and Y20 (mean ages of 35 and 45 years) on CT-assessed abdominal and thoracic fat depots at Y25 (mean age 50 years).

	Rapid FEV_1 decline (n=754)	Non-rapid FEV_1 decline (n=1504)	p- value*	Sex interaction p-value
	Mean ± S.D.	Mean ± S.D.		
Intra-thoracic Visceral Adiposity				
Female	50.3 ± 24.7	42.4 ± 20.6	0.001	0.36
Male	73.5 ± 43.3	59.9 ± 31.8	<0.001	
Abdominal Subcutaneous Adiposity				
Female	381.9 ± 179.2	351.8 ± 167.8	0.03	0.26
Male	272.9 ± 122.7	243.2 ± 116.4	<0.001	
Abdominal Intramuscular Adiposity				
Female	134.8 ± 69.7	115.1 ± 56.6	<0.001	0.34
Male	171.7 ± 82.1	156.4 ± 72.6	0.01	
Intra-Abdominal Visceral Adiposity				
Female	116.4 ± 63.0	98.8 ± 51.7	<0.001	0.28
Male	153.7 ± 75.6	140.0 ± 67.3	0.01	

***** P value obtained after a logarithmic transformation of fat data due to its non-normal distribution.
Note 1: Similar results were obtained for rapid decline in FVC. Data are not presented.
Note 2: Definitions of regional adiposity are provided in the text.

Table E-II: Metabolic syndrome at or before CARDIA Y10 (mean age 35 years) is temporally associated with significant annualized decline in FVC but not FEV_1 (studied as continuous variables) between Y10 and Y20 (mean ages of 35 and 45 years), in unadjusted analyses

Annualized decline in spirometric function between mean ages of 35 and 45 years	Metabolic syndrome present at or before mean age 35 years	Metabolic syndrome absent at or before mean age 35 years	P value
Δ FEV_1 (in ml/yr.)	37 ± 34	36 ± 27	0.66
Δ FVC (in ml/yr.)	43 ± 41	37 ± 33	0.04
Δ FEV_1/FVC	0.40 ± 1.88	0.35 ± 0.97	0.68

Note 1: Similar analyses, using rapid decline as binary and ternary variables is presented in Table 2 in the main text and Table E-III of the online data supplement respectively.

Table E-III: Metabolic syndrome at or before CARDIA Y10 (mean age 35 years) is temporally associated with tertiles of decline in FVC over subsequent 10 years, in unadjusted analyses

	Rapid FEV_1 decline (tertile 1)	Middle tertile of FEV_1 decline (tertile 2)	Lowest tertile of FEV_1 decline (tertile 3)	Unadjusted model (tertile 1 vs. 2+3)	Unadjusted model tertile 1+2 vs. 3	Rapid FVC decline (tertile 1)	Middle tertile of FVC decline (tertile 2)	Lowest tertile of FVC decline (tertile 3)	Unadjusted model (tertile 1 vs. 2+3)	Unadjusted model (tertile 1+2 vs. 3)
	Row %	Row %	Row %	O.R. (95% C.I.)	O.R. (95% C.I.)	Row %	Row %	Row %	O.R. (95% C.I.)	O.R. (95% C.I.)
Metabolic syndrome present (n=261/2519)	36.8%	28.7%	34.5%	1.18 (0.91, 1.55) p=0.21	0.95 (0.72, 1.24) p =0.68	40.2%	32.6%	27.2%	1.39 (1.07, 1.81) p= 0.01	1.38 (1.04, 1.84) p =0.03
Metabolic syndrome absent (n= 2258/2519)	33.0%	33.8%	33.2%			32.6%	33.4%	34.0%		

Note 1: Similar analyses, using rapid decline as binary and continuous variables is presented in Table 2 in the main text and Table E-II of the online data supplement respectively.

Note 2: The overall analysis for the ternary variables of decline in lung function was not significant for FEV_1 (p=0.22) but was significant for FVC (p=0.03).

Table E-IV: Annualized decline in lung function (as continuous variables) between CARDIA Y10 and Y20 (mean age 35 and 45 years respectively) is temporally associated with incident metabolic syndrome at Y20/Y25 (mean age 45/50 years), in unadjusted analyses

	Unadjusted model
	O.R. (95% C.I.)
FEV_1 decline (per 10 ml./yr.)	1.10 (1.06, 1.14) p<0.001
FVC decline (per 10 ml/yr.)	1.15 (1.11, 1.18) p<0.001

Note 1: Similar analyses, using rapid decline as binary and ternary variables is presented in Table 4 in the main text and Table E-V of the online data supplement respectively.

Table E-V: Decline in lung function (as ternary variables) between CARDIA Y10 and Y20 (mean ages of 35-45 years) is temporally associated with incident metabolic syndrome at Y20 or Y25 (mean age of 45 or 50 years), in unadjusted analyses

	Incident metabolic syndrome	Unadjusted model	
	%	O.R. (95% C.I.)	P value
Rapid tertile of FEV_1 decline or tertile 1 (n=754)	26.9%	1.74 (1.36-2.23)	<0.001
Middle tertile of FEV_1 decline or tertile 2 (n=753)	20.3%	1.21 (0.93-1.56)	
Lowest tertile of FEV_1 decline or tertile 3; referent (n=751)	17.4%	1.0	
Rapid tertile of FVC decline or tertile 1 (n=753)	30.0%	3.12 (2.38-4.08)	<0.001
Middle tertile of FVC decline or tertile 2 (n=752)	22.6%	2.13 (1.61-2.81)	
Lowest tertile of FVC decline or tertile 3; referent (n=753)	12.1%	1.0	

Note 1: Similar analyses, using rapid decline as binary and continuous variables, are presented in Table 4 in the main text and Table E-IV of the online data supplement respectively.

Table E-VI: Rapid decline in lung function (as a binary variable) between CARDIA Y10 and Y20 (mean ages of 35-45 years) is temporally associated with all incident components of the metabolic syndrome at Y20 or Y25 (mean age of 45 or 50 years), in unadjusted analyses

	Enlarged waist circumference	Hypertension	Elevated glucose	Low HDL Cholesterol	Elevated triglycerides
	O.R. (95% C.I.)	O.R. (95% C.I.)	O.R. (95% C.I.)	O.R. (95% C.I.)	O.R. (95% C.I.)
Rapid FEV_1 decline	1.51 (1.26, 1.80), p<0.001	1.39 (1.16, 1.66) p<0.001	1.53 (1.20, 1.96) p<0.001	1.27 (1.06, 1.52) p=0.009	1.22 (0.99, 1.51) p=0.06
Rapid FVC decline	1.94 (1.62, 2.32) p<0.001	1.82 (1.52, 2.17) p<0.001	1.94 (1.52, 2.48) p<0.001	1.37 (1.14, 1.64) p<0.001	1.56 (1.27, 1.92) p<0.001

Note 1: Individuals with metabolic syndrome at or before CARDIA Y10 were excluded.

Table E-VII: Rapid decline in lung function between CARDIA Y10 and Y20 is not temporally associated with subsequent increase in general adiposity between Y20 & Y25

Decline in lung function	General adiposity measure	Change in value between CARDIA Y20 & Y25 for rapid decliners	Change in value between CARDIA Y20 & Y25 for non-rapid decliners	P value
FEV_1 decline	BMI (in kg/m^2)	0.31 ± 4.96	0.72 ± 2.43	0.04
	Waist circumference (in cms.)	2.02 ± 6.20	2.43 ± 5.66	0.15
	Waist to height ratio	0.01 ± 0.04	0.01 ± 0.03	0.11
FVC decline	BMI (in kg/m^2)	0.20 ± 5.11	0.78 ± 2.25	0.005
	Waist circumference (in cms.)	1.75 ± 6.47	2.57 ± 5.49	0.004
	Waist to height ratio	0.01 ± 0.04	0.02 ± 0.03	0.003

Supplemental References

E1. American Thoracic Society (ATS). ATS statement--Snowbird workshop on standardization of spirometry. *Am Rev Respir Dis* 1979;119(5):831-8.

E2. American Thoracic Society. Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med* 1995;152(3):1107-36.

E3. Smith LJ, Arynchyn A, Kalhan R, Williams OD, Jensen R, Crapo R, et al. Spirometry guidelines influence lung function results in a longitudinal study of young adults. *Respir Med* 2010;104(6):858-64.