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### Authors

Aaron, Carrie P  
Schwartz, Joseph E  
Hoffman, Eric A  
et al.

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# A Longitudinal Cohort Study of Aspirin Use and Progression of Emphysema-like Lung Characteristics on CT Imaging

## The MESA Lung Study



Carrie P. Aaron, MD; Joseph E. Schwartz, PhD; Eric A. Hoffman, PhD; Elsa Angelini, PhD; John H. M. Austin, MD; Mary Cushman, MD; David R. Jacobs Jr, PhD; Joel D. Kaufman, MD; Andrew Laine, DSc; Lewis J. Smith, MD; Jie Yang, MS; Karol E. Watson, MD, PhD; Russell P. Tracy, PhD; and R. Graham Barr, MD, DrPH

**BACKGROUND:** Platelet activation reduces pulmonary microvascular blood flow and contributes to inflammation; these factors have been implicated in the pathogenesis of COPD and emphysema. We hypothesized that regular use of aspirin, a platelet inhibitor, would be associated with a slower progression of emphysema-like lung characteristics on CT imaging and a slower decline in lung function.

**METHODS:** The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled participants 45 to 84 years of age without clinical cardiovascular disease from 2000 to 2002. The MESA Lung Study assessed the percentage of emphysema-like lung below -950 Hounsfield units ("percent emphysema") on cardiac (2000-2007) and full-lung CT scans (2010-2012). Regular aspirin use was defined as 3 or more days per week. Mixed-effect models adjusted for demographics, anthropometric features, smoking, hypertension, angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker use, C-reactive protein levels, sphingomyelin levels, and scanner factors.

**RESULTS:** At baseline, the 4,257 participants' mean ( $\pm$  SD) age was 61  $\pm$  10 years, 54% were ever smokers, and 22% used aspirin regularly. On average, percent emphysema increased 0.60 percentage points over 10 years (95% CI, 0.35-0.94). Progression of percent emphysema was slower among regular aspirin users compared with patients who did not use aspirin (fully adjusted model: -0.34% /10 years, 95% CI, -0.60 to -0.08;  $P = .01$ ). Results were similar in ever smokers and with doses of 81 and 300 to 325 mg and were of greater magnitude among those with airflow limitation. No association was found between aspirin use and change in lung function.

**CONCLUSIONS:** Regular aspirin use was associated with a more than 50% reduction in the rate of emphysema progression over 10 years. Further study of aspirin and platelets in emphysema may be warranted.

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**KEY WORDS:** COPD; CT; platelets

FOR EDITORIAL COMMENT, SEE PAGE 3

**ABBREVIATIONS:** COX = cyclooxygenase; MDCT = multidetector CT; MESA = Multi-Ethnic Study of Atherosclerosis; PD15 = 15th percentile of lung density

**AFFILIATIONS:** From the Department of Medicine (Drs Aaron, Schwartz, and Barr) and the Department of Radiology (Dr Austin), College of Physicians and Surgeons, the Department of Biomedical Engineering (Drs Angelini and Laine and Mr Yang), and the Department of Epidemiology (Dr Barr), Mailman School of Public Health, Columbia University, New York, NY; the Department of Radiology (Dr Hoffman), University of Iowa, Iowa City, IA; the Department of

Medicine (Dr Cushman) and the Department of Pathology (Drs Cushman and Tracy), Larner College of Medicine at the University of Vermont, Colchester, VT; the Division of Epidemiology and Community Health (Dr Jacobs), University of Minnesota School of Public Health, Minneapolis, MN; the Department of Environmental Medicine and Occupational Health Sciences (Dr Kaufman), University of Washington, Seattle, WA; the Department of Medicine (Dr Smith), Northwestern University, Chicago, IL; and the Department of Medicine (Dr Watson), University of California, Los Angeles, CA.

COPD and emphysema are jointly the third leading cause of death in the United States and the world.<sup>1,2</sup> Emphysema is defined as destruction of alveolar walls distal to the terminal bronchioles on pathologic specimens<sup>3</sup> and has also been measured on CT imaging as the percentage of emphysema-like lung (hereafter referred to as “percent emphysema”). Percent emphysema has been associated with lower left ventricular filling<sup>4</sup> and reduced daily activity,<sup>5</sup> as well as increased respiratory and all-cause mortality in COPD<sup>6</sup> and in the general population without airflow obstruction.<sup>7,8</sup>

The pathogenesis of COPD and emphysema is incompletely understood, but altered pulmonary blood flow and inflammation may be relevant factors.<sup>9,10</sup> Pulmonary capillaries are damaged in emphysematous lung in humans,<sup>11,12</sup> and factors that inhibit angiogenesis lead to emphysema in animals.<sup>13,14</sup> Platelet activation is increased in the setting of vessel injury and inflammation,<sup>15</sup> and in animal models of acute lung injury, platelet activation reduces pulmonary microvascular blood flow and increases lung

neutrophils,<sup>16,17</sup> findings that are improved with aspirin.<sup>17,18</sup> Additionally, platelet factor 4, which is released on platelet activation, increased the extent of neutrophil elastase-induced emphysema in an animal study.<sup>19</sup> Finally, platelet activation was found to be increased in patients with COPD compared with control subjects<sup>20</sup> and during exacerbation among those with COPD,<sup>21</sup> and thrombocytosis was associated with increased mortality after hospitalization for COPD, a finding that was not present for those taking aspirin.<sup>22</sup> These findings suggest a potential role of platelets in emphysema and COPD; however, it is unknown whether aspirin use alters the progression of emphysema or the decline in lung function.

We hypothesized that regular use of aspirin would be associated with slower progression of percent emphysema seen on CT over 10 years. We also examined the change in lung function over 5 years. We tested this hypothesis in a general population sample with mostly subclinical emphysema, as doing so may provide insights into strategies for treatment and prevention.

## Methods

### *Multi-Ethnic Study of Atherosclerosis*

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study that recruited 6,814 participants in 2000 to 2002 from six US communities; they were aged 45-84 years and were free of clinical cardiovascular disease.<sup>23</sup> The MESA Air Pollution Study recruited an additional 257 participants using the same criteria in 2004 to 2007.<sup>24</sup> The MESA Lung Study enrolled 3,965 MESA participants in 2004 to 2006 (at the second and third visits).<sup>25</sup> All MESA Air participants included were at one site. An additional 410 MESA participants were enrolled in 2010 to 2012 (e-Fig 1). The protocols of MESA and all studies described herein were approved by the institutional review boards of all collaborating institutions and the National Heart Lung and Blood Institute. All participants provided written informed consent.

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**CORRESPONDENCE TO:** Carrie P. Aaron, MD, Department of Medicine, Columbia University, College of Physicians and Surgeons, PH 9 E Room 105, 630 W 168 St, New York, NY 10032; e-mail: cp2346@columbia.edu

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### *Aspirin Use Assessment*

Medication use was assessed at each visit by a medication inventory.<sup>26</sup> Participants were instructed to bring all prescription and over-the-counter medications used in the preceding 2 weeks to the visit; staff recorded the name, strength, and frequency. Participants were separately asked whether they were taking aspirin, and if so how many days per week.

The primary exposure was regular use of aspirin at baseline, defined as use of any aspirin dose 3 or more days per week, as even 81 mg every 3 days inhibits platelet activation.<sup>27</sup> Additional analyses evaluated any aspirin use at baseline, regular aspirin use at each visit, time-varying aspirin use, and doses of 81 and 300 to 325 mg.

### *Measurement of Percent Emphysema*

All participants underwent cardiac CT scans at baseline following a standardized protocol at full inspiration on electron beam tomography and multidetector CT (MDCT) scanners.<sup>28</sup> Participants were coached to total lung capacity, and two scans were obtained. Lung volumes on replicate cardiac CT scans were highly correlated ( $r = 0.95$ ), and unless image quality differed, the scan with the greatest lung volume was selected for analysis. Follow-up cardiac CT scans used the same protocol. Forty-five off-protocol scans and 312 acquired on Aquilion scanners (Toshiba), which produce unreliable lung density measures, were excluded. Full-lung scans were performed on 3,204 MESA Lung participants at the 10-year follow-up examination at full inspiration on MDCT scanners following the Subpopulations and Intermediate Outcome Measures in COPD study (SPIROMICS) protocol.<sup>29</sup>

The percentage of emphysema-like lung (percent emphysema) was measured by trained readers at a reading center without knowledge of other participant information using modified Pulmonary Analysis Software Suite software for cardiac scans and Apollo 1.2 (an updated

version of Pulmonary Analysis Software Suite; VIDA Diagnostics) for full-lung scans. Since cardiac CT images go from approximately the carina to the lung base, the upper third was excluded from full-lung scans to compare the same lung regions over time. Cardiac CT measures of percent emphysema are highly correlated with measures on full-lung scans from the same participants ( $r = 0.95$  on MDCT scanners).<sup>30</sup> Percent emphysema was defined as the percentage of lung voxels below  $-950$  Hounsfield units, adjusted for the attenuation of air outside the chest to account for scanner variation. Sensitivity analyses use the lower 15th percentile of lung density (PD15) and a hidden Markov measure field model, which reduces variability in percent emphysema measures across different CT imaging protocols and levels of inspiration.<sup>31,32</sup> Monthly averages of outside air from all scans demonstrated little scanner drift over  $> 11$  years, with one exception (e-Fig 2).

### Spirometry

Spirometry was conducted between 2004 and 2007 and was repeated in 2010 to 2012 in accordance with American Thoracic Society/European Respiratory Society guidelines following the MESA Lung protocol; all examinations were reviewed by one investigator.<sup>33</sup> At the time of the participants' first spirometry measurement, airflow obstruction was defined as prebronchodilator  $FEV_1/FVC < 0.70$ , and restrictive ventilatory defect was defined as FVC less than the lower limit of normal and  $FEV_1/FVC \geq 0.7$ .

### Other Covariates

Age, sex, race/ethnicity, educational attainment, and smoking history were self-reported. Current smoking was defined as a self-report of smoking within 30 days or urinary cotinine levels  $> 100$  ng/mL, measured at baseline and 10-year follow-up.<sup>25</sup> Height, weight, BP, and C-reactive protein levels were measured using standard techniques.<sup>34</sup> Plasma sphingomyelin levels were measured with a validated four-step enzymatic assay.<sup>35</sup> Medication use was assessed by a medication inventory.<sup>26</sup> Hypertension was defined as systolic or diastolic BP  $\geq 140/90$  mm Hg, or self-reported hypertension and antihypertensive medication use. Participants were asked about a physician diagnosis of asthma at each visit. The Framingham Risk Score was calculated<sup>36</sup> and categorized as  $< 10\%$  or  $\geq 10\%$ , as this was the indication for

aspirin use in primary prevention of atherosclerotic events.<sup>37</sup> The Agatston coronary artery calcium score was calculated on phantom-adjusted gated cardiac CT scans.<sup>28</sup>

### Statistical Analysis

Participants were stratified by baseline regular aspirin use for descriptive purposes. Mixed linear regression growth curve models with random intercepts and slopes were used to assess the relationship between regular aspirin use and change in percent emphysema over time (ie, interaction term between aspirin use and time since baseline examination). The initial adjusted model included baseline age, sex, race/ethnicity, education, time-varying height, weight, scanner model, voxel size, milliamperes, and the interactions of sex and race/ethnicity with time. The subsequent model added baseline pack-years, time-varying cigarettes per day for current smokers, and the interaction of pack-years with time. The final model included baseline hypertension, C-reactive protein levels, sphingomyelin levels, angiotensin-converting enzyme (ACE)-inhibitor or angiotensin II-receptor blocker (ARB) use, and the interaction of ACE inhibitor or ARB use with time, which have been associated with the progression of percent emphysema.<sup>38,39</sup> Missing data were minimal except for pack-years (11% of ever smokers) and cigarettes per day (5% of current smokers) and were addressed by single imputation. Effect measure modification was assessed for sex, age, race/ethnicity, smoking status, airflow limitation, emphysema, and scanner manufacturer. Secondary analyses adjusted for other baseline medication use, including inhalers (inhaled steroids, beta-agonists, and anticholinergic agents alone or in combination), nonsteroidal antiinflammatory drugs, cyclooxygenase (COX)-2 inhibitors, adenosine diphosphate-receptor inhibitors, statin drugs, and diuretic agents), report of physician diagnosis of asthma, Framingham Risk Score  $> 10\%$ , coronary artery calcium score, baseline emphysema, and the interaction of baseline emphysema and time. Sensitivity analyses were performed after excluding subjects with a change in smoking status and with propensity-score weighting for likelihood of aspirin use. Analyses for lung function used a similar statistical approach. Statistical significance was defined as a two-tailed  $P$  value  $< .05$ . Analyses were performed using SAS, version 9.3 (SAS Institute).

## Results

### Study Participants

Of 4,472 participants, 215 (5%) were excluded from the main analysis for self-reported irregular aspirin use. The 4,257 included participants were somewhat different from those not included (e-Table 1), but aspirin use was similar. Eighty-one percent had a follow-up cardiac CT scan and 3,041 (71% of total; 74% of those still living) underwent a full-lung CT scan at the 10-year follow-up. At baseline, participants were  $61 \pm 10$  years of age, 49% men, 37% white, 27% black, 21% Hispanic, and 15% Chinese American. Forty-six percent were never smokers, 40% were former smokers, and 14% were current smokers.

At baseline, 22% reported taking aspirin regularly, with doses of 81 mg in 50%, 300 to 325 mg in 43%, alternative doses in 4%, and missing data in 3%. Compared with

those not taking aspirin, participants taking aspirin regularly at baseline were more likely to be older white male former smokers with a higher education and greater hypertension, percent emphysema, and airflow limitation; follow-up time was similar in both groups (Table 1).

### Regular Aspirin Use and Longitudinal Change in Percent Emphysema

The 4,257 participants underwent CT imaging a median of three times over a median of 9.3 years (interquartile range, 5.0-9.7), resulting in 11,465 measurements of percent emphysema. Median baseline percent emphysema was 2.97% (interquartile range, 1.23-5.83) (e-Table 1). The mean increase in percent emphysema was 0.60 percentage points over 10 years (95% CI, 0.30-0.90;  $P < .001$ ).

Regular aspirin use was associated with a significantly slower progression of percent emphysema in unadjusted

**TABLE 1 ] Selected Baseline Characteristics of Participants by Regular Aspirin Use**

Characteristic	Not Taking Aspirin at Baseline (n = 3,331)	Taking Aspirin Regularly at Baseline (n = 926)
Age, y	60.2 ± 9.8	65.3 ± 8.9
Male sex	46.3	57.2
Race		
White, non-Hispanic	32.2	53.7
Black	28.3	23.9
Hispanic	23.3	12.2
Chinese American	16.2	10.3
Education		
Did not complete high school	16.9	12.1
Completed high school	18.6	16.7
Some college	28.5	26.2
Completed college	18.7	19.0
Graduate degree	17.2	25.8
Height, cm	166.0 ± 9.9	168.9 ± 10.0
Weight, kg	77.8 ± 17.2	80.8 ± 16.6
BMI, kg/m <sup>2</sup>	28.1 ± 5.4	28.1 ± 4.7
Smoking status		
Never	48.4	39.6
Former	37.2	48.5
Current	14.4	11.9
Pack-years <sup>a</sup>	24 ± 25	29 ± 28
Cigarettes/d <sup>b</sup>	13 ± 21	14 ± 11
Hypertension	39.1	55.2
Systolic BP, mm Hg	124 ± 20	127 ± 20
Total cholesterol, mg/dL	195 ± 35	189 ± 34
Diabetes	9.9	15.7
Medication use		
ACE inhibitor or ARB	10.5	17.6
NSAID	17.0	12.1
COX-2 inhibitor	5.9	8.5
ADP-receptor inhibitor	0.2	0.4
Statin drug	11.6	26.7
Diuretic agent	13.5	24.8
Framingham Risk Score 10-y CHD risk ≥ 10%	36.3	48.3
FEV <sub>1</sub> , mL <sup>c</sup>	2381 ± 732	2387 ± 712
FEV <sub>1</sub> /FVC ratio <sup>d</sup>	0.75 ± 0.08	0.74 ± 0.09
Airflow limitation, % <sup>e</sup>	23.1	30.0
Asthma, self-report of physician diagnosis	9.7	9.7
Percent emphysema <sub>a950</sub> , median (IQR)	2.82 (1.17-5.55)	3.47 (1.56-7.09)
Emphysema on CT, %	7.3	10.7
C-reactive protein, mg/dL	3.6 ± 5.6	3.1 ± 4.4

*(Continued)*

TABLE 1 ] (Continued)

Characteristic	Not Taking Aspirin at Baseline (n = 3,331)	Taking Aspirin Regularly at Baseline (n = 926)
Sphingomyelin, mg/dL	47.8 ± 15.7	47.9 ± 14.8
Follow-up time, median (IQR), y	9.3 (4.5-9.7)	9.1 (4.6-9.6)

Data are presented as mean ± SD or %, except where noted. ACE = angiotensin converting enzyme; ARB = angiotensin II-receptor blocker, NSAID = nonsteroidal antiinflammatory drug (not including aspirin); ADP = adenosine diphosphate; CHD = coronary heart disease; IQR = interquartile range; percent emphysema<sub>950</sub> = percent of emphysema-like lung below -950 Hounsfield units.

<sup>a</sup>Among ever smokers reporting pack-years (1,511 not taking aspirin, 505 taking aspirin regularly).

<sup>b</sup>Among current smokers reporting cigarettes per day (451 not taking aspirin, 105 taking aspirin regularly).

<sup>c</sup>Among 3,759 subjects with FEV<sub>1</sub> data (2,966 not taking aspirin, 793 taking aspirin regularly).

<sup>d</sup>Among 3,742 subjects with FEV<sub>1</sub>/FVC data (2,951 not taking aspirin, 791 taking aspirin regularly).

<sup>e</sup>Airflow limitation defined as prebronchodilator FEV<sub>1</sub>/FVC ratio < 0.7 among 3,431 subjects with FEV<sub>1</sub>/FVC data and no restrictive ventilatory defect (2,705 not taking aspirin, 726 taking aspirin regularly).

and fully adjusted analyses (-0.34 percentage points over 10 years; 95% CI, -0.60 to -0.08; *P* = .01) (Table 2). Results were similar after propensity-score weighting (Table 2) and when the exposure was defined as any aspirin use at baseline (Fig 1). The association was of greater magnitude when considering regular aspirin use at all follow-up visits and attenuated for regular aspirin use at all but one follow-up visit and for time-varying aspirin use (Fig 1). The association for regular use of 81 mg aspirin was similar to that of a 300 to 325 mg dose (Fig 1). Results were similar using PD15 (e-Table 2) and attenuated with percent emphysema hidden Markov measure field (fully adjusted, -0.21 percentage points over 10 years; 95% CI, -0.51 to 0.08; *P* = .16).

There was no evidence for effect modification of the association of regular aspirin use and percent emphysema by age, race/ethnicity, emphysema, or scanner manufacturer; however, the association was of greater magnitude among participants with airflow limitation (*P* interaction = .03), and there was a suggestion that results were stronger among men and current smokers (Fig 2).

Results were similar after adjustment for inhaler use, nonsteroidal antiinflammatory drug use, COX-2-inhibitor use, adenosine diphosphate receptor-inhibitor use, statin drug and diuretic agent use, self-report of physician-diagnosed asthma, Framingham Risk Score > 10%, and coronary artery calcium and baseline emphysema, whereas the addition of baseline emphysema and time interaction weakened the results (Fig 2). Results were unchanged after excluding 340 participants (8%) who quit or resumed smoking (-0.34 percentage points over 10 years; 95% CI, -0.61 to -0.06; *P* = .017).

### Regular Aspirin Use and Longitudinal Change in Lung Function

Valid spirometry measurements were obtained in 3,889 participants (98% of completed tests), and 68% had repeated valid tests a median of 4.8 years later. Thirty-four percent used aspirin regularly at the time of first spirometry measurements, and 3% were excluded due to self-reported irregular aspirin use. The mean decline in FEV<sub>1</sub> was 28.9 mL/y (95% CI, -30.6 to -27.2; *P* < .001). There was no evidence for an association between regular aspirin use at time of first spirometry measurement and change in FEV<sub>1</sub> or FEV<sub>1</sub>/FVC (e-Table 3).

### Discussion

Regular aspirin use was associated with a > 50% slower progression of percent emphysema-like lung on CT imaging over 10 years in this general population sample. Results were similar across aspirin doses and many subgroups and were of greater magnitude among those with airflow obstruction. These findings, along with supportive results in animals, suggest that further study of aspirin and platelet activation in emphysema may be warranted.

This is the first study that we are aware of to show an association between aspirin use and longitudinal progression of percent emphysema. Prior studies have found platelet-related genes serotonin receptor 4 (*HTR4*), von Willebrand factor (*VWF*), and its platelet-receptor *GP1BA* to be associated with FEV<sub>1</sub> and COPD.<sup>40,41</sup> Additionally, platelet factor 4 increased emphysema when added to a neutrophil elastase animal model of emphysema,<sup>19</sup> and platelet activation was found to be greater in patients with COPD compared with control subjects and during exacerbations.<sup>20,21</sup>

**TABLE 2 ]** Predicted Change in Percent Emphysema Over 10 Years for Participants Taking Aspirin Regularly Compared With Those Not Taking Aspirin, With and Without Propensity-Score Weighting

Model	Change in Percent Emphysema Over 10 Years (95% CI)	P Value
<b>Unweighted</b>		
Unadjusted	-0.42 (-0.70 to -0.14)	.003
Model 1	-0.35 (-0.62 to -0.09)	.009
Model 2	-0.36 (-0.63 to -0.10)	.007
Model 3	-0.34 (-0.60 to -0.08)	.011
<b>Weighted by propensity score</b>		
Unadjusted	-0.35 (-0.62 to -0.09)	.009
Model 1	-0.33 (-0.58 to -0.08)	.010
Model 2	-0.33 (-0.58 to -0.08)	.009
Model 3	-0.31 (-0.56 to -0.06)	.014

Model 1: Adjusted for baseline age, sex, race/ethnicity, sex × time and race/ethnicity × time interactions, education, time-varying height, weight, CT scanner model, milliamperes, and voxel size. Model 2: Additionally adjusted for baseline pack-years, pack-years × time interaction, and time-varying cigarettes per day for current smokers. Model 3: Additionally adjusted for baseline hypertension, C-reactive protein levels, sphingomyelin levels, ACE inhibitor or ARB use, and ACE-inhibitor or ARB use × time interaction. See Table 1 legend for expansion of abbreviations.

The consistency of the results for low-dose (81 mg) and full-strength (300 to 325 mg) aspirin suggests that inhibiting platelet activation is the most likely explanation for these findings, as 81 mg every 3 days impacts platelet activation.<sup>27</sup> Platelet activation causes pulmonary microvascular constriction, which is reversed by aspirin.<sup>18</sup> This may be relevant, as reduced pulmonary microvascular blood flow is seen in emphysema and even mild COPD,<sup>10</sup> may contribute to

disease pathogenesis, and early vascular changes in emphysema may be reversible.<sup>42</sup> Additionally, platelet activation causes greater neutrophilic inflammation,<sup>17</sup> which is also implicated in COPD.<sup>9</sup>

However, other mechanisms of aspirin such as the anti-inflammatory and potentially bronchodilatory effect of reducing COX-1-dependent prostaglandins cannot be ruled out.<sup>43</sup> Although we did not perform expiratory CT scans to evaluate functional small airways disease, gas trapping is likely a minor contributor to the results for percent emphysema measured at full inspiration, and the normal results for lung function also suggest that this is unlikely.

The lack of an association between regular aspirin use and change in lung function may be due to the smaller sample size and shorter follow-up time in those with spirometry measurements. However, the result is consistent with normal results for aspirin and lung function in the National Health and Nutrition Examination Survey III.<sup>44</sup> Importantly, progression of emphysema and airflow obstruction in COPD may represent distinct processes, as supported by findings from many biomarker and genetic studies.<sup>40,41,45,46</sup>

Results were stronger in those with airflow limitation, and results were somewhat stronger in men and current smokers. These findings may be related, as people with airflow limitation are more likely to be male current and former smokers. However, smoking and sex may also contribute to differences in platelet activation and aspirin response.<sup>47,48</sup>

Although the strengths of this study include repeated CT scans over 10 years, the large sample size, and multi-ethnic population-based sample, several limitations

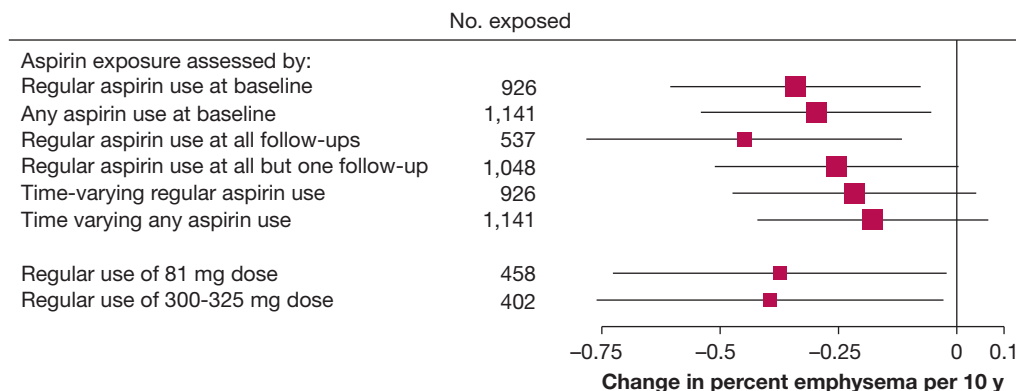


Figure 1 – Association of different aspirin exposures with change in percent emphysema over 10 years. Analyses adjust for baseline age, sex, race/ethnicity, education, pack-years of smoking, hypertension, angiotensin-converting enzyme (ACE)-inhibitor or angiotensin II receptor-blocker (ARB) use, C-reactive protein levels, sphingomyelin levels, time-varying height, weight, cigarettes smoked per day, scanner model, milliamperes, voxel size, and interactions of sex, race/ethnicity, pack-years of smoking, and ACE-inhibitor or ARB use with time.

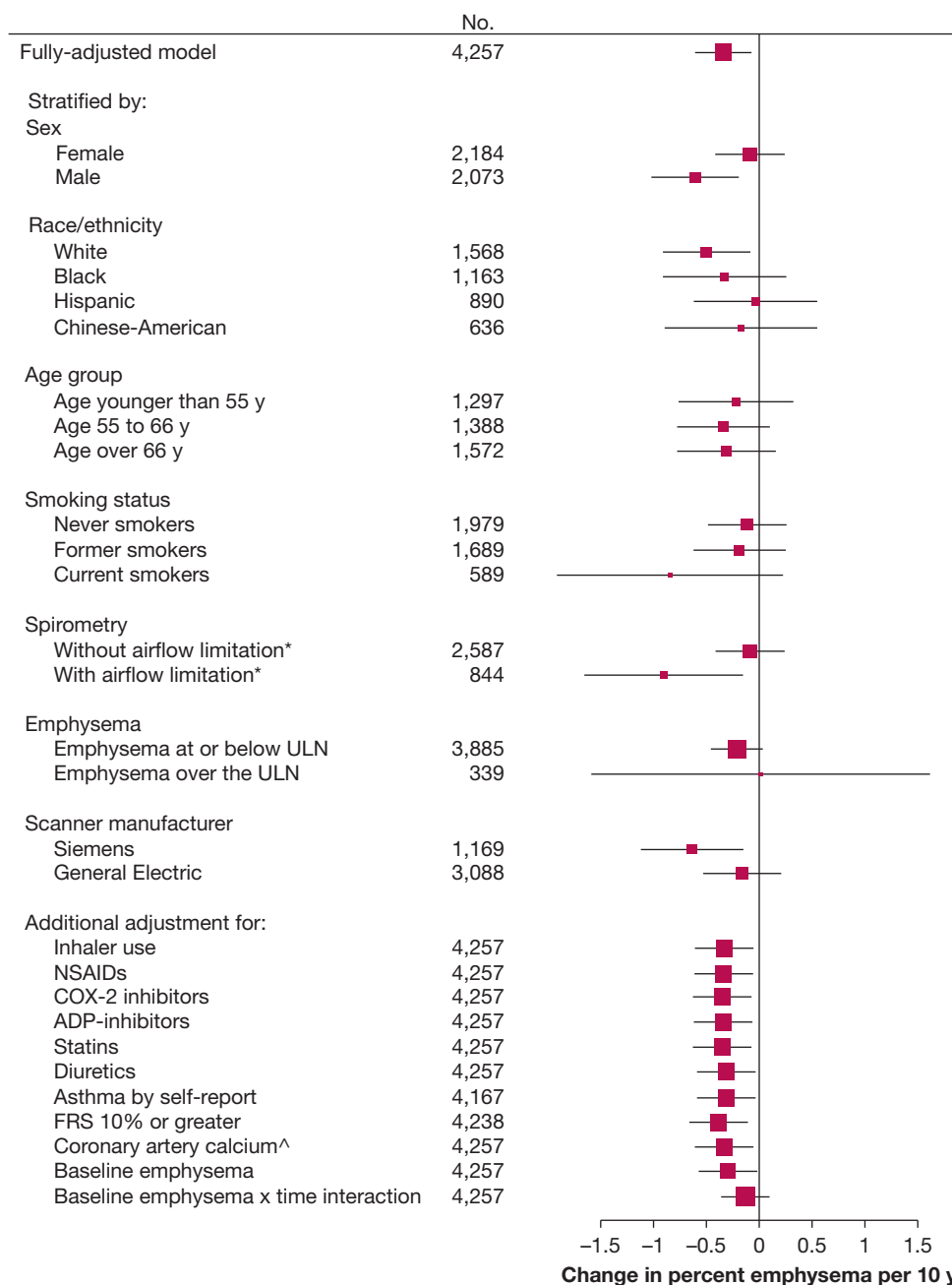


Figure 2 – Sensitivity analysis showing the effect estimate of the change in percent emphysema over 10 years for those taking aspirin regularly compared with those not taking aspirin. Analyses adjust for baseline age, sex, race/ethnicity, education, pack-years of smoking, hypertension, angiotensin-converting enzyme-inhibitor or angiotensin II receptor-blocker use, C-reactive protein levels, sphingomyelin levels, and time-varying height, weight, cigarettes per day, scanner model, milliamperes, voxel size, and interactions of sex, race/ethnicity and pack-years of smoking with time. P value for interaction: sex, 0.09; race/ethnicity, 0.86; age, 0.84; smoking status, 0.09; airflow limitation, 0.03; emphysema, 0.40; and scanner manufacturer, 0.74. \*Airflow limitation defined as FEV<sub>1</sub>/FVC < 0.7; ^Coronary artery calcium measured as Agatston score on cardiac CTs. ADP = adenosine diphosphate; COX-2, cyclooxygenase-2; FRS = Framingham Risk Score; NSAIDs = nonsteroidal antiinflammatory drugs; ULN = upper limit of normal.

should be discussed. Confounding by indication is possible in this observational study. However, aspirin is not indicated for lung disease, and in this general population sample without clinical cardiovascular disease at baseline, the likely indication was primary prevention of atherosclerotic events. Adjustment for

Framingham Risk Score > 10% and coronary artery calcium scores did not alter the results, and propensity score-adjusted results were similar. Other medication use was more common among those taking aspirin; however, the main analysis adjusted for ACE inhibitors and ARBs and further adjustment for other medication



use did not impact the results. Nonetheless, residual confounding may exist given discrepancies between observational and interventional studies in respiratory disease.<sup>49,50</sup> Thus, small studies using an intermediate end point, such as pulmonary microvascular blood flow,<sup>10</sup> may be a prudent next step.

Aspirin adherence is uncertain, as frequency was self-reported and aspirin was inevitably started and stopped over the nearly 10-year study. However, nonadherence would be expected to weaken the effect of aspirin, not strengthen it. The association for regular aspirin use at each follow-up was of greater magnitude and similar when considering any aspirin use at baseline, which was assessed by the more reliable medication inventory.<sup>26</sup>

The progression of percent emphysema was modest, likely due to the general population sample. Given the mostly subclinical emphysema, the presence of baseline emphysema was previously confirmed by visual assessment in subsets.<sup>46,51</sup> In this cohort, percent emphysema has also been associated with all-cause mortality,<sup>7</sup> and a reduction of this magnitude may still be relevant in disease prevention. Importantly, aspirin use was associated with a > 50% reduction in the rate of overall progression.

At baseline, subjects taking aspirin regularly had greater percent emphysema compared with those not taking aspirin. Although the results were weakened with the interaction between baseline emphysema and time, there

is disagreement about whether to adjust for baseline levels in longitudinal analyses,<sup>52</sup> and there was not significant effect modification by baseline emphysema. Additionally, longitudinal associations are generally favored when results are discrepant.<sup>53</sup>

Percent emphysema was assessed in the lower two-thirds of the lungs, omitting the top portion of the upper lobes, a common location for centrilobular emphysema; however, measures of percent emphysema from this region of the lung are highly correlated with those from full-lung scans in MESA.<sup>30</sup> Over the course of the study, advances in image acquisition and processing and changes in scanner models inevitably occurred, which may contribute to variation in quantitative emphysema. However, the attenuation of outside air was remarkably stable over more than a decade, and analyses of PD15 yielded similar results. Additionally, alterations in lung inflammation and perfusion, proposed mechanisms of aspirin, also alter CT lung attenuation. However, this effect would be small in a longitudinal analysis, particularly among those consistently taking or not taking aspirin.

## Conclusions

Regular aspirin use was associated with a slower progression of percent emphysema-like lung on CT scans over 10 years in this general population sample. These findings suggest that further studies of platelet activation and aspirin in COPD and emphysema may be warranted.

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