Original Research

Effect of Common Medications on Longitudinal Pectoralis Muscle Area in Smokers

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Running Head: **Statin and Aspirin Effects on Muscle in Smokers**

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Abbreviations: CT = computed tomography; PMA = pectoralis muscle area; PMD = pectoralis muscle density; PSM = propensity score matching; HU = hounsfield units (HU); ACEI = angiotensin-converting enzyme Inhibitor; ARB = angiotensin receptor blocker; BMI= body mass index; COPD = chronic obstructive pulmonary disease; 6MWD = 6-minute walk distance; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; GERD = gastroesophageal reflux disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; SGRQ = St. George's Respiratory Questionnaire; GOLD = global initiative for chronic obstructive lung disease; IQR = interquartile range; HTN = hypertension; DM = diabetes mellitus; HL = hyperlipidemia; CAD = coronary artery disease; SAM = statin-associated myopathy; COX = cyclooxygenase; PGE2 = Prostaglandin E2

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Abstract

Background: Cigarette smoke contributes to skeletal muscle wasting. While exercise and nutritional therapies are effective in improving skeletal muscle quantity and quality, the effect of medications on longitudinal muscle loss is unclear. We investigated whether long-term use of common medications affects longitudinal skeletal muscle changes in current and former smokers.

Methods: Using quantitative computed tomography (CT) imaging, we measured the 5-year changes in pectoralis muscle area (delta-PMA) and pectoralis muscle density (delta-PMD) of 4,191 participants in the Genetic Epidemiology of COPD (COPDGene) study. We tested whether specific medications were associated with delta-PMA and/or delta-PMD using regression analyses. Propensity score matching (PSM) analysis was performed to determine the effect of the medications on longitudinal changes on delta-PMA.

Results: Over the study period, the median delta-PMA for the entire population showed a decrease of 2.23 cm^2 (IQR: -6.52, 1.54). Regression analyses demonstrated statin use was associated with less loss of PMA, whereas aspirin use was associated with a greater loss of PMA. Specifically in the PSM adjusted analysis, statin use was associated with attenuated loss of PMA (median; -1.5 vs -2.5 cm^2, p=0.017), while aspirin use was associated with increased loss of PMA (median; -2.5 vs -1.9 cm^2, p=0.040).

Conclusions: In current and former smokers, statin use was associated with reduced pectoralis

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muscle wasting, while aspirin use was associated with increased muscle loss. Additional research is needed to verify these findings.

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Introduction

Cigarette smoking is arguably one of the most significant health risk behaviors in our society. Although the prevalence of smoking among adults aged over 18 years in the United States has declined from 20.9% in 2005 to 12.5% in 2020, estimates suggest that 30.8 million adults are still current smokers and more than 16 million Americans live with a smoking-related disease [1,2]. Importantly, cigarette smoke contributes to the development of many chronic diseases, including skeletal muscle wasting and dysfunction [3-5].

There are a variety of approaches to measuring muscle loss, such as dual energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), ultrasound and magnetic resonance imaging (MRI) [6-8]. Body composition is generally measured by these methods but our research and that of others has shown chest computed tomography (CT) scans can be used to obtain good approximation of fat free mass index (FFMI) [9,10]. In previous studies, the CT cross-sectional area of the pectoralis muscles (PM) have been reported to be independently associated with energy expenditure, disease severity and prognosis in smokers both with and without chronic obstructive pulmonary disease (COPD) [10-14]. Given the recommendations for CT lung cancer screening in current and former smokers with a significant smoking history, one area of interest has been the secondary use of these images to identify extrapulmonary diseases such as muscle loss [15].

Although prior research has consistently shown an association between skeletal muscle loss

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and numerous adverse outcomes in smokers, especially those with COPD, limited interventions exist to directly target the loss of muscle mass[16,17]. For example, the American Thoracic Society and European Respiratory Society recommend pulmonary rehabilitation and nutritional supplement for patients with chronic lung disease to improve exercise capacity, reduce dyspnea, muscle volume, and enhance health-related quality of life.[18]. While the identification of novel agents to treat muscle loss may be of longer-term interest, it is possible that medications commonly used for other indications in this at risk population may prevent or attenuate the loss of skeletal muscle. In this study, we aimed to identify specific medications affecting skeletal muscle change as assessed by CT imaging using data from the Genetic Epidemiology of COPD (COPDGene) study [19]. We hypothesized that medications used for treatment of conditions common in smokers would be associated with longitudinal skeletal muscle loss. We further hypothesized that the medication effect would be dependent on persistent long-term use of the medication.

Material and Methods

Study population and design

The COPDGene study have been previously described in detail [19]. In brief, the COPDGene Study (Clinicaltrials.gov identifier NCT00608764), is ongoing and enrolled a total of 10,198

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Non-Hispanic White and African American ever smokers from 21 centers in the United States, including those with and without COPD. The participants were aged 45–80 at enrollment and had a history of at least 10 pack-years of smoking. The institutional review board of each center approved the study and written informed consent was obtained from all participants. Each subject's assessments were conducted approximately every 5 years. All participants underwent anthropometric measurements, lung function tests, 6-minute walk distance (6MWD) test, and chest CT at each visit. In addition, incidence of exacerbations and prescription data at the baseline and follow-up visits were recorded. Spirometry was performed before and after the administration of bronchodilator. Diagnosis and severity of COPD were defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline with a post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) less than 0.7 [20]. In this study, we utilized COPDGene data from their first (phase 1) and second (phase 2) visits, which were an average of 5 years apart. The dataset included 4,191 subjects who had reported medication and chest computed tomography scan data available from both visits. The details of the assembly of the cohort are presented in the diagram detailed in Figure 1.

Imaging analysis

We used an established protocol to estimate CT-derived muscle measurements which has

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been described in detail in previous reports [12,13]. In brief, we measured the cross-sectional area of the pectoralis muscle (PMA) from a single axial slice of chest CT at the top of the aortic arch using a deep learning approach to select the CT slice [21] and a uNet-based network to segment the pectoral muscles [22,23] and implemented in the Chest Imaging Platform (www.chestimagingplatform.org). In addition, we measured pectoralis muscle density (PMD) in the areas where PMA was measured, as PMD is considered to reflect muscle quality and physical function [24]. The PMA and PMD were defined as the sum and mean attenuation of the right and left pectoralis major and minor muscles, expressed in centimeters squared (cm^2) and Hounsfield units (HU), respectively.

Statistical analysis

All statistical analyses were performed using JMP pro version 16 software (SAS Institute Inc., Cary, NC, USA). Univariate linear regression analysis was performed to examine the relationship between the change in PMA and prescribed medications. Multivariable regression analysis was performed to identify independent associations between delta-PMA and medications using the medications with p-value <0.2 from the univariate regression analyses [25]. The change in PMA/PMD (delta-PMA/PMD) is defined as PMA/PMD at phase 2 – PMA/PMD at phase 1. Prescribed medications that affect body composition were tested in the models if they were reported or reportedly prescribed for over at least 5% of the study

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population. Data observed were not normally distributed and nonparametric statistical methods were used for statistical analysis. Data pertaining to the continuous variables were described in the median and interquartile range (IQR). The Wilcoxon test was used for group comparison, and multiple comparison was performed with Kruskal-Wallis test followed by Steel test. Proportional data were analyzed using the chi-squared test.

We carried out a propensity score matching (PSM) analysis using a logistic regression procedure to determine the effects of medications after matching age, gender, race, body mass index (BMI), percent predicted forced expiratory volume in one second (%FEV_1), smoking status, pack-years, comorbidities, and the use of independently associated medication except for the index medication in each analysis (i.e., PSM for statins used aspirin use as a covariate while PSM for aspirin used statins use as a covariate). The caliper distance of the propensity score matching was determined by 0.2 of the standard deviation of the logit transformation score [26]. To determine the robustness of the primary analysis, we performed a sensitivity analysis using all subjects. In addition, we divided the patients into three groups to investigate the long-term effectiveness of the specific medications as follows; (i) continuous use, (ii) never use, (iii) status change, which means those who reported receiving medication in phase 1 but did not in phase 2, or vice versa. We also investigated whether there are differences in the effects on muscles based on type of statins. p values less than 0.05 were considered statistically significant and all tests were two sided.

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Results

Characteristics and demographics of study subjects

The selection of the study subjects is diagramed in Figure 1 with the baseline characteristics of the study subjects shown in Table 1. The median age of all subjects was 59.6 years, and 50.4% were male. The median PMA and PMD were 38.7 cm^2 and 33.5 HU, respectively, at their first visit. Comorbidities included hypertension (HTN) which was reported by 42.5%, hyperlipidemia (HL) by 40.8% of participants, COPD by 34.6%, diabetes mellitus (DM) by 12.2% and coronary artery disease (CAD) by 6.9%. Regarding prescribed medications, antihypertensive use was reported by 42.5% of participants, anti-hyperlipidemia agents for 29.4% and anti-platelet agents for 19.2% and anti-diabetes mellitus agents for 8.4%

Regression analyses for delta-PMA with prescribed medications

Over the five-year period in the complete population of current and former smokers with longitudinal chest CTs, the median delta-PMA was -2.23 cm^2 (IQR: -6.52, 1.54) and the median delta-PMD was -3.22 HU (IQR: -8.44, 1.82). Bivariate regression analysis indicated statin use was associated with a less decrease in PMA (β=0.018, SE=0.005, $p<0.001$) in comparison with non-users. When adjustments were made for all medications with p-value <0.2 from the bivariate analyses (calcium channel (Ca) blockers, diuretics, aspirin, and statins), aspirin use

Published online December 4, 2024 https://doi.org/10.15326/jcopdf.2024.0557

was associated with loss of PMA (delta-PMA: β=-0.44, SE=0.16, p<0.01) while statin use was robustly associated with less loss of PMA (delta-PMA: β=0.57, SE=0.14, p<0.0001) (Table 2). In the same analysis with PMD, statin use was associated with less loss of PMD (delta-PMD: β=0.40, SE=0.15, p<0.01) while aspirin use had no association with delta-PMD (β=0.003, SE=0.005, p=0.546).

Propensity score matching analysis for statins and aspirin

Of the 4191 participants included in this study, 1158 were statin users, and 742 were aspirin users. After 1:1 PSM, 692 pairs of subjects for statin users and non-users, and 726 pairs for aspirin users and non-users were included, and the characteristics of PSM subjects with or without statin use, and aspirin use were shown in table 3. As expected, PSM subjects did not differ based on age, gender, BMI, smoking status, pack-years, %FEV_1 and comorbidities. There were no significant differences in COPD prevalence or in the number of patients using inhaled COPD treatments between the matched groups (statin vs. non-statin (38.0% vs 36.0%, p=0.737), and aspirin vs. non-aspirin (42.7% vs 38.6%, p=0.183). Among subjects who reported receiving statins, 49.6% were prescribed simvastatin, 27.9% atorvastatin, 7.5% pravastatin, 7.8% rosuvastatin, and 7.1% lovastatin. In addition, one individual reported using multiple statins (0.1%).

Published online December 4, 2024 https://doi.org/10.15326/jcopdf.2024.0557

Single regression analysis for longitudinal muscle changes with statin or aspirin use after propensity score matching

Reported statin use was associated with a reduced loss of PMA compared to non-users (median delta-PMA; -1.53 vs -2.54 cm^2, p=0.017) while aspirin users lost more PMA than that of non-users (median; -2.59 vs -1.92 cm^2, p=0.040) (Figure 2). When evaluating delta-PMD, statin use inhibited PMD worsening (median; -2.45 vs -3.71 HU, p=0.004), demonstrating less muscle density loss in participants taking statins. On the other hand, no significant difference in delta-PMD was found between aspirin users and non-users (median; -3.11 vs -2.89 HU, p=0.566) (Supplementary e-Figure 1),

For participants taking statins, no significant differences in delta-PMA were observed on the basis of which statin a participant was taking (p=0.946), nor was there a significant difference between hydrophilic (Pravastatin and Rosuvastatin) and lipophilic (Simvastatin, Atorvastatin and Lovastatin) classes (p=0.728).

Effect of Persistent Statin Use

Participants were stratified into three groups based on the statin status during the study: continuous statin use (n=539), never statin use (n=457), and intermittent statin use (n=353). Figure 3 depicts the differences in delta-PMA among the three groups and the continuous use group showed less decrease in PMA than never use group and status change group (p=0.019

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and p=0.022, respectively). On the other hand, for aspirin, continuous aspirin use (n=514) lost more PMA compared to only never use group (n=542) (p=0.047).

All subjects' analysis

In terms of all subjects (n=4,191), the statin user group (n=1,158) had a less decrease in PMA and PMD compared to non-user group (n=3,033) throughout the period (median delta-PMA; -1.73 vs -2.43 cm^2, p=0.0014, and median delta-PMD; -2.45 vs -3.55 HU, p=<0.0001, respectively). In addition, after adjusting for the exact time between the two measurements, the yearly decline in PMA and PMD showed similar trends, with statin users having a smaller yearly decrease compared to non-users (median delta-PMA; -0.44 vs -0.31 cm^2, p=0.0019, and median delta-PMD; -0.63 vs -0.44 HU, p=0.0001). When stratifying by smoking status, we found that statin users had a statistically significant beneficial effect in current smokers, with the statin user group showing significantly less muscle deterioration compared to non-users (median delta-PMA; -1.82 vs -2.81 cm^2, p=0.0132, and median delta-PMD; -1.56 vs -3.74 HU, p<0.0001, respectively). However, in former smokers, there was no statistically significant difference in muscle outcomes between the statin user and non-user groups (median delta-PMA; -1.71 vs -2.00 cm^2, p=0.160, and median delta-PMD; -2.91 vs -3.15 HU, p=0.354, respectively). As for aspirin, we did not observe any statistically significant differences in muscle deterioration between aspirin users and non-users in either current or former smokers.

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Discussion

In this study, we provided support for statin use among current and former smokers was associated with attenuated muscle loss in terms of mass (PMA) and quality (PMD). Conversely, our study showed that aspirin use is associated with increased loss of pectoralis muscle area. As skeletal muscle loss impacts disease prognosis and quality of life in elderly patients, there is a need to determine whether our findings indicate medications currently being prescribed could be personalized to minimize skeletal muscle loss and/or reflect underlying co-morbid illness needing treatment.

Many studies have reported that statins have a negative side effect on skeletal muscle mass termed statin-associated myopathy (SAM) [27-29]. On the other hand, our findings indicate longitudinal statin may attenuate loss skeletal muscle mass. There are several plausible reasons for the seemingly contradictory findings. First, patients who experience SAM typically discontinue statin use and in our study the relationship between statin and less muscle loss was seen in participants with a history of statin use of at least 5 years. SAM occurs in approximately 10-25% of patients receiving statin therapy [30], and accounts approximate ninety percent discontinuation cases [31]. Second, pleiotropic effects of statins can be considered. Statins have anti-inflammatory, antithrombotic and immunomodulatory properties, reducing inflammatory mediators induced by tobacco exposure such as CRP, TNF-α, IL-6 [32]. Given that inflammation

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significantly influences muscle mass and function, it offers a basis for suggesting a direct impact of statins on muscle loss in smokers [33]. Smokers including COPD have a higher risk of cardiovascular diseases and diabetes, and statins can prevent events from cardiovascular diseases, improve lung function, and reduce the risk of acute exacerbations [34,35]. As a result, statins probably can prevent overall health deterioration, resulting in the preservation of muscle proteins. Finally, skeletal muscles attenuation on CT scans have suggested the lipid infiltration of the muscle and is associated with changes in the metabolic health of skeletal muscles. The increase in muscle density due to statins may reflect differences in lipid metabolism, and as a result, it could be considered that the muscles of patients taking statins appear to be hypertrophic [36]. In addition, as we described above, we demonstrated that the patients who took statins continuously for 5 years showed the less muscle loss in comparison with non-continuous or intermittent statin users, which may suggest the importance of persistent treatment. However, it is possible that other unaccounted confounders explain the relationship between statin use and decreased pectoralis muscle loss. Additional work is needed, including prospective studies, but if confirmed, these findings would provide new insights into the role of statins for smokers and their potential importance independent of other indications for their use.

Interestingly, we found an opposite effect for aspirin. Aspirin is well-known cyclooxygenase (COX) inhibitor that is commonly used as analgesic, antipyretic, anti-inflammatory and cardioprotective medication. Prostaglandin E2 (PGE2), an inflammatory regulator whose

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synthesis is catalyzed by cyclooxygenases, has been associated with muscle regeneration, and its synthesis is induced by muscle damage [37-39]. Aspirin, even at low-dose, reduces PGE2/COX pathway activity in resting human skeletal muscle [40,41]. Thus, aspirin may hinder muscle regeneration and potentially lead to muscle degradation by inhibiting the synthesis of PGE2. This could explain why aspirin affects muscle area (PMA) but not muscle density (PMD). Since PMA reflects the size of the muscle, the inhibition of muscle regeneration through the suppression of PGE2 could lead to a reduction in muscle mass over time. On the other hand, PMD reflects muscle quality, including aspects like fat infiltration and structural integrity, which may be less affected by the PGE2 pathway. Therefore, while aspirin may impair the regenerative processes that influence muscle size, it might not significantly alter the underlying muscle quality. This distinction highlights the differential effects of aspirin on muscle mass and quality, which warrants further investigation.

This study has several limitations. First, medication use was self-reported, and dosage information, particularly for aspirin, was not available, limiting our ability to assess dose-dependent effects. Second, adherence to medication and reasons for prescription changes were not captured, which could influence the results. Third, the absence of a non-smoking control group prevents us from distinguishing muscle loss due to smoking from age-related decline. Additionally, the lack of data on physical activity, particularly in participants with respiratory or cardiovascular conditions, may confound the association between medications and muscle

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changes. Furthermore, while our study used forced spirometry data, including measures such as CT-derived emphysema scores could provide a more comprehensive understanding of the relationship between emphysema and muscle mass loss. Finally, although propensity score matching was used to reduce confounding, unmeasured factors related to medication indications may still have influenced the findings. Future research should address these limitations, including incorporating non-smoking controls, physical activity measures, and detailed medication dosage data.

Conclusion

In conclusion, our study illuminated the contrasting effects of statin and aspirin use on longitudinal pectoralis muscle area in ever smokers. Statin use among current and former smokers appears to be associated with a reduction in muscle loss, both in terms of mass (PMA) and quality (PMD), potentially attributed to the pleiotropic effects of statins. Clarifying the impact of statins and aspirin on skeletal muscle mass in ever smokers is crucial for tailoring medication prescriptions to minimize muscle loss and improve overall health outcomes in this population. Although additional research is needed, these findings raise new questions regarding the role and importance of statin and aspirin use in smokers.

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Author contributions

T.S., R.S.J.E, S.Y.A. G.R.W. and F.N.R. contributed towards conception and design of the study. T.S., S.Y. A. and F.N.R. analyzed the data. N.A.E., V.C., B.C., A.A.D. provided critical interpretation of the data and contributed towards manuscript preparation. J.C. and M.N.M. reviewed the statistics and provide critical insights. T.S. wrote the manuscript. All authors have approved the final version of the manuscript.

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Declarations

Ethical Approval

COPDGene were approved by the institutional review boards at each center.

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Published online December 4, 2024 https://doi.org/10.15326/jcopdf.2024.0557

Table 1 Baseline characteristics of all subjects (n=4191)

Variables	N=4191		Variables	
Age, years	59.6 (52.7, 66.2)		Asthma	1040 (24.8)
Male, n(%)	2112 (50.4)		Coronary Artery Disease	290 (6.9)
Race, white(%)	2965 (70.7)		Rheumatoid Arthritis	253 (6.0)
BMI, kg/㎡	28.2 (24.8, 32.2)		Osteoarthritis	851 (20.3)
Smoking status, current(%)	2034 (48.5)		Osteoporosis	364 (8.7)
Pack-year, n	38.9 (26.0, 53.8)			
SBP, mmHg	128.0(118.0, 140,0)		Prescribed medications, n(%)	
DBP, mmHg	77.0 (70.0, 84.0)		·HTN treated	
Between phase 1 and 2, y	5.34 (5.00, 5.84)		ACEI	683 (16.3)
FEV_1, L	2.31 (1.74, 2.90)		ARB	248 (5.9)
Predicted FEV1, %	83.3 (66.5, 96.4)		β blocker	583 (13.9)
6MWD, m	439.8 (365.8, 509.9)		Diuretic	677 (16.2)
Exacerbation, n(%)	782 (18.7)		Ca blocker	439 (10.5)
PMA, ㎠	38.7 (29.8, 49.6)		·DM treated	
PMD, HU	33.5 (26.7, 39.3)		Biguanides	283 (6.8)
Comorbidity, n(%)			·Gastric acid treated	
Hypertension (HTN)	1781 (42.5)		Proton pump inhibitor	245 (5.9)
Diabetes mellitus (DM)	510 (12.2)		·HL treated	
Hyperlipidemia (HL)	1709 (40.8)		Statins	1158 (27.6)
GERD	1118 (26.7)		·Antiplatelet therapy	
COPD	1451 (34.6)		Aspirin	742 (17.7)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Published online December 4, 2024 https://doi.org/10.15326/jcopdf.2024.0557

Table2. Multivariable regression analysis for the delta-PMA

	β	*Standard* error	p
Diuretic	0.17	0.16	0.28
Calcium blocker	0.19	0.19	0.32
Statin	0.57	0.14	<0.0001
Aspirin	-0.44	0.16	<0.01

Published online December 4, 2024 https://doi.org/10.15326/jcopdf.2024.0557

Table 3 Characteristics of propensity score matched subjects for statins and aspirin.

	PSM subjects for statins (n=1384)			PSM subjects for aspirin (n=1452)		
	Non-user (n=692)	User (n=692)	p	Non-user (n=726)	User (n=726)	p
Age, years	62.2 (56.3, 68,2)	62.4 (57.1, 68.0)	0.513	65.0 (59.0 70.4)	64.3 (58.4, 69.6)	0.218
Male, n(%)	337 (48.7)	355 (51.3)	0.333	403 (55.7)	412 (57.0)	0.633
Race, white(%)	564 (81.5)	576 (83.2)	0.397	603 (83.4)	590 (81.6)	0.368
BMI, kg/㎡	29.0 (25.4, 33.4)	28.8 (25.7, 32.8)	0.923	29.1 (26.0, 33.0)	29.2 (25.7, 33.0)	0.937
Smoking status, current (%)	265 (38.3)	249 (36.0)	0.373	229 (31.7)	248 (34.3)	0.288
Pack-year, n	41.9 (28.5, 56.0)	40.5 (28.0, 56,0)	0.422	42.0 (30.4, 60.0)	44.0 (27.4, 59.5)	0.916
FEV_1, L	2.27 (1.66, 2.89)	2.23 (1.67, 2.80)	0.420	2.13 (1.58, 2.74)	2.13 (1.59, 2.70)	0.942
Predicted FEV1, %	82.8 (65.5, 95.4)	81.1 (64.3, 94.3)	0.388	78.2 (61.4, 92.2)	78.1 (60.1, 93.9)	0.827
6MWD, m	438.9 (364,8 509,9)	438.9 (365.8, 507.8)	0.936	433.4 (360.0, 509.9)	426.7 (359.7, 496.8)	0.391
Exacerbation, n(%)	155 (22.4)	141 (20.4)	0.359	152 (21.0)	157 (21.7)	0.748
Duration (P1 to P2), year	5.33 (5.00, 5.75)	5.25 (5.00, 5.67)	0.442	5.34 (5.01, 5.84)	5.34 (5.00, 5.67)	0.138
PMA, ㎠	37.2 (29.5, 48.9)	36.7 (28.9, 47.2)	0.219	37.8 (29..4, 46.9)	38.1 (29.7, 47.7)	0.486
Comorbidity, n(%)						
Hypertension (HTN)	372 (53.8)	373 (53.9)	0.957	455 (62.9)	433 (59.9)	0.235
Diabetes mellitus (DM)	119 (17.2)	123 (17.8)	0.777	150 (20.8)	160 (22.1)	0.522
Hyperlipidemia (HL)	565 (81.7)	549 (79.3)	0.278	449 (62.1)	437 (60.4)	0.517
GERD	238 (34.4)	231 (33.4)	0.691	246 (34.0)	239 (33.1)	0.697
COPD	259 (37.4)	240 (34.7)	0.288	257 (35.6)	286 (39.6)	0.115
Asthma	186 (26.7)	164 (23.7)	0.174	186 (25.7)	164 (22.7)	0.177
Coronary Artery Disease	57 (8.2)	75 (10.8)	0.100	110 (15.2)	136 (18.8)	0.069
Rheumatoid Arthritis	43 (6.2)	42 (6.1)	0.911	42 (5.8)	43 (6.0)	0.911
Osteoarthritis	175 (25.3)	170 (24.6)	0.756	189 (26.1)	200 (27.7)	0.514
Osteoporosis	75 (10.8)	67 (9.7)	0.478	80 (11.1)	67 (9.3)	0.258

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Published online December 4, 2024 https://doi.org/10.15326/jcopdf.2024.0557

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Figure legends

Figure 1. Flowchart depicting participant selection.

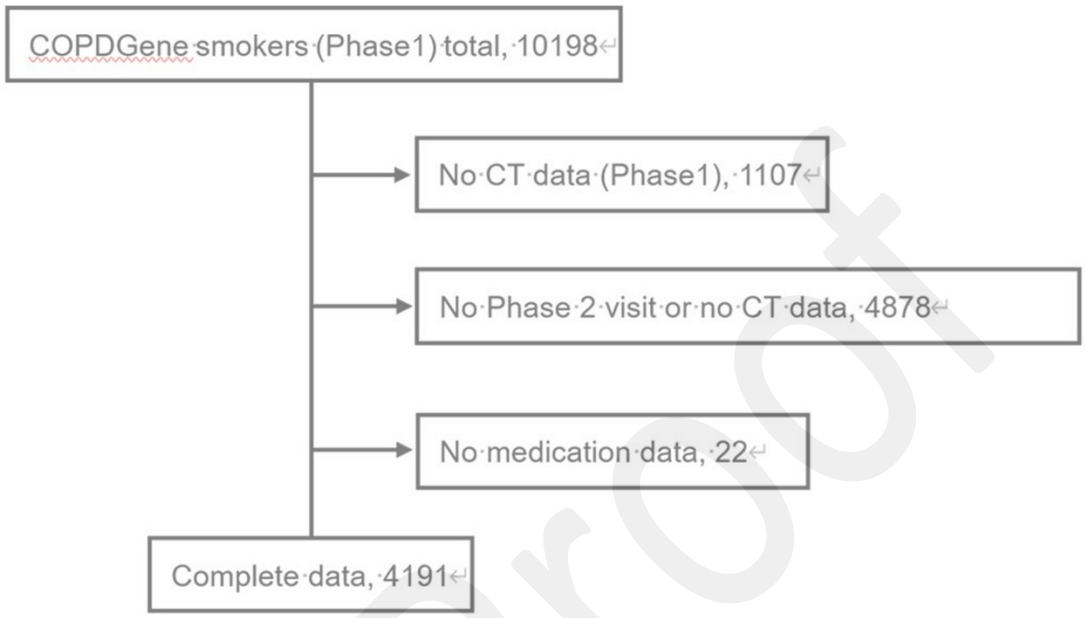

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Figure 2. The relationship between longitudinal skeletal muscle changes and medication use of propensity matched subjects. (A) delta-PMA with or without statin use, (B) delta-PMA with or without aspirin use. Significant differences were found among the two groups (statins; *p=0.017, aspirin; **p=0.040). The boxplot shows median delta-PMA and IQR.

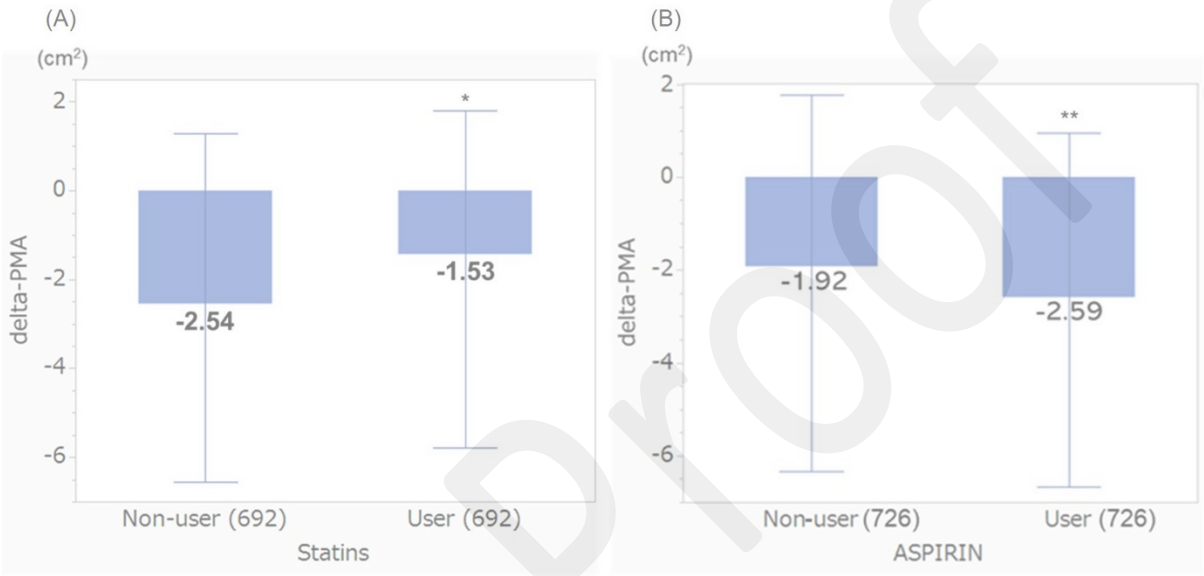

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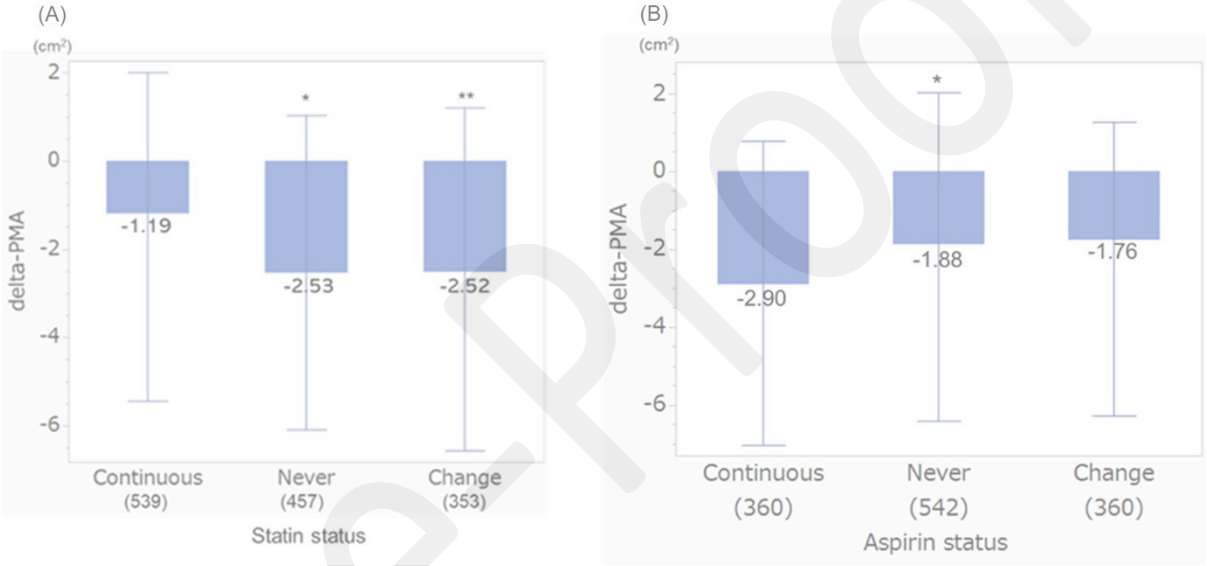
Figure 3. The relationship between longitudinal skeletal muscle changes and the status of (A) statin and (B) aspirin prescription during the period. Continuous statin user group significantly protected PMA wasting compared to never user group and status change group. *p= 0.019 versus never user group, **p = 0.022 versus status change group. On the other hand, continuous aspirin user group lost more PMA than never user group (*p=0.047). The boxplot shows median delta-PMA and IQR.



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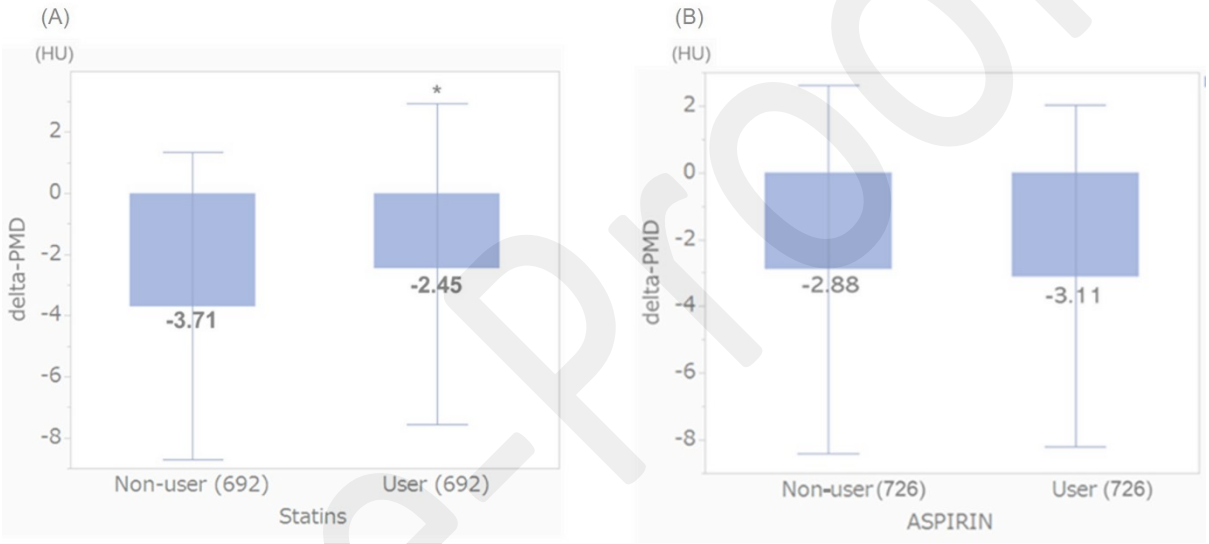
Online Supplement

e-Figure 1. The relationship between longitudinal skeletal muscle density and medication use of propensity matched subjects. (A) delta-PMD with or without statin use, (B) delta-PMD with or without aspirin use. Statin user inhibited PMD decrease (*p=0.041) but no significant difference was found with or without aspirin use(p=0.566). The boxplot shows median delta-PMD and IQR.



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