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Supplemental Methods

Reasoning for utilizing biomarkers of muscle quality

Traditional methods of evaluating statin-related muscle adverse effects have relied on changes in muscle strength and contractile force (7,8). However, these measures can be affected by muscle atrophy, which may be caused by muscle disuse associated with potential statin-associated muscle symptoms (SAMS) or other comorbidities in statin users, such as insufficient physical activity (9). Consequently, while muscle strength is commonly used to assess muscle atrophy and is easily measured, it may not be sensitive enough to detect early changes in muscle quality resulting from statin use. Recent studies have demonstrated that magnetic resonance imaging (MRI) of the muscle is a reliable, sensitive, and precise noninvasive tool for monitoring the development and progression of myopathies. Furthermore, MRI can accurately quantify muscle quality, regardless of muscle atrophy (i.e., loss of muscle volume) (10-18). These MRI measures have been extensively employed in various neuromuscular disorders, diabetes mellitus, obesity, stroke, and other conditions that affect muscle mass and composition (11-15).

Variables incorporated in propensity-score matching

The variables included in propensity-score matching (PS-matching) encompassed age (in years), gender (male/female), race/ethnicity (White or non-white race), body-mass index (BMI, Weight/(Height)2 in Kg/m2), physical activity scale for the elderly score (PASE), abdominal obesity (defined as a waist circumference of ≥94 cm in men and ≥80 cm in women, according to the international diabetes foundation criteria) (19), alcohol consumption (number of drinks consumed per week during the last 12 months, categorized as none, <1/week, 1-3 drinks/week, 4-7 drinks/week, 8-14 drinks/week, 15 drinks or more), smoking (smoking pipe, cigars, or cigarillos

categorized as never, past smoker, currently smoking <14 cigarettes/day, currently smoking >14 cigarettes/day), diabetes (self-reported diabetes or use of oral or injective diabetes medications, yes/no), hypertension (Physical examination at OAI baseline visit, indexed as systolic blood pressure of ≥130 mm/Hg or diastolic blood pressure of ≥80 mm Hg, yes/no), cerebrovascular accident (self-reported history of stroke, cerebrovascular accident, blood clot or bleeding in brain, or transient ischemic attack), heart attack (self-reported history of heart attack, yes/no), heart failure (self-reported history of having heart failure or receiving treatment for heart failure, yes/no), peripheral artery disease (self-reported, yes/no), malignancy (self-reported history of cancer, other than skin cancer, leukemia or lymphoma, yes/no), chronic obstructive pulmonary disease (self-reported, having emphysema, chronic bronchitis, or chronic obstructive lung disease, yes/no), kidney dysfunction (self-reported, ever had a problem with kidneys, poor kidney function based on high blood creatinine, yes/no), advanced liver dysfunction (self-reported, have cirrhosis or serious liver damage, yes/no), peptic ulcer (self-reported stomach ulcers or peptic ulcer disease, yes/no), Charlson comorbidity score (calculated from the list of comorbidities by OAI centers), medications other than statin (MIF form), and KL grade (based on baseline X-ray, grade 0/1/2/3/4). The units, levels, and categories of these variables are provided in Table 1 in the main text.

Assessment of missing data pattern using Little's test

To evaluate the pattern of missing data, we employed Little's test for missing completely at random, visual representation, and logistic regression models. The results indicated a non-random pattern of missing data (20) in the OAI dataset, with less than 2.8% missing values for all matching variables (Supplemental Table 2). Despite the non-random missing data pattern, we included all matching variables in multiple imputation models, as previous studies have suggested this approach to minimize potential associated biases (21).

Supplemental Tables

Supplemental Table 1. Osteoarthritis Initiative (OAI) datasets used in the analysis.

Dataset	Visit	Release version
All clinical	allclinical00	0.2.2
(data regarding all clinical information)	allclinical01	1.2.1
	allclinical03	3.2.1
	allclinical05	5.2.1
	allclinical06	6.2.1
Medical inventory form (MIF)	MIF00	0.2.2
(data regarding drug history)	MIF01	1.2.1
	MIF03	3.2.1
	MIF05	5.2.1
	MIF06	6.2.1
Enrollees	Enrollees	25
(data regarding baseline enrollment of OAI participants)		
Knee X-ray semi-quantitative reading (Kxr sq)	Kxr sq 00	0.8
MRI tracking and QA	mri00	0.2.2

(data regarding availability of MRI and	mri03	3.2.1
quality assessment)	mri06	6.2.1

Supplemental Table 2. Percentage of missing data of the covariate included in the multiple imputations and PS-matching methods.

Variables	Missing %
Subject characteristics	
Age	0.00%
No. of women	0.00%
Race, non-white	0.07%
Comorbidities and Risk factors	
PASE score	0.55%
BMI	0.10%
Waist circumference	0.21%
Abdominal (central) obesity	0.21%
Alcohol use	0.58%
Smoking	1.16%
Diabetes	2.12%
Hypertension	0.00%
CVA	1.61%
Heart attack	1.92%
Heart failure	1.30%

Peripheral artery disease	0.79%
Malignancy	1.61%
Advanced liver disease	1.64%
Kidney dysfunction	2.70%
COPD	2.05%
Peptic ulcer	2.81%
Charlson Comorbidity score	1.03%
KL grade	0.00%
Medication data	0.00%

BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, CVA: Cerebrovascular Accident, KL: Kellgren-Lawrence grade, PASE: Physical Activity for Elderly Scale, PS: Propensity-score.

Supplemental Table 3. Baseline characteristics of study groups as with and without/at-risk of KOA, included in the study before and after propensity-score matching according to statin use.

	With KOA (KL≥2)					Without/at-risk of KOA (KL<2)				
	Statin (-) N: 1494	**Statin (+)** N: 1032	**SMD**	**Statin (-)** N: 847	**Statin (+)** N: 847	**SMD**	**Statin (-)** N: 2040	**Statin (+)** N: 1262	**SMD**	**Statin (-)** N: 1039	**Statin (+)** N: 1039	**SMD**
Subject characteristics												
Age (year) [mean (SD)]	61.35 (9.21)	63.62 (8.32)	**0.26**	63.22 (9.13)	63.30 (8.16)	0.01	58.48 (8.86)	62.03 (8.84)	**0.40**	61.27 (9.25)	61.02 (8.76)	0.03
No. of women [N (%)]	914 (61.3)	552 (53.5)	**0.16**	432 (51.0)	461 (54.4)	0.07	1176 (57.6)	616 (48.8)	**0.18**	522 (50.2)	527 (50.7)	0.01

Race, non-white [N (%)]	348 (23.3)	248 (24.0)	0.02	185 (21.8)	198 (23.4)	0.04	317 (15.5)	196 (15.5)	0.00	142 (13.7)	157 (15.1)	0.04
Comorbidities and Risk factors												
PASE score [mean (SD)]	168.09 (82.08)	146.62 (73.85)	**0.28**	151.36 (76.42)	150.64 (75.90)	0.01	174.76 (83.15)	161.45 (81.26)	**0.16**	161.92 (80.00)	167.46 (82.90)	0.07
BMI (kg/m^2) [mean (SD)]	28.82 (4.92)	30.39 (4.58)	**0.33**	29.92 (5.07)	29.90 (4.44)	0.00	27.08 (4.45)	28.27 (4.03)	**0.28**	27.90 (4.51)	27.89 (3.97)	0.00
Waist circumference, (cm) [mean (SD)]	102.55 (12.35)	106.55 (11.48)	**0.34**	105.40 (11.79)	105.46 (11.35)	0.01	98.16 (12.84)	102.03 (11.16)	**0.32**	101.10 (12.41)	100.88 (10.85)	0.02
Abdominal (central) obesity [N (%)]	1076 (72.1)	826 (80.0)	**0.19**	639 (75.4)	661 (78.0)	0.06	1224 (60.0)	870 (68.9)	**0.19**	693 (66.7)	688 (66.2)	0.01
Alcohol use [N (%)]			**0.14**			0.05			**0.10**			0.07

None	291 (19.5)	202 (19.6)		159 (18.8)	158 (18.7)		372 (18.2)	221 (17.5)		183 (17.6)	179 (17.2)	
<1 drink/wk	558 (37.4)	428 (41.5)		335 (39.6)	348 (41.1)		737 (36.1)	472 (37.4)		365 (35.1)	383 (36.9)	
1-3 drinks/wk	191 (12.8)	126 (12.2)		111 (13.1)	109 (12.9)		372 (18.2)	192 (15.2)		164 (15.8)	172 (16.6)	
4-7 drinks/wk	247 (16.6)	128 (12.4)		105 (12.4)	106 (12.5)		301 (14.8)	193 (15.3)		172 (16.6)	152 (14.6)	
8-14 drinks/wk	130 (8.7)	84 (8.1)		80 (9.4)	71 (8.4)		173 (8.5)	124 (9.8)		100 (9.6)	103 (9.9)	
+15 drinks/wk	75 (5.0)	64 (6.2)		57 (6.7)	55 (6.5)		85 (4.2)	60 (4.8)		55 (5.3)	50 (4.8)	
Smoking [N (%)]			**0.13**			0.06			**0.16**			0.05
Never smoked	840 (56.3)	522 (50.6)		458 (54.1)	437 (51.6)		1179 (57.8)	658 (52.1)		567 (54.6)	549 (52.8)	

Past smoker	568 (38.1)	434 (42.1)		344 (40.6)	355 (41.9)		736 (36.1)	548 (43.4)		411 (39.6)	434 (41.8)	
Smoker < 14 cigarettes/day	62 (4.2)	50 (4.8)		31 (3.7)	37 (4.4)		77 (3.8)	30 (2.4)		35 (3.4)	30 (2.9)	
Smoker ≥ 14 cigarettes/day	22 (1.5)	26 (2.5)		14 (1.7)	18 (2.1)		48 (2.4)	26 (2.1)		26 (2.5)	26 (2.5)	
Diabetes [N (%)]	66 (4.4)	139 (13.5)	**0.32**	65 (7.7)	81 (9.6)	0.07	38 (1.9)	146 (11.6)	**0.40**	35 (3.4)	47 (4.5)	0.06
Hypertension [N (%)]	356 (23.9)	252 (24.4)	0.01	214 (25.3)	208 (24.6)	0.02	320 (15.7)	240 (19.0)	0.09	192 (18.5)	192 (18.5)	0.00
CVA [N (%)]	36 (2.4)	52 (5.0)	**0.14**	29 (3.4)	28 (3.3)	0.01	29 (1.4)	37 (2.9)	**0.10**	24 (2.3)	23 (2.2)	0.01
Heart attack [N (%)]	15 (1.0)	34 (3.3)	**0.16**	11 (1.3)	20 (2.4)	0.08	10 (0.5)	47 (3.7)	**0.23**	10 (1.0)	14 (1.3)	0.04

Heart failure [N (%)]	22 (1.5)	32 (3.1)	**0.11**	19 (2.2)	16 (1.9)	0.03	20 (1.0)	34 (2.7)	**0.13**	12 (1.2)	8 (0.8)	0.04
Peripheral artery disease [N (%)]	8 (0.5)	12 (1.2)	0.07	4 (0.5)	6 (0.7)	0.03	2 (0.1)	22 (1.7)	**0.17**	2 (0.2)	2 (0.2)	0.00
Malignancy [N (%)]	58 (3.9)	52 (5.0)	0.06	35 (4.1)	35 (4.1)	0.00	60 (2.9)	46 (3.6)	0.04	34 (3.3)	40 (3.8)	0.03
Advanced liver disease [N (%)]	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00	10 (0.5)	2 (0.2)	**0.06**	4 (0.4)	0 (0.0)	0.09
Kidney dysfunction [N (%)]	14 (0.9)	10 (1.0)	0.00	10 (1.2)	9 (1.1)	0.01	11 (0.5)	30 (2.4)	**0.15**	9 (0.9)	11 (1.1)	0.02
COPD [N (%)]	26 (1.7)	27 (2.6)	0.06	17 (2.0)	13 (1.5)	0.04	41 (2.0)	36 (2.9)	0.06	30 (2.9)	27 (2.6)	0.02
Peptic ulcer [N (%)]	23 (1.5)	40 (3.9)	**0.14**	21 (2.5)	19 (2.2)	0.02	61 (3.0)	27 (2.1)	0.05	16 (1.5)	19 (1.8)	0.02

Charlson Comorbidity score [mean (SD)]	0.30 (0.73)	0.52 (0.99)	**0.25**	0.38 (0.83)	0.40 (0.86)	0.03	0.26 (0.73)	0.49 (0.92)	**0.27**	0.27 (0.67)	0.31 (0.69)	0.06
KL grade [N (%)]			0.02			0.01			**0.14**			0.02
Grade 0	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1414 (69.3)	792 (62.8)		650 (62.6)	658 (63.3)	
Grade 1	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		626 (30.7)	470 (37.2)		389 (37.4)	381 (36.7)	
Grade 2	958 (64.2)	666 (64.5)		540 (63.8)	539 (63.6)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Grade 3	436 (29.2)	302 (29.3)		255 (30.1)	254 (30.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Grade 4	98 (6.6)	64 (6.2)		52 (6.1)	54 (6.4)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Medications												

Diuretics [N (%)]	248 (16.6)	286 (27.7)	**0.27**	203 (24.0)	206 (24.3)	0.01	276 (13.5)	308 (24.4)	**0.28**	216 (20.8)	207 (19.9)	0.02
B blocker [N (%)]	172 (11.5)	228 (22.1)	**0.29**	148 (17.5)	158 (18.7)	0.03	192 (9.4)	266 (21.1)	**0.33**	154 (14.8)	168 (16.2)	0.04
Calcium channel blocker [N (%)]	118 (7.9)	166 (16.1)	**0.25**	100 (11.8)	108 (12.8)	0.03	98 (4.8)	148 (11.7)	**0.25**	90 (8.7)	92 (8.9)	0.01
Non-statin lipid-lowering drug [N (%)]	40 (2.7)	56 (5.4)	**0.14**	32 (3.8)	37 (4.4)	0.03	50 (2.5)	86 (6.8)	**0.21**	46 (4.4)	45 (4.3)	0.01
ACEI/ARB [N (%)]	272 (18.2)	310 (30.0)	**0.28**	218 (25.7)	209 (24.7)	0.02	268 (13.1)	390 (30.9)	**0.44**	228 (21.9)	239 (23.0)	0.03
Oral hypoglycemic [N (%)]	44 (2.9)	104 (10.1)	**0.29**	44 (5.2)	66 (7.8)	0.09	24 (1.2)	126 (10.0)	**0.39**	24 (2.3)	35 (3.4)	0.06
NSAID [N (%)]	256 (17.2)	230 (22.3)	**0.13**	173 (20.4)	162 (19.1)	0.03	246 (12.1)	184 (14.6)	0.07	143 (13.8)	152 (14.6)	0.03

Aspirin [N (%)]	36 (2.4)	40 (3.9)	0.08	28 (3.3)	29 (3.4)	0.01	36 (1.8)	70 (5.5)	**0.20**	34 (3.3)	35 (3.4)	0.01
SSRI [N (%)]	94 (6.3)	98 (9.5)	**0.12**	66 (7.8)	74 (8.7)	0.03	136 (6.7)	138 (10.9)	**0.15**	102 (9.8)	98 (9.4)	0.01
Tricyclic antidepressant [N (%)]	14 (0.9)	26 (2.5)	**0.12**	14 (1.7)	10 (1.2)	0.04	24 (1.2)	24 (1.9)	0.06	20 (1.9)	20 (1.9)	0.00
Sedative [N (%)]	64 (4.3)	60 (5.8)	0.07	43 (5.1)	41 (4.8)	0.01	84 (4.1)	92 (7.3)	**0.14**	68 (6.5)	66 (6.4)	0.01
Systemic corticosteroid [N (%)]	112 (7.5)	92 (8.9)	0.05	72 (8.5)	70 (8.3)	0.01	192 (9.4)	178 (14.1)	**0.15**	128 (12.3)	131 (12.6)	0.01
Thyroid hormones [N (%)]	160 (10.7)	116 (11.2)	0.02	76 (9.0)	95 (11.2)	0.08	192 (9.4)	144 (11.4)	0.07	101 (9.7)	113 (10.9)	0.04

Antineoplastic agents [N (%)]	38 (2.5)	32 (3.1)	0.03	26 (3.1)	22 (2.6)	0.03	34 (1.7)	36 (2.9)	0.08	25 (2.4)	29 (2.8)	0.02
Anticoagulants [N (%)]	34 (2.3)	30 (2.9)	0.04	19 (2.2)	22 (2.6)	0.02	30 (1.5)	36 (2.9)	**0.10**	22 (2.1)	23 (2.2)	0.01
Muscle quality measures												
Knee extension specific contractile force (N/cm2) [mean (SD)]	6.85 (2.01)	6.77 (1.91)	0.04	6.81 (1.99)	6.82 (1.89)	0.00	7.27 (2.00)	7.00 (1.95)	**0.14**	7.25 (2.00)	7.09 (1.93)	0.08
Knee flexion maximum contractile force (N) [mean (SD)]	144.46 (67.10)	143.17 (66.58)	0.02	150.48 (71.07)	142.06 (65.37)	**0.12**	151.30 (70.63)	149.68 (72.40)	0.02	152.76 (71.55)	151.52 (73.86)	0.02

Knee flexion specific contractile force (N/cm2) [mean (SD)]	4.39 (1.67)	4.24 (1.66)	0.09	4.35 (1.65)	4.22 (1.61)	0.08	4.78 (1.85)	4.58 (1.83)	**0.11**	4.70 (1.83)	4.66 (1.83)	0.03
Knee extension maximum contractile force (N) [mean (SD)]	338.63 (125.68)	347.50 (127.85)	0.07	350.20 (131.26)	348.50 (126.91)	0.01	364.02 (134.69)	357.44 (131.84)	0.05	366.77 (134.21)	360.75 (134.08)	0.05
Total thigh muscle CSA (mm2) [mean (SD)]	9920.32 (2674.35)	10249.18 (2572.75)	**0.13**	10266.11 (2744.65)	10193.40 (2541.73)	0.03	9810.57 (2683.01)	10046.65 (2631.22)	0.09	9951.72 (2741.96)	9966.49 (2636.37)	0.01
Intra-MAT CSA (mm2) [mean (SD)]	458.96 (359.60)	549.32 (345.83)	**0.26**	519.83 (385.70)	512.62 (321.50)	0.02	352.33 (234.31)	446.33 (310.24)	**0.34**	398.25 (264.63)	419.74 (292.99)	0.08

Total thigh muscles contractile [mean (SD)]	**%**	95.25 (3.37)	94.53 (3.29)	**0.22**	94.80 (3.41)	94.85 (3.13)	0.01	96.33 (2.34)	95.49 (2.98)	**0.31**	95.91 (2.59)	95.70 (2.90)	0.08

ACEI: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blocker, BMI: Body Mass Index, CSA: Cross-sectional Area, COPD: Chronic Obstructive Pulmonary Disease, CVA: Cerebrovascular Accident, Intra-MAT: Intra-muscular Adipose tissue, KL: Kellgren-Lawrence grade, KOA: Knee Osteoarthritis, NSAIDs: Non-steroidal Anti-inflammatory Drugs, PASE: Physical Activity for Elderly Scale, PS: Propensity-score, SMD: Standardized Mean Difference, SD: Standard Deviation, SSRI: Selective Serotonin Reuptake Inhibitor. A significant difference for SMD was defined as ≥ 0.1 and is shown as bold.

† Race of participants was categorized as white and non-white considering the small number of participants in each non-white race group.

* Abdominal obesity was defined as a waist circumference of ≥94 cm in men and ≥80 cm in women on physical examination according to international diabetes foundation criteria.

Supplemental Table 4. Baseline characteristics of the study participants included in sensitivity analysis of exclusion of participants with adherent and prevalent statin use (Sensitivity analysis #1) before and after propensity score matching according to statin use.

	All participants			PS-matched participants		
	Statin (-)	**Statin (+)**		**Statin (-)**	**Statin (+)**	
	N: 3532	N: 836	**SMD**	N: 794	N: 794	**SMD**
Subject characteristics						
Age (year) [mean (SD)]	59.69 (9.12)	61.32 (8.98)	**0.179**	61.10 (9.19)	61.21 (9.02)	0.012
No. of women [N (%)]	2090 (59.2)	436 (52.2)	**0.142**	419 (52.8)	422 (53.1)	0.008
Race, non-white [N (%)]†	665 (18.8)	186 (22.2)	0.085	153 (19.3)	167 (21.0)	0.044
Comorbidities and Risk factors						
PASE score [mean (SD)]	171.94 (82.75)	160.58 (81.78)	**0.138**	160.66 (79.16)	161.90 (82.39)	0.015
BMI (kg/m^2) [mean (SD)]	27.81 (4.73)	29.03 (4.55)	**0.262**	29.12 (5.00)	28.92 (4.54)	0.043
Waist circumference, (cm) [mean (SD)]	100.01 (12.82)	103.01 (12.13)	**0.240**	103.58 (13.36)	102.74 (12.28)	0.065
Abdominal (central) obesity [N (%)]*	2300 (65.1)	594 (71.1)	**0.128**	573 (72.2)	558 (70.3)	0.042

Alcohol use per week [N (%)]			**0.118**			0.066
None	663 (18.8)	155 (18.5)		133 (16.8)	139 (17.5)	
<1 drink/wk	1295 (36.7)	335 (40.1)		334 (42.1)	324 (40.8)	
1-3 drinks/wk	563 (15.9)	110 (13.2)		105 (13.2)	106 (13.4)	
4-7 drinks/wk	548 (15.5)	112 (13.4)		95 (12.0)	105 (13.2)	
8-14 drinks/wk	303 (8.6)	78 (9.3)		87 (11.0)	76 (9.6)	
+15 drinks/wk	160 (4.5)	46 (5.5)		40 (5.0)	44 (5.5)	
Smoking [N (%)]			**0.135**			0.099
Never smoked	2019 (57.2)	431 (51.6)		395 (49.7)	418 (52.6)	
Past smoker	1304 (36.9)	335 (40.1)		343 (43.2)	308 (38.8)	
Smoker < 14 cigarettes/day	139 (3.9)	42 (5.0)		31 (3.9)	40 (5.0)	
Smoker ≥ 14 cigarettes/day	70 (2.0)	28 (3.3)		25 (3.1)	28 (3.5)	
Diabetes [N (%)]	104 (2.9)	66 (7.9)	**0.220**	36 (4.5)	53 (6.7)	0.093

Hypertension [N (%)]	676 (19.1)	204 (24.4)	**0.128**	198 (24.9)	192 (24.2)	0.018
CVA [N (%)]	65 (1.8)	28 (3.3)	**0.095**	16 (2.0)	24 (3.0)	0.064
Heart attack [N (%)]	25 (0.7)	14 (1.7)	0.089	7 (0.9)	7 (0.9)	0.001
Heart failure [N (%)]	42 (1.2)	18 (2.2)	0.075	14 (1.8)	12 (1.5)	0.020
Peripheral artery disease [N (%)]	10 (0.3)	6 (0.7)	0.062	2 (0.3)	4 (0.5)	0.041
Malignancy [N (%)]	118 (3.3)	28 (3.3)	0.001	28 (3.5)	26 (3.3)	0.014
Advanced liver disease [N (%)]	10 (0.3)	0 (0.0)	0.075	6 (0.8)	0 (0.0)	0.099
Kidney dysfunction [N (%)]	25 (0.7)	8 (1.0)	0.027	5 (0.6)	5 (0.6)	0.001
COPD [N (%)]	67 (1.9)	19 (2.3)	0.026	22 (2.8)	14 (1.8)	0.068
Peptic ulcer [N (%)]	84 (2.4)	24 (2.9)	0.031	26 (3.3)	20 (2.5)	0.045
Charlson Comorbidity index [mean (SD)]	0.28 (0.73)	0.39 (0.78)	**0.151**	0.33 (0.77)	0.34 (0.70)	0.014
KL grade [N (%)]			**0.105**			0.055
Grade 0	958 (27.1)	224 (26.8)		215 (27.1)	218 (27.5)	

Grade 1	436 (12.3)	124 (14.8)		109 (13.7)	112 (14.1)	
Grade 2	98 (2.8)	32 (3.8)		38 (4.8)	32 (4.0)	
Grade 3	1414 (40.0)	306 (36.6)		278 (35.0)	289 (36.4)	
Grade 4	626 (17.7)	150 (17.9)		154 (19.4)	143 (18.0)	
Medications						
Diuretic [N (%)]	524 (14.8)	190 (22.7)	**0.203**	202 (25.4)	173 (21.8)	0.086
B blocker [N (%)]	364 (10.3)	126 (15.1)	**0.144**	109 (13.7)	111 (14.0)	0.007
Calcium channel blocker [N (%)]	216 (6.1)	100 (12.0)	**0.205**	81 (10.2)	77 (9.7)	0.017
Non-statin lipid-lowering drug [N (%)]	90 (2.5)	42 (5.0)	**0.130**	33 (4.2)	35 (4.4)	0.012
ACEI/ARB [N (%)]	540 (15.3)	192 (23.0)	**0.196**	183 (23.0)	173 (21.8)	0.030
Oral hypoglycemic [N (%)]	68 (1.9)	50 (6.0)	**0.209**	28 (3.5)	37 (4.7)	0.057
NSAIDs [N (%)]	502 (14.2)	168 (20.1)	**0.157**	162 (20.4)	152 (19.1)	0.032
Aspirin [N (%)]	72 (2.0)	34 (4.1)	**0.118**	29 (3.7)	22 (2.8)	0.050

SSRI [N (%)]	230 (6.5)	86 (10.3)	**0.136**	64 (8.1)	84 (10.6)	0.087
Tricyclic antidepressant [N (%)]	38 (1.1)	16 (1.9)	0.069	10 (1.3)	12 (1.5)	0.022
Sedative [N (%)]	148 (4.2)	34 (4.1)	0.006	30 (3.8)	34 (4.3)	0.026
Systemic corticosteroid [N (%)]	304 (8.6)	110 (13.2)	**0.147**	113 (14.2)	100 (12.6)	0.048
Thyroid hormones [N (%)]	352 (10.0)	92 (11.0)	0.034	87 (11.0)	88 (11.1)	0.004
Antineoplastic agents [N (%)]	72 (2.0)	22 (2.6)	0.039	20 (2.5)	20 (2.5)	0.001
Anticoagulants [N (%)]	64 (1.8)	12 (1.4)	0.030	6 (0.8)	8 (1.0)	0.027
Statins						
atorvastatin	0 (0.0)	270 (32.3)		0 (0.0)	252 (31.7)	
fluvastatin	0 (0.0)	4 (0.5)		0 (0.0)	2 (0.3)	
lovastatin	0 (0.0)	44 (5.3)		0 (0.0)	42 (5.3)	
pravastatin	0 (0.0)	58 (6.9)		0 (0.0)	58 (7.3)	
rosuvastatin	0 (0.0)	78 (9.3)		0 (0.0)	70 (8.8)	

simvastatin	0 (0.0)	382 (45.7)		0 (0.0)	370 (46.6)	
Muscle quality measures						
Knee extension maximum contractile force (N) [mean (SD)]	9856.93 (2679.52)	10186.68 (2716.31)	**0.122**	10086.83 (2731.41)	10145.45 (2707.85)	0.022
Knee extension specific contractile force (N/cm^2) [mean (SD)]	397.37 (298.47)	473.94 (312.62)	**0.251**	475.02 (343.18)	465.55 (309.67)	0.029
Knee flexion maximum contractile force (N) [mean (SD)]	95.87 (2.87)	95.29 (2.82)	**0.206**	95.20 (3.28)	95.36 (2.74)	0.053
Knee flexion specific contractile force (N/cm^2) [mean (SD)]	1062.19 (394.24)	1166.89 (403.65)	**0.262**	1158.77 (409.89)	1153.59 (395.07)	0.013
Total thigh muscle CSA (mm^2) [mean (SD)]	353.32 (131.54)	352.28 (137.51)	0.008	353.58 (126.33)	351.81 (137.08)	0.013
Total thigh muscles intra-MAT CSA (mm^2) [mean (SD)]	7.10 (2.01)	6.85 (2.06)	**0.123**	6.97 (1.97)	6.87 (2.07)	0.049

Total thigh muscles contractile % [mean (SD)]	148.42 (69.24)	146.49 (72.23)	0.027	149.99 (64.67)	146.33 (72.02)	0.054

Data are presented in numbers of thighs. Statin users with >30 days of statin use before baseline visit (prevalent users) or adherent use of statins through all annual visits of 4-year follow-up were excluded. ACEI: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blocker, BMI: Body Mass Index, CSA: Cross-sectional Area, COPD: Chronic Obstructive Pulmonary Disease, CVA: Cerebrovascular Accident, Intra-MAT: Intra-muscular Adipose tissue, KL: Kellgren-Lawrence grade, N: Newton, NSAIDs: Non-steroidal Anti-inflammatory Drugs, PASE: Physical Activity for Elderly Scale, PS: Propensity-score, SMD: Standardized Mean Difference, SD: Standard Deviation, SSRI: Selective Serotonin Reuptake Inhibitor. A significant difference for SMD was defined as ≥ 0.1 and is shown as bold.

† Race of participants was categorized as white and non-white considering the small number of participants in each non-white race group.

* Abdominal obesity was defined as a waist circumference of ≥94 cm in men and ≥80 cm in women on physical examination according to international diabetes foundation criteria.

Supplemental Table 5. Sensitivity analysis results.

	Average Difference/year (95% CI), P
#1. Exclusion of adherent and prevalent statin users	
Muscle contractile force	
Knee extension maximum contractile force (N)	-2.15 (-4.35 - 0.05), P:0.056
Knee extension specific contractile force (N/cm2)	**-0.05 (-0.10 - -0.01), P:0.018***
Knee flexion maximum contractile force (N)	0.01 (-1.22 - 1.23), P:0.993
Knee flexion specific contractile force (N/cm2)	-0.01 (-0.05 - 0.03), P:0.562
Muscle size & composition	
Total thigh muscle CSA (mm2)	7.14 (-10.03 - 24.32), P:0.415
Total thigh muscle Intra-MAT CSA (mm2)	**7.45 (3.61 - 11.29), P:<0.001***
Total thigh muscles contractile %	**-0.07 (-0.11 - -0.03), P:<0.001***
#2. Data imputation	
Muscle contractile force	
Knee extension maximum contractile force (N)	**-2.21 (-3.67 – -0.75), P:0.003***
Knee extension specific contractile force (N/cm2)	**-0.05 (-0.07 – -0.02), P:0.002***
Knee flexion maximum contractile force (N)	0.02 (-0.82 – 0.86), P:0.963
Knee flexion specific contractile force (N/cm2)	-0.00 (-0.03 – 0.02), P:0.733
Muscle size & composition	

Total thigh muscle CSA (mm2)	5.29 (-6.35 – 16.94), P:0.373
Total thigh muscle Intra-MAT CSA (mm2)	**3.65 (1.04 – 6.26), P:0.006***
Total thigh muscles contractile %	**-0.04 (-0.07 – -0.01), P:0.004***
#3. All patients cohort (without PS-matching)	
Muscle contractile force	
Knee extension maximum contractile force (N)	**-1.70 (-2.89 – -0.52), P:0.005***
Knee extension specific contractile force (N/cm2)	**-0.03 (-0.05 – -0.00), P:0.022***
Knee flexion maximum contractile force (N)	0.09 (-0.57 – 0.75), P:0.792
Knee flexion specific contractile force (N/cm2)	0.01 (-0.01 – 0.03), P:0.412
Muscle size & composition	
Total thigh muscle CSA (mm2)	-6.02 (-15.82 – 3.79), P:0.229
Total thigh muscle Intra-MAT CSA (mm2)	**5.60 (3.30 – 7.90), P:<0.001***
Total thigh muscles contractile %	**-0.06 (-0.09 – -0.04), P:<0.001***

We conducted several sensitivity analyses to assess the impact of different factors on the results. Firstly, we evaluated the sensitivity of the results to the exclusion of adherent and prevalent statin users. This involved excluding statin users who had taken statins for more than 30 days before the baseline visit or who consistently adhered to statin use throughout the four-year follow-up period (Sensitivity analysis #1 in Figure 1). Secondly, we examined the sensitivity of the results to data imputation by excluding 437 participants with missing data in covariates (Sensitivity analysis #2 in Figure 1). Thirdly, we assessed the sensitivity of the results to the

propensity-score matching (PS-matching) methods by performing adjusted analyses on all included OAI participants (Sensitivity analysis #3 in Figure 1). In these analyses, linear mixed-effect regressions were utilized. For the sensitivity to the exclusion of adherent and prevalent statin users and data imputation, random slopes and intercepts were considered for clusters of matched participants, while a random intercept was included to account for both thighs in all three sensitivity analyses. To minimize the influence of knee osteoarthritis (KOA)-related knee joint pain on the assessment of muscle contractile force, all statistical models with muscle maximum and specific contractile forces as dependent variables were adjusted for baseline knee joint pain, measured by the Western Ontario and McMaster Universities (WOMAC) pain score. In addition, we used CSA (Cross-sectional Area) and Intra-MAT (Intra-muscular Adipose Tissue) as relevant variables in the analysis.

* Significant FDR corrected p-value

Supplemental Figures

Supplemental Figure 1. Illustration of the study muscle biomarkers.

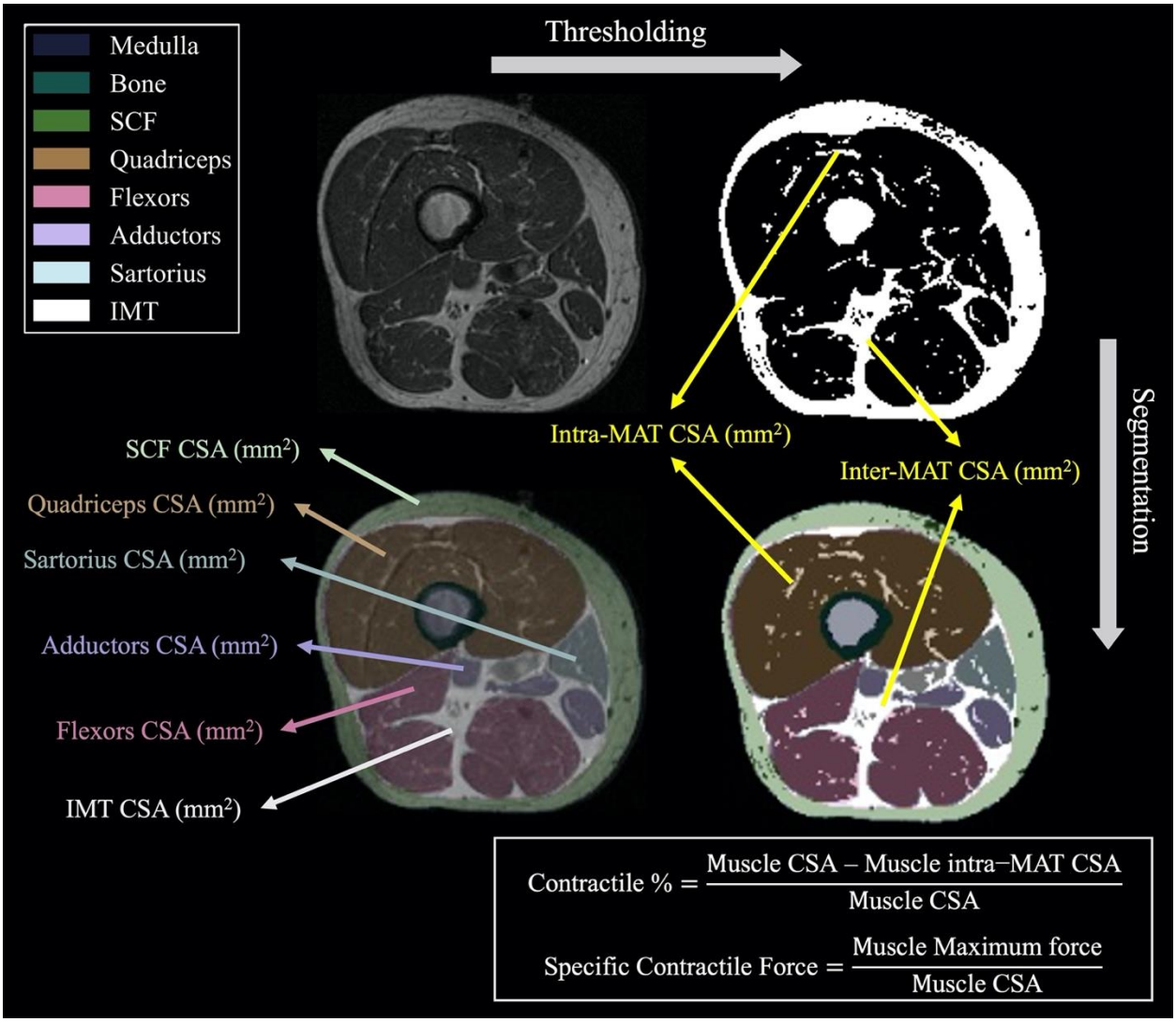

Illustration of study outcome variables. CSA: Cross-sectional Area, IMT: Inter-muscular Tissue, Inter-MAT: Inter-muscular Adipose Tissue, Intra-MAT: Intra-muscular Adipose Tissue, SCF: Subcutaneous Fat.

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