Oral corticosteroid use and sarcopenia-related traits in older people with chronic airway disease: a population-based study

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Among subjects with COPD, oral corticosteroid use is associated with lower muscle function in a cumulative frequency and duration-dependent effect https://bit.ly/3q0Ihi6

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Abstract

Background Sarcopenia is characterised by two major phenotypic components: low handgrip strength (HGS) and appendicular skeletal muscle index (ASMI). Oral corticosteroid (OCS) use is an important medication for acute respiratory exacerbations in patients with COPD and asthma. However, the association of OCS and sarcopenia components in older people is largely unexplored. The aim of this study was to examine the association between OCS use and HGS or ASMI in the general population and explore interactions with chronic airway diseases.

Methods From the population-based Rotterdam Study, 5054 participants (age 69.0±8.8 years; 56% females) were included in the cross-sectional analysis and 1324 in the longitudinal analysis. Associations between OCS and muscle strength and mass were analysed using linear regression models adjusted for age, sex, fat %, height, kidney function, smoking and comorbidities.

Results At baseline, ever-OCS users had lower handgrip strength (β= −0.48, 95% CI −0.84– −0.12) than never-OCS users, with cumulative frequency (⩾10 OCS prescriptions)-dependent effects (β= −1.25, 95% CI −2.16– −0.33). COPD ever-OCS users, but not asthma, had lower handgrip strength (β= −0.98, 95% CI −1.91– −0.06) and lower lean mass (β= −0.14, 95% CI −0.27– −0.01) than never-OCS users. After 5.6 years of follow-up in those free of sarcopenia traits at baseline, COPD ever-OCS users developed lower handgrip strength (β= −1.64, 95% CI −2.87– −0.40) with frequency (β= −3.64, 95% CI −6.57– −0.72) and duration (β= −1.51, 95% CI −2.87– −0.15) association compared to never-OCS users.

Conclusions OCS use is associated with a decline in handgrip strength in people with COPD in a cumulative frequency and duration-dependent manner. Routine muscle examination may be necessary for patients with COPD.

Introduction

Oral corticosteroids (OCS) are well-known anti-inflammatory agents to treat COPD or asthma and other chronic inflammatory conditions [1]. However, OCS have been linked to adverse effects such as bone remodelling when used for an extended period of time or in high doses [2–4]. Emerging evidence suggests that subjects who use OCS, particularly those with chronic airway disease, may experience more musculoskeletal adverse effects [1, 5–11]. Sarcopenia and its phenotypic components have received considerable attention as one of the major musculoskeletal comorbidities of chronic airway disease [12–15]. Sarcopenia is defined as a progressive loss of muscle function and mass, and may be more prevalent in patients with chronic airway disease [12]. Cut-offs for muscle function (*i.e.* handgrip strength) and appendicular skeletal muscle index (ASMI) (*i.e.* appendicular lean mass (ALM) adjusted for height^2) are

available for diagnosis of respectively low muscle function and mass in older people [12]. It is unknown whether OCS users with chronic airway disease are also more prone to develop sarcopenia.

Multiple factors such as smoking, systemic inflammation, malnutrition, hypoxia, comorbidities and physical inactivity are all potential drivers of muscle deterioration in patients with COPD [5, 16]; and OCS, in particular, may be considered an additional risk factor. OCS are extensively used in Western countries (>1–2% of the general population) [17, 18]. Approximately half of the patients with COPD experience one or more acute exacerbation (AECOPD) each year, necessitating treatment with OCS [5, 19]. Deterioration in muscle strength may worsen COPD severity, resulting in a vicious circle of more frequent AECOPD, and thereby more frequent OCS use, with more potential to experience adverse effects [20–22]. Similarly, OCS is critical in the treatment of chronic airway inflammation in asthmatic patients due to respiratory exacerbations or severe presentation of the disease [21, 23].

Despite interest in the long-term effects of OCS use in patients with chronic airway diseases, the adverse effects of OCS on sarcopenia-related traits have not been studied in subjects with COPD or asthma in a population-based study. Thus, it is unclear whether OCS use implies clinically relevant alterations in lean muscle mass/function in the general and COPD/asthma populations. Bridging these knowledge gaps could lead to early identification of people with muscle health impairment.

Therefore, we hypothesised that in a population-based setting and in a subset of subjects with chronic airway diseases, OCS users would have lower sarcopenia-related traits. Our secondary objective was to investigate if the association of OCS and handgrip strength and ASMI are cumulative frequency and duration-dependent.

Methods

Study design and participants

This study was conducted within the Rotterdam Study, an ongoing population-based cohort that started in 1989, involving ∼15 000 participants aged ⩾45 years. Every 4–5 years, participants from Ommoord, a district in Rotterdam, the Netherlands, undergo a home interview and a visit to the research centre for clinical examination.

This study contains a cross-sectional and a longitudinal part. First, all participants with interpretable spirometry, and data on sarcopenia traits and OCS use, who visited the research centre between 2009 and 2014 (Stage 1) were included. Second, participants free of sarcopenia traits in stage 1 were followed up until 2014–2016 (Stage 2) (supplementary figure S1).

The Rotterdam Study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam (registration number MEC 02.1015), and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, licence number 1071272–159521-PG). All participants provided written informed consent to participate in the Rotterdam Study and to have their information obtained from treating physicians.

Assessments

Assessment of chronic airway diseases

Trained paramedic personnel performed pre-bronchodilator spirometry using a Master Screen PTF Pro spirometer (CareFusion, Houten, the Netherlands) according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines [8]. Regarding chronic airway diseases, we identified participants with COPD or asthma before or at the time of the dual-energy radiograph absorptiometry exam (DXA). COPD was defined by spirometry (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.7). Asthma was diagnosed by a physician, as evidenced by medical records. Asthma–COPD overlap (ACO) cases were defined as asthmatic participants who met the obstructive spirometry definition of COPD. Participants who had restrictive spirometry (FEV_1 or FVC <80% pred and FEV_1/FVC ⩾0.7) were classified as other lung diseases. Participants with ACO and other lung diseases were excluded from all analyses. If there was no diagnosis of COPD/asthma in the medical records or normal spirometry (FEV_1/FVC ⩾0.7 and FEV_1 ⩾80%) at the time of the DXA scan, participants were assumed to have a normal lung function (without COPD, asthma, ACO or other lung diseases).

Assessment of sarcopenia traits

We defined sarcopenia-phenotypic components according to the updated European Working Group of Sarcopenia in Older People (EWGSOP2) criteria (supplementary table S1). Maximum handgrip strength was obtained from the non-dominant hand after three trials using a hydraulic hand dynamometer

(Fabrication Enterprises Inc., White Plains, NY, USA). Low handgrip strength was defined as <27 kg for males and <16 kg for females [3]. Lean mass was measured using an iDXA total body-beam densitometer (GE Lunar Corp, Madison, WI, USA), and each scan was analysed with enCORE software V13.6. The sum of the lean mass from the upper and lower limbs is called appendicular lean mass (ALM). ASMI was calculated as ALM divided by the height squared (m^2). Low lean mass was classified as an ASMI of <7.0 $kg \cdot m^{-2}$ for males and <5.5 $kg \cdot m^{-2}$ for females [3].

Assessment of OCS use

Information about the total number of OCS prescriptions was obtained through linkage with the pharmacies serving the Ommoord area, which has been monitored since January 1991. OCS was classified as never and ever use. If a participant had received at least one prescription for OCS between the start of the study and the index date (DXA measurement date), he/she was defined as ever-OCS user. Participants who did not have OCS exposure were considered as never-OCS users.

The duration of OCS was calculated as the total days of use between the start of the study and the DXA date. Despite the unclear association between the duration of OCS treatment and the occurrence of muscle dysfunction, some studies have shown that cumulative use of OCS for >90 or 120 days is associated with general adverse effects, as well as on peripheral muscle [24, 25]. Therefore, the duration was categorised into three groups: 0 days, 1–119 days, and ⩾120 days. The higher cut-off of 120 days was chosen due to its clinical relevance in previous studies [24–26]. Subjects with implausible data on OCS duration (>5000 days) were excluded [17]. Furthermore, a frequency–response relationship was indirectly investigated by categorising the total number of OCS prescriptions prior to undergoing the DXA scan into three groups: 0, 1–9 and ⩾10 prescriptions.

Assessment of covariates

For each participant in this study, we retrieved information on the following variables: age at time of DXA scan; sex; smoking status (never, current and former); smoking pack-years (years smoked by daily number of smoked cigarettes divided by 20); and body mass index (weight (kg) divided by height (m) squared). Total body fat percentage (fat %) was calculated as total fat mass (kg) divided by weight (kg) multiplied by 100. Estimated glomerular filtration rate (eGFR) was calculated with calibrated creatinine values using the equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and expressed as $mL \cdot min^{-1}$ per 1.73 m^2. The comorbidity count distinguished none, one, and two or more comorbidities (supplementary table S2).

Protein intake was extracted from the daily energy intake ($g \cdot kcal^{-1}$) adjusted for body weight. Physical activity (PA) levels were assessed using a validated adapted version of the Longitudinal Aging Study Amsterdam (LASA) Physical Activity Questionnaire (LAPAQ) and expressed in metabolic equivalent of task (MET)-hours per week.

Statistical analyses

We explored the differences in baseline characteristics between never- and ever-OCS, using a t-test or Mann–Whitney test for continuous variables according to their distribution. Categorical variables were compared by use of χ^2 tests. We investigated the association of handgrip and ASMI, and the use of OCS at baseline using the step-forward approach as follows. Firstly, in the total population, we focused on the association of handgrip and ASMI as continuous outcomes and the use of OCS as continuous exposure (number of prescriptions) using linear regression models. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for fat %, height and kidney function (eGFR). Model 3 was additionally adjusted for smoking status and the number of comorbidities. Secondly, we re-ran these analyses using the categorised OCS use (never/ever), OCS frequency (0, 1–9 and ⩾10 prescriptions) and duration of OCS use (0 days, 1–119 days and ⩾120 days). Thirdly, effect modification by chronic airway diseases in the association of handgrip strength and ASMI with OCS was confirmed (p for interaction=0.071 and 0.008, respectively). Fourthly, we stratified analyses for COPD and asthma and performed three linear models adjusted for age, sex (model 1) and fat %, height, kidney function (model 2), and smoking status and other comorbidities (model 3).

Finally, in the longitudinal part, we repeated all analyses by restricting to participants with normal handgrip and ASMI at baseline, using handgrip and ASMI at follow-up as the outcome variables. We did separate analyses for the total population as well as COPD and asthma subpopulations.

In addition, we performed multiple sensitivity analyses for the cross-sectional analysis: 1) adjustments for β_2-agonists; 2) lung function FEV_1; 3) smoking pack-years; 4) physical activity; 5) protein intake; 6) oxygen saturation; 7) with exclusion of participants with cancer and eGFR <60 $mL \cdot min^{-1}$ per 1.73 m^2 at baseline.

Missing data for covariates were addressed by performing multiple imputations by chained equations, with 20 imputations with 30 iterations, with the *mice* package for R software [27]. We reported pooled effect results of the imputed datasets. A p-value <0.05 was considered to indicate significance in all analyses. Statistical analyses were carried on R version 1.4.1106 (Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

At baseline, from 7162 participants of the Rotterdam Study, 5054 had interpretable spirometry, reliable sarcopenia traits and OCS data (figure 1). Baseline characteristics of participants with COPD or asthma are presented in supplementary table S3. 779 (15.4%) persons had COPD and 439 (8.7%) had asthma.

Ever-OCS users were older, more frequently female, had a higher fat %, lower protein intake, lower PA, more likely to have two or more comorbidities, and had a higher prevalence of sarcopenia traits than never OCS users (table 1).

Cross-sectional analysis (stage 1)

OCS use (continuously)

Among the total population, for each additional prescription of OCS, handgrip strength decreased by 0.07 kg (95% CI −0.10– −0.03), and ASMI reduced by 0.01 $kg \cdot m^{-2}$ (95% CI −0.011– −0.001), independent of age, sex, fat %, height, kidney function, smoking status and comorbidities.

In the COPD subgroup, each prescription of OCS was associated with reduced handgrip strength (β= −0.08 kg, 95% CI −0.163– −0.003) and ASMI (β= −0.01 $kg \cdot m^{-2}$, 95% CI −0.02– −0.003). We did not observe significant associations between OCS use and both muscle outcomes within asthmatic participants (table 2).

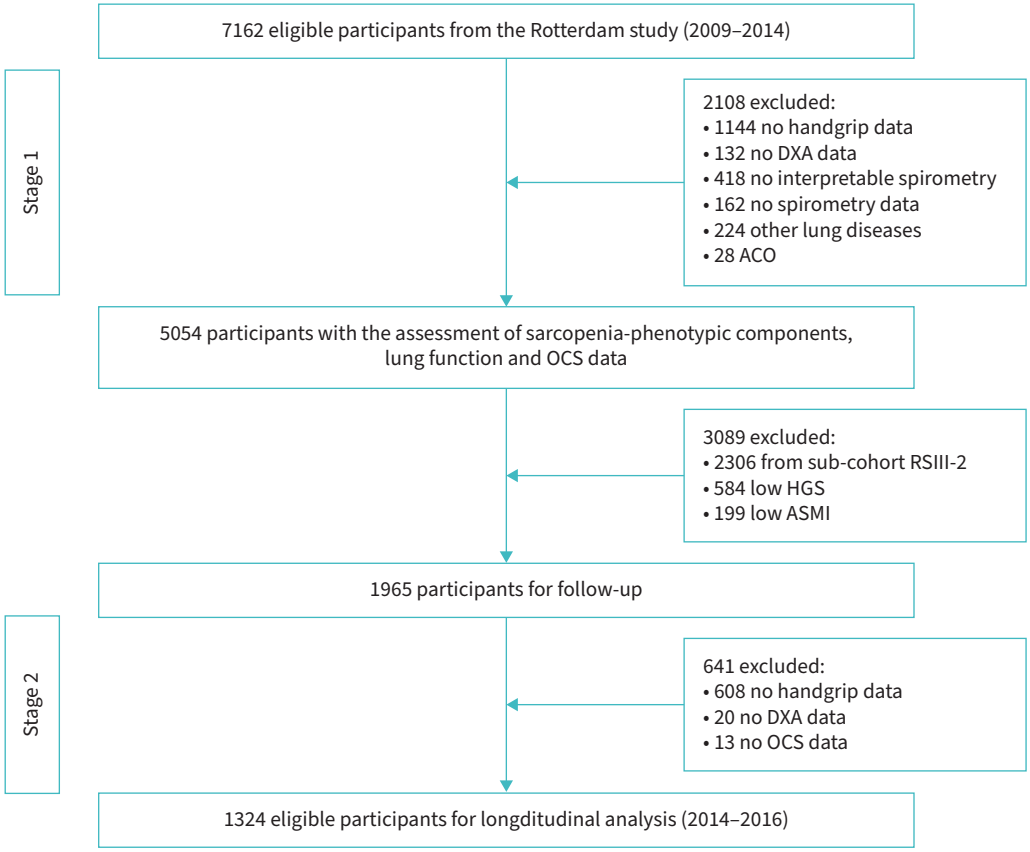

FIGURE 1 Flowchart of the study population. DXA: dual-energy radiograph absorptiometry exam; ACO: asthma–COPD overlap; OCS: oral corticosteroid; HGS: handgrip strength; ASMI: appendicular skeletal muscle index.

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TABLE 1 Main characteristics of the study population at baseline (n=5054) and at follow-up (n=1324)

	Baseline (total)	Never OCS users	Ever OCS users	p-value	Follow-up (total)	Nevers OCS users	Ever OCS users	p-value
Participants n	5054	3356	1698		1324	797	527	
Age years, mean±SD	69.0±8.8	68.3 ±8.7	70.3±9.0	<0.001	78.0±4.8	77.7±4.6	78.3±5.2	0.031
Sex, female, n (%)	2849 (56.4)	1788 (53.3)	1061 (62.5)	<0.001	746 (56.3)	417 (52.3)	329 (62.4)	<0.001
BMI kg·m^{-2}, mean±SD	27.4±4.2	27.2±4.1	27.9±4.5	<0.001	27.6±4.1	27.3±3.8	28.1±4.4	<0.001
Fat %, mean±SD								
Male	31.0±5.5	30.7±5.4	31.7±5.7	<0.001	31.7±5.4	31.3±5.4	32.5±5.6	0.012
Female	40.0±6.1	39.7±6.1	40.6±6.1	<0.001	39.5±5.9	39.3±5.9	39.9±5.8	0.164
Protein intake g·kg^{-1}·day^{-1}, mean±SD	1.10±0.38	1.11±0.40	1.08±0.39	0.039	na	na	na	na
PA[#], MET-hours·week^{-1}, median (IQR)	42.5 (17.3–81.2)	44.7 (18.0–83.3)	37.6 (15.6–76.4)	0.024	39.5 (16.5–72.5)	40.0 (16.9–74.2)	39.1 (15.3–70.6)	0.266
Current smoker[#], n (%)	610 (12.1)	378 (11.3)	232 (13.7)	0.027	76 (5.7)	46 (5.8)	30 (5.7)	0.095
Smoking pack-years, median (IQR)	5.0 (0.0–22.8)	4.3 (0.0–21.0)	6.8 (0.0–27.0)	<0.001	4.5 (0.0–23.5)	3.5 (0.0–22.0)	7.0 (0.0–26.4)	0.017
FEV_1 % predicted, mean±SD	98.7±17.7	100±16.4	95.1±19.6	<0.001	99.2±18.2	100.5±17.9	97.4±18.6	0.005
FEV_1 <80%, n (%)	621 (12.3)	319 (9.5)	302 (17.8)	<0.001	148 (12.6)	75 (10.7)	73 (15.3)	0.0241
COPD, n (%)	779 (15.4)	457 (13.6)	322 (19.0)	<0.001	146 (11.0)	82 (10.3)	64 (12.1)	<0.001
Asthma, n (%)	439 (8.7)	150 (4.5)	289 (17.0)	<0.001	112 (8.5)	34 (4.3)	78 (14.8)	<0.001
eGFR[#] mL·min^{-1} per 1.73 m^2, mean±SD	75.8±14.7	76.2±14.5	74.9±15.1	0.006	na	na	na	na
O_2 saturation[#] %, median (IQR)	97.0 (96–97)	97.0 (96–98)	96.0 (96–97)		na	na	na	na
Number of comorbidities, n (%)				<0.001	na	na	na	na
0	374 (7.4)	287 (8.6)	87 (5.1)	<0.001				
1	1313 (26.0)	979 (29.2)	334 (49.7)					
⩾2	3154 (62.4)	1974 (58.8)	1180 (69.5)					
β_2-agonist, n (%)								
Never	4803 (95.0)	3301 (98.4)	1502 (88.5)	<0.001	1230 (95.6)	765 (98.7)	465 (90.8)	<0.001
Ever	251 (5.00)	55 (1.6)	196 (11.5)		57 (4.4)	10 (1.3)	47 (9.2)	
Handgrip strength kg, mean±SD								
Male	37.1±8.8	37.6±8.6	35.7±9.2	<0.001	32.3±7.0	32.9±6.9	31.2±6.9	0.006
Female	22.1±5.8	22.6±5.6	21.4±5.9	<0.001	19.5±4.5	19.4±4.3	19.6±4.7	0.651
Low handgrip strength, n (%)	584 (11.6)	317 (9.4)	267 (15.7)	<0.001	250 (18.9)	143 (17.9)	107 (20.3)	0.283
ASMI kg·m^{-2}, mean±SD								
Male	8.3±1.0	8.4±0.9	8.2±1.0	0.010	8.0±0.8	8.0±0.7	8.1±0.8	0.624
Female	6.9±0.9	6.8±0.9	6.9±0.9	0.187	6.7±0.8	6.7±0.8	6.8±0.9	0.166
Low ASMI, n (%)	281 (5.6)	168 (5.0)	113 (6.7)	0.019	71 (5.4)	44 (5.5)	27 (5.1)	0.753
Walking speed[#] m·s^{-1}, mean±SD	1.2±0.20	1.2±0.20	1.2±0.20	<0.001	1.1±0.2	1.1±0.2	1.1±0.2	0.717
Low walking speed, n (%)	116 (2.3)	63 (1.9)	53 (3.1)	0.002	43 (5.8)	25 (4.3)	18 (6.6)	0.859

Predicted values of FEV_1 and FVC were calculated using the reference equations obtained from the Global Lung Function Initiative (GLI), which takes into account age, sex, height and ethnicity. OCS: oral corticosteroid; BMI: body mass index; PA: physical activity; FEV_1: forced expiratory volume in 1 s; ASMI: appendicular skeletal muscle index; MET: metabolic equivalent of task; eGFR: estimated glomerular filtration rate; FVC: forced vital capacity. [#]: number (%) of missing values per variable: smoking pack-years: 11 (0.2); oxygen saturation: 2558 (50.6%); walking speed: 1415 (28.0%); physical activity: 598 (11.8%); Type 2 diabetes: 92 (1.8%); hypertension: 1 (0.0%); depression: 23 (0.5%); eGFR: 80 (1.6%); osteoporosis: 105 (2.1%); number of comorbidities: 231 (4.6%); protein intake: 968 (19.2%).

TABLE 2 Associations between use, frequency and duration of OCS and sarcopenia traits (cross-sectional analysis) (n=5054)

Oral corticosteroid use	Handgrip β (95% CI)			ASMI β (95% CI)		
	All population	COPD	Asthma	All population	COPD	Asthma
Participants n	5054	779	439	5054	779	439
Continuous	**−0.07 (−0.100– −0.030)**	**−0.08 (−0.163– −0.003)**	−0.04 (−0.105–0.022)	**−0.010 (−0.011– −0.001)**	**−0.014 (−0.024– −0.003)**	0.003 (−0.007–0.012)
Use of OCS						
Never-users	Ref	Ref	Ref	Ref	Ref	Ref
Ever-users	**−0.48 (−0.84– −0.12)**	**−0.98 (−1.91– −0.06)**	−0.96 (−2.20–0.29)	0.01 (−0.04–0.06)	**−0.14 (−0.27– −0.01)**	0.05 (−0.14–0.23)
Number of OCS prescriptions						
No use	**Ref**	Ref	Ref	Ref	Ref	Ref
1–9 prescriptions	**−0.39 (−0.76– −0.02)**	−0.81 (−1.78–0.16)	−1.05 (−2.34–0.25)	0.02 (−0.03–0.08)	**−0.14 (−0.27– −0.004)**	0.05 (−0.14–0.24)
⩾10 prescriptions	**−1.25 (−2.16– −0.33)**	**−2.01 (−3.91– −0.10)**	−0.22 (−2.16–1.72)	−0.10 (−0.23–0.03)	−0.17 (−0.44–0.09)	0.08 (−0.21–0.36)
Duration of OCS days#						
No use	Ref	Ref	Ref	Ref	Ref	Ref
1–119 days	**−0.42 (−0.82– −0.03)**	**−1.06 (−2.05– −0.07)**	−1.22 (−2.54–0.09)	0.03 (−0.02–0.09)	−0.14 (−0.27–0.001)	0.06 (−0.13–0.26)
⩾120 days	**−0.71 (−1.35– −0.08)**	−1.09 (−2.71–0.53)	−0.01 (−1.71–1.69)	−0.07 (−0.16–0.02)	−0.21 (−0.43–0.02)	0.03 (−0.23–0.28)

Models adjusted for age, sex, fat %, height, eGFR, smoking status and comorbidities. Significant estimates (p<0.05) are indicated in bold. OCS: oral corticosteroid; ASMI: appendicular skeletal muscle index; eGFR: estimated glomerular filtration. #: 10 subjects with OCS duration >5000 days were excluded.

OCS use (never/ever users)

Ever corticosteroid users had a lower handgrip (β= −0.48 kg, 95% CI −0.84– −0.12) and comparable ASMI (β=0.01 kg·m^{-2}, 95% CI −0.04–0.06) than never-users in the total population. COPD ever-OCS users had a lower handgrip of −0.98 kg (95% CI −1.91– −0.06) and a lower ASMI of −0.14 kg·m^{-2} (95% CI −0.27– −0.01) compared to COPD never-OCS users. No significant associations between OCS use and muscle outcomes were observed within asthmatic participants (figure 2).

Frequency and duration of OCS

In the total study population, participants with 1–9 and ⩾10 OCS prescriptions had lower handgrip strength (β= −0.39 kg, 95% CI −0.76– −0.02; and β= −1.25 kg, 95% CI −2.16– −0.33, respectively) and comparable ASMI (β= −0.10 kg·m^{-2}, 95% CI −0.23–0.03) than those without OCS prescriptions (table 2). COPD with ⩾10 prescriptions of OCS had lower handgrip strength (β= −2.01 kg, 95% CI −3.91– −0.10) and not significantly lower ASMI (β= −0.17 kg·m^{-2}, 95% CI −0.44–0.09) than those without OCS use. There were no significant associations between OCS use and handgrip strength or ASMI in participants with asthma (table 2).

Participants with 1–119 and ⩾120 days OCS use had lower handgrip strength (β= −0.42 kg, 95% CI −0.82– −0.03; and β= −0.71 kg, 95% CI −1.35– −0.08, respectively) than non-OCS users. Participants with COPD with 1–119 days of OCS had lower handgrip strength (β= −1.06 kg, 95% CI −2.05– −0.07)

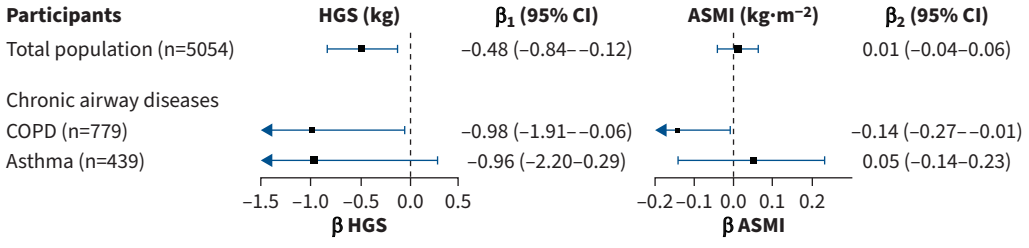

FIGURE 2 Association between oral corticosteroid use (never *versus* ever) and handgrip strength (HGS) and appendicular skeletal muscle index (ASMI) at baseline, adjusted for sex, age, height, fat %, estimated glomerular filtration rate, smoking status and comorbidities.

compared to COPD never-OCS users, though this lower handgrip strength was no longer significant for COPD participants with ⩾120 days OCS use (p=0.1861). The association of OCS use and ASMI was small and not significant in all populations (table 2).

Longitudinal analysis (stage 2)

1965 participants free of sarcopenia traits at baseline were followed for a median of 5.6 years, and 1324 (67.2%) subjects had sarcopenia measurements with complete OCS data (figure 1).

OCSs use (continuously)

In the total population, for each prescription of OCS, the handgrip strength decreased by 0.05 kg (95% CI −0.09– −0.01), and 0.18 kg (95% CI −0.29– −0.06) in the subgroup of COPD. We did not observe a significant association of OCS use with muscle outcomes among asthmatic participants.

OCSs use (never/ever users)

Only among participants with COPD, ever-OCS users developed lower handgrip strength (β= −1.64 kg, 95% CI −2.87– −0.40) but not significantly lower ASMI (β= −0.05 $kg \cdot m^{-2}$, 95% CI −0.20–0.10) compared to never-users. Handgrip and ASMI were not significantly different in the total population or asthma who ever use OCS in comparison to never use (figure 3).

Frequency and duration of OCS

Similarly, only COPD participants who had ⩾10 OCS prescriptions developed significantly lower handgrip strength (β= −3.64 kg, 95% CI −6.57– −0.72) and lower ASMI (β= −0.33, 95% CI −0.68– −0.02) than those who had no OCS prescriptions. Also in participants with COPD, 1–119 days of OCS use was significantly associated with lower handgrip strength during follow-up (β= −1.51 kg, 95% CI −2.87– −0.15) but not with ASMI (β= −0.02 $kg \cdot m^{-2}$, 95% CI −0.18–0.15) compared to no OCS use (table 3).

In the total population or participants with asthma, the associations of frequency and duration of OCS with handgrip strength or ASMI were smaller or similar when compared to no OCS prescriptions.

Sensitivity analysis

When additionally adjusted for β_2-agonists, the effect estimates of OCS as continuous (β= −0.06, 95% CI −0.10– −0.02) or categorical exposure (β= −0.41, 95% CI −0.78– −0.44) on handgrip strength did not substantially change, but significance was lost in the COPD subgroup (β= −0.08, 95% CI −0.16–0.01 or β= −0.91, 95% CI −1.91–0.08), similarly to ASMI (supplementary tables S4, S5).

Adjustments for FEV_1 maintained similar results when OCS was treated as continuous exposure. When stratified by FEV_1, among the COPD subpopulation, OCS ever-users with FEV_1 <80% had a significantly lower handgrip strength (β= −1.72, 95% CI −2.89– −0.55) than no users (supplementary table S6).

Results remained similar after extra adjustments for smoking pack-years, physical activity, protein intake and oxygen saturation (supplementary tables S4, S5 and S7) as well as after exclusion of participants with cancer and eGFR <60 $mL \cdot min^{-1}$ per 1.73 m^2 (supplementary table S8).

Results for longitudinal analyses did not substantially change after multiple adjustments (supplementary tables S9–10).

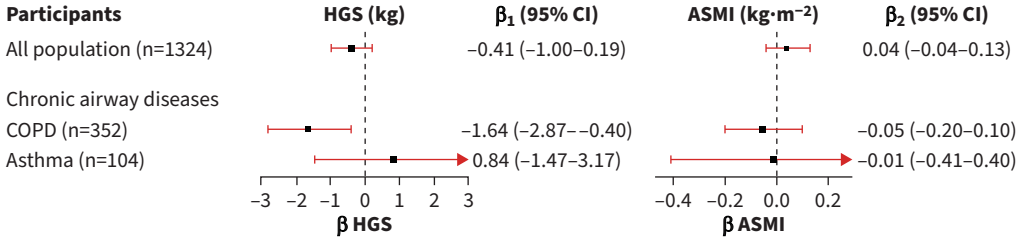

FIGURE 3 Association between oral corticosteroid use (never *versus* ever) and handgrip strength (HGS) and appendicular skeletal muscle index (ASMI) at follow-up time, adjusted for sex, age, height, fat %, estimated glomerular filtration rate, smoking status and comorbidities.

TABLE 3 Associations between use, frequency and duration of OCS and sarcopenia traits (longitudinal analysis) (n=1324)

Oral corticosteroid use	Handgrip β (95% CI)			ASMI β (95% CI)		
	All population	COPD	Asthma	All population	COPD	Asthma
Participants n	1324	352	104	1324	352	104
Continuous	**−0.05 (−0.09– −0.01)**	**−0.18 (−0.29– −0.06)**	−0.03 (−0.08–0.14)	−0.004 (−0.010–0.002)	−0.010 (−0.024–0.003)	0.006 (−0.013–0.025)
Use of OCS						
Never-users	Ref	Ref	Ref	Ref	Ref	Ref
Ever-users	−0.41 (−1.00–0.19)	**−1.64 (−2.87– −0.40)**	0.84 (−1.47–3.17)	0.04 (−0.04–0.13)	−0.05 (−0.20–0.10)	−0.01 (−0.41–0.40)
Number of OCS prescriptions						
No use	Ref	Ref	Ref	Ref	Ref	Ref
1–9 prescriptions	−0.29 (−0.92–0.32)	**−1.43 (−2.70– −0.160)**	0.97 (−1.46–3.41)	0.04 (−0.04–0.13)	−0.02 (−0.17–0.13)	−0.02 (−0.45–0.40)
⩾10 prescriptions	−1.37 (−2.78–0.05)	**−3.64 (−6.57– −0.72)**	0.47 (−2.78–3.73)	−0.12 (−0.32–0.09)	**−0.33 (−0.68– −0.02)**	0.04 (−0.53–0.61)
Duration of OCS (days)						
No use	Ref	Ref	Ref	Ref	Ref	Ref
1–119 days	−0.43 (−1.09–0.23)	**−1.51 (−2.87– −0.15)**	0.76 (−1.72–3.25)	0.04 (−0.05–0.14)	−0.02 (−0.18–0.15)	−0.06 (−0.49–0.38)
⩾120 days	−0.35 (−1.28–0.59)	−1.94 (−3.91–0.03)	1.05 (−1.95–4.05)	−0.01 (−0.14–0.12)	−0.14 (−0.38–0.09)	0.09 (−0.43–0.61)

Model 3: adjusted for age, sex, height, fat %, eGFR, smoking status and the number of comorbidities. Significant estimates (p<0.05) are indicated in bold. OCS: oral corticosteroid; ASMI: appendicular skeletal muscle index; eGFR: estimated glomerular filtration.

Discussion

From this population-based study, we can make four main conclusions. First, participants from the general population who ever used OCS had lower handgrip strength than those who never used. Second, this association is stronger in those who had ⩾10 OCS prescriptions. Third, the association of OCS use and handgrip was more pronounced for people with COPD but not different for people with asthma. These results remained consistent across a wide range of sensitivity analyses. Finally, in those with COPD free of sarcopenia traits at baseline, OCS use was associated with reduced HGS (but not with reduced ASMI) after 5.6 years of follow-up.

This study provides additional value to the previous studies by presenting data on the effect of OCS on muscle function at a population-based level and specifically in a population with well-defined chronic airway disease. Low handgrip strength is a primary criterion for sarcopenia, and it is a simple, inexpensive and noninvasive test to use in clinical practice [12]. Moreover, the SARC-F questionnaire (strength, assistance walking, rising from a chair, climbing stairs and falls) is a recommended screening tool for sarcopenia [12].

Understanding the effect of OCS on muscle health may lead to specific recommendations for their use in COPD patients who experience frequent exacerbations [28–30]. While recent treatment guidelines still include a conditional recommendation of OCS in acute COPD or asthma exacerbations, their use should not be for >5–7 days [23, 31]. Glucocorticoids cause insulin resistance by directly inhibiting the glucose transporter 4 protein (GLUT4) and also increase muscle protein breakdown by the activation of the ubiquitin-proteasome system, and the lysosomal systems (autophagy) [28, 30, 32–34]. In our study, asthmatic OCS ever-users with long OCS duration (1–119 days) (n=204/439) had a borderline significant association with low handgrip strength, however, this effect did not further increase in the group with a OCS duration of 120 days and above (n=82/439). By contrast, COPD ever-users showed the greatest effect when having 10 or more prescriptions and had a more consistent association in terms of duration of OCS use with muscle function. This suggests that patients with COPD are more predisposed to the sarcopenia-related complications of OCS when having frequent exacerbations. This might be explained by the fact that OCS primarily affects fast-twitch muscle glycolytic fibres (type II), related to muscle strength, and it is more likely to be present in patients with COPD [35–37].

Important strengths of our study include the large sample size with a long period of follow-up, and the robust data on OCS use, sarcopenia and chronic airway diseases. Before interpreting the results, some

limitations of this study should be acknowledged. First, reversibility testing for spirometry could not be carried out in this population-based study, which may introduce some differential misclassification. Nevertheless, using post-bronchodilator testing to confirm the presence of airflow limitation adds minimal predictive utility over pre-bronchodilator testing [38, 39]. Moreover, we did our best to differentiate asthma from COPD by validating the self-reported cases of asthma according to the medical records. In addition, we would have only underestimated true OCS effects by mislabeling some people with normal post-bronchodilator spirometry as COPD. Second, we might have missed some use of OCS if participants received their OCS prescription reimbursed from another pharmacy outside the area. However, we had all pharmacy data from all nine pharmacies in the residential area of Ommoord, and therefore potential misclassification of the exposure is considered small and would imply that the true effect of OCS might even be higher than that observed in this study. Finally, the vast majority of participants are Caucasian (>90%), limiting the generalizability of these results to other ethnicities.

To conclude, use of OCS was associated with low handgrip strength in the total population and in the subset of people with COPD. Importantly, the association of OCS and handgrip strength was related to the number and duration of prescriptions, and it was greater in COPD than in the general population. Therefore, earlier muscle function evaluation in all OCS users, particularly in those with COPD, may become routine in clinical practice.

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