

Commentary: Prevalence of Three Prominent Corticosteroid Side Effects in a Large Asthma Population by Age, Sex and ICD-10 Asthma Severity with Recommendations for Screening¹

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Article Info

Article Notes

Received: October 29, 2025

Accepted: December 10, 2025

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This article utilizes the Colorado all-payer claims-based database composed of 3.5 million unique patients (January 1, 2017, to June 30, 2020) to identify specific subsets of asthmatics based on age, sex and ICD-10 diagnosis of asthma severity at greater risk for cataracts and two conditions relevant to the practicing orthopedist: corticosteroid induced osteoporosis and corticosteroid induced osteonecrosis of the femur. Fracture rates were not evaluated. Based on the data presented, the article makes recommendations pertinent to specific higher risk asthmatic subsets for osteoporosis screening supplemental to those of the US Preventive Services Task Force and suggests more aggressive diagnostics when osteonecrosis is in the differential of hip pain. The subset data on osteoporosis and osteonecrosis are presented as percent prevalence and relative risk compared with age and sex matched non-asthmatics. No attempt is made to quantify either the potential savings of healthcare dollars or the alleviation of disability and suffering based on the authors' goal of raising awareness towards earlier diagnosis and treatment of these conditions, but a prudent practitioner might conclude that both would be substantial.

An asthma patient's cumulative exposure to corticosteroids is the sum of parenteral, oral and inhaled corticosteroid therapy over the duration of the disease and, definitionally, this cumulative dosing is greater in those with more severe asthma. In our population, there were 209,351 cases of asthma. Fifty seven percent were female. Group percentages by age in years were as follows: 0 to 24 (42.2%), 25 to 34 (12.7%), 35 to 44 (11.5%), 45 to 54 (10.5%), 55 to 64 (12.4%) and 65+ (12.4%). Among the asthmatic cohort, 47% were classified as mild, 19% as moderate, 4% as severe and 30% as unclassified as per ICD-10 physician diagnosis. As an internal control, we determined any exposure to oral corticosteroids within the time parameters of our database and documented increased exposure rates correlating with increased asthma severity by ICD-10 classification as follows: no asthma, 1.32%; mild asthma 4.88%; moderate asthma 9.03%; severe asthma 18.28% ($P < .0001$). There were 7546 patients diagnosed with osteoporosis (3.6 percent of our total cohort of asthmatics) and 461 patients diagnosed with osteonecrosis (0.2 percent of our total cohort of asthmatics). Among severe asthmatics, the percent prevalence of osteoporosis by age and sex category was as follows: females age 0-<25, 0.38%; 25-<35, 0.31%; 35-<45, 1.54%; 45-<55, 2.61%; 55-<65, 10.26%; 65 or older, 18.6% and for males age 0-<25, 0%; 25-<35, 0%; 35-<45, 0.28%;

45-<55, 2.09%; 55-<65, 1.91%; 65 or older, 3.6%. Among severe asthmatics, the percent prevalence of osteonecrosis by age and sex category was as follows: females age 0-<25, 0%; 25-<35, 0.31%; 35-<45, 0.56%; 45-<55, 0.91%; 55-<65, 0.65%; 65 or older, 0.4% and for males age 0-<25, 0%; 25-<35, 0.61%; 35-<45, 0.56%; 45-<55, 0.79%; 55-<65, 0.43%; 65 or older, 0.2%.

The US preventive Services Task Force (USPSTF) recommends bone density screening for osteoporosis in women aged 65 and older or postmenopausal women younger than 65 determined to be at increased risk for osteoporosis by a formal risk assessment tool: *Osteoporosis Risk Assessment Instrument*, *Osteoporosis Index of Risk*, *Osteoporosis Self-Assessment tool*, *Simple Calculated Osteoporosis Risk Estimation and Fracture Risk Assessment Tool (FRAX)*². There are few studies that assess the utility of these risk assessment tools in women under age 65 and one large study called into question the accuracy of these risk assessment tools for women under age 65³. Based on our study data, we proposed that women with an ICD-10 diagnosis of severe asthma receive bone density screening regardless of menopausal status beginning at age 35 to 45 when the prevalence of diagnosed osteoporosis was 1.54% and 8.5 times that of age and sex matched controls with mild or no asthma.

The USPSTF has concluded that current evidence is insufficient to recommend screening for osteoporosis in men³, though a recent expert panel literature review advocated for targeted screening in men⁴. The actual rate of screening among men over 50 with a history of corticosteroid exposure is not available based on published literature. Studies have shown a low rate of bone density screening (between 10% and 20%) in the general population of men over 70 years⁵. Though osteoporosis is less frequent in men, mortality risk after osteoporotic fractures is higher in men. Based on our study data, we proposed bone density screening beginning at age 45 to 55 for men with severe asthma who showed a 2.09% prevalence of osteoporosis, a 10-fold increased in prevalence compared with age and sex matched controls who had mild or no asthma.

Osteonecrosis is a rare condition involving abnormal microcirculation, necrosis, subsequent subchondral bone collapse and progressive secondary arthritis. The most frequent site for osteonecrosis is the femoral head. Corticosteroid therapy has been identified as the most common risk factor for nontraumatic osteonecrosis and risk increases with longer durations and higher doses of corticosteroid therapy. There are no widely accepted screening protocols for asymptomatic patients with a prior or current history of corticosteroid therapy. Localized pain in the hip or thigh worsened by weight bearing is a usual presenting symptom. Early diagnosis and appropriate therapy can prevent progression, loss of hip function and

the need for total hip arthroplasty. Plain films of the hip are normal in the early stages of osteonecrosis. Magnetic resonance imaging (MRI) is the gold standard for early diagnosis of osteonecrosis of the femoral head⁶.

For both males and females with an ICD-10 diagnosed severe asthma, our study showed a marked trend toward increasing prevalence of diagnosed osteonecrosis beginning in the 25 to 35 age group and peaking in the 45 to 55 age group, where the relative risk for females was 10-fold and for males 3-fold compared with age and sex matched non-asthmatics. The prevalence of diagnosed osteonecrosis in mild and moderate asthma was also somewhat higher for both sexes at all ages above 25 years up to 65 years. It should be noted that the prevalence of osteonecrosis for either sex of any asthma severity did not exceed one percent. Based on these cautionary data, we proposed that adult patients of any age with severe asthma and unexplained localized hip pain should be evaluated early with MRI imaging of the hip with the goal of timely intervention for osteonecrosis. We suggested that mild and moderate asthmatics who have previously received short courses of systemic steroids should be evaluated with a higher index of suspicion for osteonecrosis when presenting with persistent hip pain.

The limitations of our claims-based study included lack of access to actual medical records which prevented independent verification of ICD-10 asthma severity classifications and quantification of exposure to systemic corticosteroid therapy. We did not evaluate potentially confounding factors such as concomitant illnesses or other drug therapies. We did not have access to data on race and, based on Colorado demographic characteristics, there might be limitations in the applicability of our conclusions to the general US population. Our data set of insurance claims covered a period of only 3.5 years which could not account for total duration of asthma or longer-term assessments of asthma severity.

The major strengths of our study included the use of a data set comprised of a large population of 3.5 million unique patients representing all third-party payers in the state of Colorado. This data set should represent an inclusive adult population for age, sex, race, lifestyle, healthcare delivery setting and socioeconomic status. The very large size of the population in our database could be expected to minimize any statistical effect of potentially confounding variables. The ICD-10 coding which allowed for provider specification of asthma severity was in use for the entire time period encompassed by our claims-based data set.

Corticosteroids are still the front line of asthma therapy. Vigilance allowing for timely detection of corticosteroid associated osteoporosis or osteonecrosis has more utility than in the past given the recent and ongoing advances in therapeutic interventions that can

stabilize or remediate these conditions. Additionally, corticosteroid sparing biologic agents for the treatment of asthma can be implemented earlier and more proactively in affected patients who might not otherwise be identified as priority candidates for biologic therapies. The expense of increased surveillance and timely initiation of effective interventions for osteoporosis⁷ or osteonecrosis⁸ can be offset by the savings realized through the prevention of disability or more costly treatments arising from a delay in diagnosis. The recent advent of well tolerated and effective biologics, the first truly corticosteroid sparing agents in the treatment of asthma, should significantly reduce the burden of corticosteroid induced orthopedic complications among patients with moderate or severe asthma in the coming decades⁹. We look forward to the realization of this optimistic expectation.

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