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The Troubling Rise of Scurvy: A Review and National Analysis of Incidence, Associated Risk Factors, and Clinical Manifestations

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ABSTRACT

Introduction: In the era of modern medicine, scurvy has been thought of as a rare disease of ancient times because of improved emphasis on diet and nutrition; however, isolated case reports are plentiful. This investigation presents a comprehensive review of scurvy, including an analysis on its rising incidence, with specific focus on its orthopaedic manifestations and commonly associated diagnoses.

Methods: This comprehensive review includes a retrospective analysis of 19,413,465 pediatric patients in the National Inpatient Sample database from 2016 through 2020. Patients with scurvy were identified by the ICD-10 code, and an estimated incidence of scurvy in the inpatient pediatric population was calculated. Concurrent diagnoses, musculoskeletal reports, and demographic variables were collected from patient records. Comparisons were made using analysis of variance or chi-square with Kendall tau, where appropriate.

Results: The incidence of scurvy increased over the study period, from 8.2 per 100,000 in 2016 to 26.7 per 100,000 in 2020. Patients with scurvy were more likely to be younger ($P < 0.001$), male ($P = 0.010$), in the lowest income quartile ($P = 0.013$), and obese ($P < 0.001$). A majority (64.2%) had a concomitant diagnosis of autism spectrum disorder. Common presenting musculoskeletal reports included difficulty walking, knee pain, and lower limb deformity. Burden of disease of scurvy was markedly greater than that of the average inpatient population, with these patients experiencing greater total charges and longer hospital stays.

Conclusion: Clinicians should be aware of the increasing incidence of scurvy in modern medicine. In cases of vague musculoskeletal reports without clear etiology, a diagnosis of scurvy should be considered, particularly if risk factors are present.

Trial registration number: NA.

Vitamin C, or ascorbic acid, is a water-soluble vitamin that plays a key role in the synthesis and maintenance of collagen.[1] Dietary deficiency of vitamin C can result in scurvy, a multisystem disease characterized by defective collagen synthesis, leading to a variety of symptoms including hyperkeratosis, bleeding, bone pain, and poor wound healing.[2,3]

Although mucocutaneous symptoms such as gingival bleeding, corkscrew hairs, and petechiae commonly present in patients with scurvy, musculoskeletal reports are also commonly associated, particularly in the pediatric population.[4,5] Musculoskeletal manifestations of scurvy are varied, and current literature includes reports of bone pain resulting from subperiosteal hemorrhage and hematomas, arthralgias from hemarthrosis, and osteopenia and fractures, particularly involving the metaphysis.[5,6] While some studies report over 80% of pediatric patients with scurvy having a musculoskeletal chief report, such as lower extremity pain, refusal to walk, or inability to bear weight, quantitative data remain limited.[6,7]

The multitude of case reports almost invariably suggests that scurvy is often overlooked in the differential diagnosis of pediatric patients with musculoskeletal pain.[7-9] This is likely due to well-characterized ability of scurvy to masquerade as a number of other more common musculoskeletal or rheumatological conditions such as bone tumors, juvenile idiopathic arthritis, or septic arthritis.[5,10-12] Furthermore, several physicians are unaware of unique presentation of scurvy in the pediatric population and fail to include it on their differential because of its rarity.

Before presenting the epidemiological results of our investigation, the following aims to summarize the findings of recent case reports and provide orthopaedic physicians with a comprehensive resource for understanding the presentation, diagnosis, and treatment of scurvy.

Diagnosis

Often thought of as an outdated diagnosis, scurvy is frequently not included on the list of differential diagnoses for pediatric musculoskeletal reports, which results in delayed diagnosis, increased morbidity, and unnecessarily invasive, costly testing.[5,7,13] The most common musculoskeletal presenting report of patients with scurvy is generalized lower extremity pain.[4-6,14,15] Upper extremity symptoms have been reported but are less common.[16,17] These musculoskeletal symptoms have been theorized as sequelae of subperiosteal or soft-tissue hemorrhage and/or hemarthrosis,[18,19] commonly presenting in the pediatric patient as refusal to walk, inability to bear weight, or an antalgic gait. In infants and young children, lower extremity pain may manifest as a pseudoparalysis. Infants may display the characteristic 'frog leg' position,[13,20] with externally rotated and flexed hips and knees, while older children may present with flexion contractures at the knee.[21]

Additional musculoskeletal manifestations may include swelling of the knee or ankle joints, which may initially be misdiagnosed as septic arthritis or other joint pathologies.[16,17] In addition, in advanced disease, skeletal growth abnormalities, delayed bone age,[14,16] or beading at the costochondral joints, known as the 'scorbutic rosary,' may be observed.[18] Spontaneous fracture may occur, and this should raise suspicion for scurvy, particularly when these fractures show inadequate or delayed healing.[22]

Mucocutaneous symptoms, such as gingival bleeding, corkscrew hairs, and petechiae, are commonly associated with scurvy (Figure 1).[14,23] Perifollicular hemorrhage and follicular hyperkeratosis, particularly of the lower extremity, may occur and are considered pathognomonic.[19] Other potential signs and symptoms include psychomotor restlessness, muscular weakness, irritability, excessive fatigue, and failure to thrive.[22,24-26] Thus, a young patient with scurvy may present with chief reports including rash, easy bruising, easy bleeding, fussiness in infant/toddler, generalized weakness/fatigue, or appetite/gastrointestinal disturbances. In addition, physicians should be aware that up to 80% of patients with scurvy may have concomitant iron-deficiency anemia, likely due to associated bleeding and potentially decreased iron absorption.[13,19] Iron-deficiency anemia may also be a manifestation of a poor diet and other co-occurring nutritional deficiencies.[3,11,19]

Radiological Findings

Radiographs often reflect vitamin C's role in collagen synthesis, yielding common findings of subperiosteal hemorrhages, cortical irregularities, metaphyseal bands or fraying, physeal widening, and osteopenia.[16,27,28] More specific findings include the Wimberger ring sign, rarefaction in the Trümmerfeld zone, Pelkan spurs, and the white line of Frankel (Figure 2).[13,16] However, in a case series by Pan et al,[6] two of nine patients did not have any of these pathognomonic radiographic findings, highlighting their low sensitivity. Therefore, the lack of

Figure 1

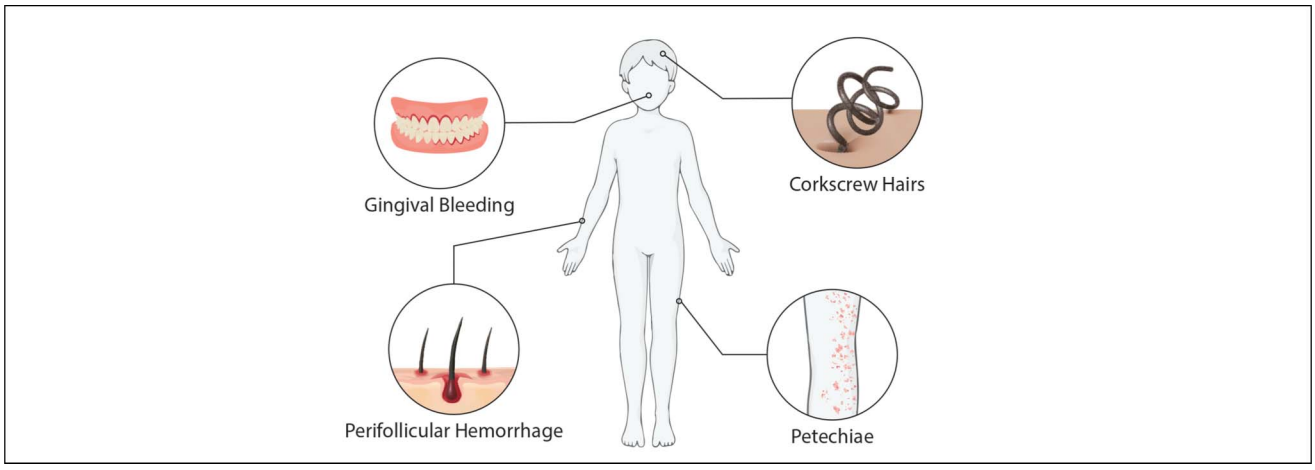


Illustration demonstrating the classical mucocutaneous findings of scurvy including gingival bleeding, perifollicular hemorrhage, petechiae, and corkscrew hairs.

these signs is not sufficient to exclude scurvy from a differential.

Advanced imaging, namely MRI, may reveal diffuse bone marrow edema or subperiosteal fluid[11,29] (Figure 3). MRI may aid in the diagnosis if other imaging and laboratory findings are inconclusive, helping to distinguish scurvy from other marrow infiltrative disorders.[29,30] Alternative imaging modalities, such as ultrasonography, may also be used, often revealing joint effusions and edema about the periosteum and the surrounding soft tissue.[10]

Figure 2

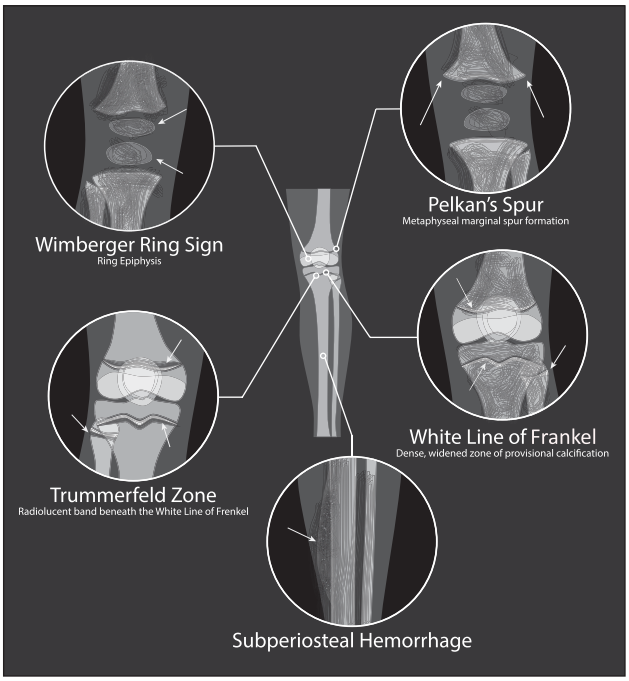


Illustration demonstrating radiographic signs of scurvy. The classic radiological signs of scurvy illustrated on a plain knee radiograph include the Wimberger ring sign, Trümmerfeld zone, subperiosteal hemorrhage, the white line of Frankel, and Pelken spur.

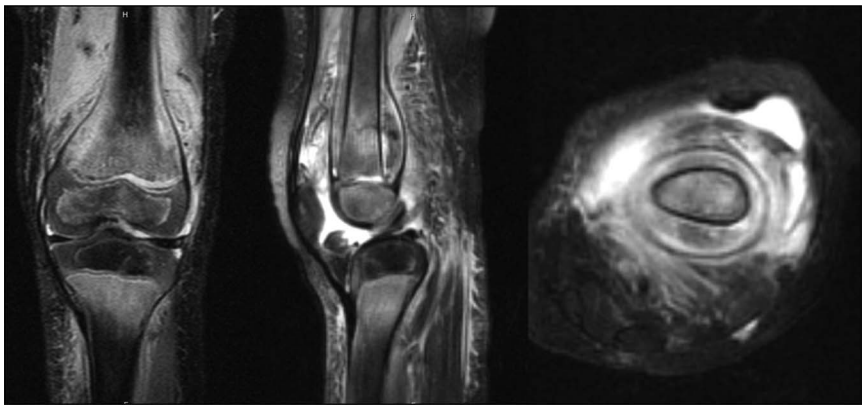
Treatment

While diagnosis may prove challenging, treatment of scurvy is simple, consisting of vitamin C supplementation. Pediatric patients are treated with 100 to 300 mg daily and adults with 500 to 1000 mg daily for 1 month or until full symptom resolution.[13] This treatment regimen is often easily achieved through multivitamin supplementation and typically highly effective with most patients recovering without sequelae.[9,10,29] However, because most children develop scurvy as a result of severe food selectivity, long-term nutritional supplementation, nutritionist consultation, and dietary changes may be necessary to prevent recurrence.[9]

In the setting of more advanced disease and severe musculoskeletal manifestations such as fracture or physeal separation, orthopaedic intervention is warranted. In cases of pathologic fracture secondary to scurvy, conservative treatment of closed reduction and immobilization should be attempted, in conjunction with vitamin C supplementation. In rare cases of delayed union, open reduction may be indicated.[13,17]

Despite numerous case reports of pediatric scurvy in the literature, epidemiological data on its incidence in the United States have yet to be sufficiently identified.

Figure 3



Radiographs demonstrating scurvy-related subperiosteal hemorrhage visualized on MRI. Images courtesy of Boston Children's Hospital.

Therefore, this study aims to assess the incidence of scurvy in the inpatient pediatric population with utilization of a large, validated national database. As a secondary aim, analysis of commonly associated diagnoses is conducted to identify risk factors, which may aid in the diagnosis of scurvy.

Methods

Data Source and Collection

This retrospective review queried the Healthcare Cost and Utilization Project National Inpatient Sample, from 2016 to 2020. The National Inpatient Sample is a nationally representative, weighted sample of approximately 20% of all inpatient visits, enabling us to extrapolate incidence across the entire pediatric inpatient population. All patients younger than 18 years were included in our analysis. Demographic data, including age, sex, race and ethnicity, household income level, and insurance status, were identified using patient records. Next, ICD-10 codes from each patient's single hospitalization were drawn, and those with a diagnosis of scurvy were identified. Concurrent diagnoses, musculoskeletal and otherwise, were further recorded using ICD-10 codes.

Statistical Analysis

Study population demographics were compared with those of the remaining pediatric inpatient population using analysis of variance or chi-square with Kendall tau, where appropriate. *P*-values of 0.05 or less were considered significant. Categorical variables were reported as counts and proportions. Continuous variables were reported as means with standard deviations. All statistical analyses were conducted using R Foundation for Statistical Computing software version 4.20 with the Python package.

Results

Incidence and Demographics

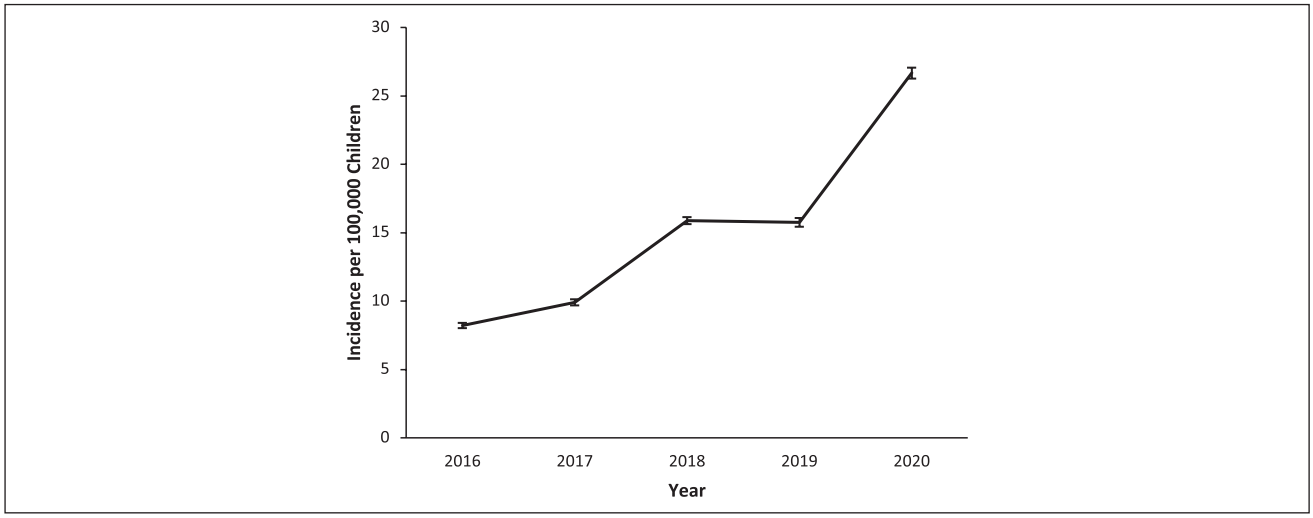
A total of 19,413,465 pediatric patients were identified and included in our analysis. A total of 265 patients with scurvy were identified. Throughout our study period, the incidence of scurvy increased from 8.2 (SE = 0.2) per 100,000 children in 2016 to 26.7 (SE = 0.4) per 100,000 in 2020 (Figure 4).

Population demographics are provided in Table 1. Of those with scurvy, the mean age was 2.15 (SD=4.78) years, 185 patients (69.8%) were male, 95 (36.5%) had a household income in the lowest quartile, and 75 (28.8%) had a household income in the highest quartile. Younger age ($P < 0.001$), male sex ($P = 0.010$), and socioeconomic status in the lowest quartile ($P = 0.013$) were significantly associated with a diagnosis of scurvy. No notable associations were observed between scurvy diagnosis and race, residential setting (urban/rural), or payer.

Concurrent Diagnoses

A number of concurrent diagnoses were common in the scurvy population (Table 2). A total of 170 (64.2%) held a diagnosis of autism spectrum disorder (ASD). Fifteen (5.7%) were diagnosed with cerebral palsy. One hundred thirty-five (50.9%) had a concomitant vitamin D deficiency. One hundred sixty-five (62.3%) had a diagnosed anemia. Ninety (33.6%) had a documented disorder of the gingiva. Twenty (7.6%) had obesity and 10 (3.8%) had morbid obesity (Table 1), both

Figure 4



Graph demonstrating the incidence of scurvy, by year, per 100,000 children. Incidence per 100,000 children (standard error) by year is as follows: 8.21 (0.20) in 2016; 9.90 (0.23) in 2017; 15.89 (0.25) in 2018; 15.74 (0.32) in 2019; 26.67 (0.41) in 2020.

significantly greater than the inpatient population ($P < 0.001$).

Regarding musculoskeletal disorders, 55 patients (20.8%) in the study population had pain in the lower extremity, 35 (13.2%) had a documented acquired deformity of the lower limb, and 30 (11.3%) had a diagnosis indicating difficulty walking (Table 2).

Burden of Illness

Patients in the study group and the hospital system experienced markedly greater burden of illness, as compared with those without scurvy (Table 3). In addition, compared with those without, patients with scurvy had a longer average length of stay (10.83 versus 4.05 days, $P < 0.001$), greater average cost of hospitalization ($163,415.90 versus $30,552.73, $P < 0.001$), and increased rate of adverse discharge, defined as any nonhome discharge (15.1% versus 2.9%, $P < 0.001$).

Discussion

Although scurvy remains rare in the modern United States, we report that the incidence of scurvy in the inpatient pediatric population has steadily increased from 8.2 per 100,000 in 2016 to 26.7 per 100,000 in 2020. Populations found to be at increased risk for the development of scurvy include those of male sex and children with families in the lowest income quartile. In patients with scurvy, concomitant diagnoses of ASD, cerebral palsy, vitamin D deficiencies, anemia, gingival disease, and obesity were common.

At-Risk Populations

Particular patient populations may be at increased risk of developing scurvy, particularly those with an elevated risk of nutritional deficiency due to biological, psychological, or environmental factors.

The vast majority of case reports in recent years have involved children with ASD or other neurodevelopmental disorders.[9,31,32] This is thought to be associated with extreme food selectivity, which predisposes patients to nutritional deficiencies.[3,9,14] This was reflected in our study because a majority (64.15%) of patients with scurvy were found to have a concomitant diagnosis of ASD. The association between ASD and scurvy may explain several other associations observed in our sample, namely the male preponderance and increased rates of obesity found in our study population. Males are 3x more likely than females to be diagnosed with ASD.[33] Furthermore, children with ASD are more likely to be overweight.[34]

Although not explored in this study, additional diagnoses such as eating disorders, end-stage renal disease, avoidant restrictive food intake disorder, celiac disease, inflammatory bowel disease, and behavioral food selectivity may also increase risk of scurvy.[35-37] Environmental factors such as lack of access to affordable, nutrient-dense foods may also pose a risk for the development of nutritional deficiencies, including scurvy. Such an association may help to contextualize the increased rates of obesity and low-income quartile among those with scurvy. This emphasizes the importance of addressing the social determinants of health,

Table 1. Demographic Data

Characteristic	Scurvy (n = 265)	Inpatient Population (n = 19,413,465)	*P*
Age: mean (SD)	**2.15 (4.78)**	**8.26 (4.87)**	**<0.001**
Sex			0.010
Male	185 (69.8%)	9,919,315 (51.1%)	
Female	80 (30.2%)	9,485,505 (48.9%)	
Self-reported race			0.61
Asian or Pacific Islander	0 (0.0%)	908,709 (4.7%)	
Black	40 (15.1%)	2,815,749 (14.5%)	
Hispanic	55 (20.8%)	3,612,958 (18.6%)	
White	125 (47.2%)	9,006,994 (46.4%)	
Other	45 (17.0%)	3,069,054 (15.8%)	
Household income quartile			0.14
0-25th percentile	95 (36.5%)	5,603,832 (29.2%)	0.013
26th-50th percentile	35 (13.5%)	4,860,912 (25.3%)	
51st-75th percentile	55 (21.2%)	4,664,067 (24.3%)	
76th-100th percentile	75 (28.8%)	4,087,493 (21.3%)	
Body mass index			
Obese	20 (7.6%)	173,585 (0.9%)	<0.001
Morbidly obese	10 (3.8%)	38,875 (0.2%)	<0.001
Residential setting			0.70
Rural	20 (7.7%)	1,068,788 (5.5%)	
Urban	240 (92.3%)	18,286,337 (94.5%)	
Payer			0.25
Medicaid	150 (56.5%)	9,360,726 (48.3%)	
Medicare	5 (1.9%)	58,005 (0.3%)	
Private insurance	100 (37.7%)	8,563,255 (44.2%)	
Self-pay	5 (1.9%)	812,674 (4.2%)	
No charge	0 (0.0%)	13,605 (0.1%)	
Other	5 (1.9%)	574,705 (3.0%)	

both in the diagnosis and treatment of patients with scurvy.

Another associated demographic factor was markedly younger age. The presence of this, or any of the above predisposing conditions, should prompt physicians to consider scurvy in a child presenting with musculoskeletal symptoms and warrants investigation into the patient's dietary habits. Consideration of daily vitamin C supplementation may also be appropriate in the aforementioned populations, as to decrease the risk of developing scurvy.

Burden of Care

Results show that scurvy places a sizable burden on patients, families, and the hospital system as measured by length of stay, cost of hospitalization, and rate of adverse discharges. However, it is important to note that these findings may be confounded by the complexity of these patients' care because of concomitant diagnoses. Nonetheless, these burdens further suggest the importance of readily considering scurvy when forming a differential diagnosis, especially given its available and efficacious treatments.

Limitations

This study was not without limitation. For example, our dataset was analyzed using ICD-10 classifications, which may be susceptible to miscoding or undercoding. Because weight classification was not available for all

Table 2. Concurrent Diagnoses

ICD-10	Diagnosis	Affected Patients (n = 265)
Scurvy		
E.54	Ascorbic acid deficiency	265 (100.0%)
Concurrent diagnoses		
F84.0	Autism spectrum disorder	170 (64.2%)
E55.9	Vitamin D deficiency, unspecified	135 (50.9%)
D50.9, D64.9, D50.0, D63.8,D50.8, D53.9, D53.8	Anemia-nutritional, iron deficiency, unspecified	165 (62.3%)
E43, E46, E44.0, E44.1	Protein-calorie malnutrition	110 (41.5%)
K06.8, K06.1, K05.11, K05.10	Disorders of the gingiva	90 (33.6%)
F41.9	Anxiety disorder, unspecified	60 (22.6%)
G80.9	Cerebral palsy	15 (5.7%)
Musculoskeletal manifestations		
M25.56, M25.57, M79.60, M79.66	Pain in the lower extremity	55 (20.8%)
M21.85, M21.86, M24.56	Acquired deformity of the lower extremity	35 (13.2%)
R26.2	Difficulty walking	30 (11.3%)

patients, it is likely that rates of obesity are underreported in our sample. Therefore, although we cannot report an accurate prevalence of scurvy among children with obesity with confidence, we can be confident in the association between these two diseases. Similarly, musculoskeletal reports, such as joint pain, are likely both underreported and underdocumented. Therefore, our reported counts of musculoskeletal manifestations likely underestimate the true number of patients with these symptoms. Still, our findings show common reports that are consistent with reports in the literature.

Secondly, this study used inpatient data to estimate the incidence of scurvy. As a result, the conclusions must be interpreted in the context of the database available to us and limit the confidence in the generalizability of our findings. We may be underestimating incidence by overlooking patients treated as outpatient; however, this number is likely small because of the rarity of disease, difficulty in diagnosis, and concomitant comorbidities in this population. With that said, this study still represents the most comprehensive epidemiological report on the subject to date.

Finally, it is important to note the potential that the increased incidence reported here is, in part, attributed to increased awareness and testing. With that said, this remains an open question because the total number of patients tested for scurvy each year is unknown.

Conclusion

While often thought of as a historic disease, pediatric scurvy has reemerged as a modern problem, with its incidence more than tripling over the 5-year period in this study (2016 to 2020). This is the first study, to our knowledge, to evaluate scurvy in the US pediatric population using a large national database. Relevant demographic factors associated with scurvy identified in this study include male sex and family income in the

Table 3. Burden of Illness

Characteristic	Scurvy (n = 265)	Inpatient Population (n = 19,413,465)	*P*
Length of stay, days: mean (SD)	10.83 (16.43)	4.05 (9.83)	<0.001
Total charge: mean (SD)	$163,416 (523,078)	$30,552 (138,463)	<0.001
Discharge disposition: N (%)			<0.001
Adverse discharge	40 (15.1%)	561,680 (2.9%)	
Home discharge with care	10 (3.8%)	371,005 (1.9%)	
Routine discharge	215 (81.1%)	18,472,375 (95.2%)	

bottom quartile. Frequently concurrent diagnoses include ASD and obesity. Musculoskeletal symptoms, typically including limb pain or deformity, are common in pediatric scurvy and among the most common presenting reports. It is important for providers to recognize its increasing incidence and keep it in the workup differential, particularly when evaluating a child presenting with unexplained musculoskeletal reports and associated risk factors.

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