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Micronutrient deficiencies in older patients with inflammatory bowel disease are not associated with worse adverse clinical outcome rates

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Abstract

Background Micronutrient deficiencies (MNDs) and age have been previously separately associated with adverse clinical outcomes in patients with inflammatory bowel disease (IBD). However, previous clinical outcomes in older patients with MNDs have been poorly described. We examined the age-related rates of adverse clinical outcomes in patients with 1 or more MNDs.

Methods We conducted a single-institution retrospective cohort study of 204 patients with IBD. Patients were divided into age-related cohorts: 1) younger adults aged 18-59; and 2) older adults aged ≥60 years. Patients were further delineated based upon the presence of zinc, vitamin D, vitamin B12, folate, and iron deficiency. We examined the age-related associations between MNDs and adverse clinical outcomes. Primary outcomes included subsequent corticosteroid use, combined intestinal complication (intra-abdominal abscess, intestinal stricture, internal fistula, perianal disease), IBD-related surgery, IBD-related hospitalization, and a composite clinical outcome. Statistical analyses included the Wilcoxon rank-sum test, chi-squared analysis, Fisher's exact test, and logistic regression.

Results Vitamin D (61.5%), iron (46.4%), and zinc (40.5%) deficiencies were common in older IBD patients, but were not significantly more prevalent. Older patients with 1 or more MNDs did not experience increased rates of adverse clinical outcomes. However, vitamin D, iron, and having multiple MNDs were associated with adverse clinical outcomes in the younger cohort.

Conclusions Vitamin D, iron and zinc deficiencies are common in IBD patients. In younger patients, vitamin D, iron, and multiple MNDs were associated with adverse clinical outcomes, but the same trend was not seen with MNDs in older patients.

Keywords Inflammatory bowel disease, micronutrient deficiency, older patients, Crohn's disease, ulcerative colitis

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Introduction

Patients with inflammatory bowel disease (IBD) are at increased risk for malnutrition [1,2]. Micronutrient deficiency (MND), one form of malnutrition, is common in IBD, occurring in 20-85% of patients [3]. Because of the enteric involvement and diarrhea, Crohn's disease (CD) has a greater incidence of MND than ulcerative colitis (UC) [4]. Sufficient micronutrient levels require adequate dietary intake; therefore, etiologies of deficiency overlap significantly with those of protein and calorie malnutrition.

Since micronutrients also regulate each other's homeostasis, deficiencies can occur concomitantly. Vitamin D deficiency has been associated with higher levels of hepcidin, which impairs enterocyte iron absorption [5]. Zinc acts as important cofactor in enterocyte iron absorption, as well as via modulation of the

divalent metal iron transporter-1 and ferroportin. Likewise, zinc deficiency also has been associated with iron deficiency [6].

Advanced age is an independent risk factor for MND in IBD and non-IBD patients [2,7]. With an aging IBD population, approximately one-third of patients are currently older than 60 years [8,9]. However, data on MNDs in older IBD patients is sparse. Though Juneja *et al* characterized individual vitamin B12, iron, and vitamin D deficiencies in a geriatric IBD population, no study has evaluated other common IBD MNDs, or the interdependency of MNDs [10].

Older IBD patients suffer from both disease and age-related etiologies for MNDs. Several IBD-related factors have been described, including symptoms restricting dietary intake, issues tied to metabolism and gut epithelial function, and iatrogenic causes, mainly due to medications and bowel resection. The severity of MND often coincides with IBD activity and matches the duration of the disease [10]. With aging, comorbidities such as cancers, cardiovascular disease, lung disease, diabetes and neuropsychiatric disease increase and impair nutrient stores, dietary intake and nutrient absorption, via increased catabolism, decreased oral intake, and dysphagia. Hospitalizations due to such comorbidities can lead to interruptions in nutrient intake. Oral health deteriorates with age, leading to difficulties such as dry mouth and impaired mastication that limit dietary intake. Lastly, older adults have increased rates of physical disabilities and disadvantageous social determinants of health that also potentiate poor nutrient intake [2,7].

The association between MNDs in older IBD patients and adverse clinical outcomes is unclear. IBD at an advanced age has been associated with an increased risk of corticosteroid adverse events, intestinal complications, surgeries and hospitalizations [11-16]. Additionally, deficiencies in folate, vitamin B12, vitamin D, iron, and zinc have been tied to increased rates of corticosteroid use, fistulizing disease, perianal disease, surgery, and hospitalizations [1,17-23].

While prior studies showed that MND and advanced age can be independently associated with poor IBD outcomes, we aimed to determine age-associated relationships between MNDs and specific adverse IBD-related outcomes. Additionally, because of the interdependency of MNDs, we sought to examine the relationship between multiple MNDs and adverse IBD-related outcomes.

Patients and methods

We conducted a retrospective cohort study of a single, tertiary-care institution IBD database and corresponding electronic medical records to collect demographic, micronutrient and clinical outcome data between January 2015 and December 2021. The study received approval from the University of Arizona Institutional Review Board. Patients were divided into 2 initial arms based upon their age when they underwent micronutrient testing: 1) younger adults, aged 18-59; and 2) older adults, aged >60 years. Patients were divided into groups based upon the presence or absence of multiple MNDs.

The inclusion criteria specified: more than 1 year of documented follow up; age >17 years; and a diagnosis of CD, UC or IBD-undefined. Exclusion criteria included a medical history of hyperthyroidism, parathyroid disease, chronic kidney disease stage III or greater, pancreatic insufficiency, celiac disease, hemochromatosis, cirrhosis, or bariatric surgery.

Demographic variables collected were age, sex, ethnicity, body mass index (BMI), smoking status, and duration of follow up. IBD characteristics consisted of age at diagnosis, disease duration, Montreal classification and medication history, including corticosteroids, immune modifying agents and other small molecules, and biologics (i.e., tumor necrosis factor [TNF]-α inhibitors, interleukin 12/23 inhibitor, and integrin receptor antagonist). MNDs included were iron (transferrin saturation <20% or ferritin <40 ng/mL), vitamin D (25-hydroxyvitamin D <30 ng/mL), zinc (zinc <0.66 µg/dL), vitamin B12 (vitamin B12 <200 pg/mL), and folate (folate <2.7 ng/mL). Patients were documented as deficient with a single value below these thresholds.

Primary outcomes included subsequent need for corticosteroids, combined intestinal complication (intra-abdominal abscess, intestinal stricture, internal fistula, perianal disease), IBD-related surgery, IBD-related hospitalization, and a composite clinical outcome of any single occurrence of the preceding outcomes. Observation of outcomes began after the first micronutrient serologies for sufficient patients. After the first noted MND, observation of outcomes began for deficient patients.

Statistical analysis

Statistical analyses included the Wilcoxon rank-sum test, chi-squared analysis, Fisher's exact test, and logistic regression. Demographic and disease characteristic continuous variables were summarized as mean ± standard deviation. The Wilcoxon rank-sum test was performed to compare each continuous variable between age groups. Fisher's exact test was performed to compare each categorical variable representing demographics, disease characteristics and medication history between age groups. Fisher's exact test was also performed to compare each MND between age groups. Logistic regression was used to identify demographic, disease characteristic, and medication history variables potentially associated with each MND. Chi-squared analysis was used to compare outcomes between patients with and without MNDs in the total study population. Outcomes were subsequently compared in the 2 initial patient arms and 4 additional subgroups using Fisher's exact test. Outcomes based upon age and number of MNDs were compared using logistic regression.

Results

The study population consisted of 204 adult IBD patients, of whom 134 were younger adults and 70 were older adults

(Supplementary Fig. 1). The mean age was 39.2 years in the younger adult group and 71.6 years in the older adult group, while the mean age of the entire study population was 50.2 years. These 2 cohorts were 56.0% and 54.3% female, respectively. Among the younger and older adult cohorts, 78.4% and 91.4%, respectively, were Caucasian (P=0.019). Mean BMI was 27.3 kg/m^2 for the younger adults, and 26.2 kg/m^2 for the older adults. Younger adults more frequently had never smoked tobacco (78.4% vs. 52.9%, P=0.038). Older adults had a higher rate of former smoking (44.3% vs. 16.4%, P<0.001). Current smoking was uncommon and similar between younger and older adults (5.2% vs. 2.9%). CD was present in 57.5% of the younger adults and 61.4% of the older adults. Disease duration was longer in the older adults (mean 23.1 vs. 12.7 years, P<0.001). Duration of follow up and use of immune suppressing therapies were similar between younger and older adults (Table 1).

The study population was also divided by primary IBD diagnosis, with 125 patients having CD and 79 patients having UC. The mean ages for CD and UC patients were 49.2 and 51.5 years, respectively. Both groups were primarily Caucasian (83.2% CD and 82.3% UC). The mean BMI was 26.7 for CD patients and 27.2 for UC patients. CD and UC patients had similar rates of never smoking, formerly smoking and currently smoking (65.6% vs. 75.9%, 28.0% vs. 22.8%, and 6.4% vs. 1.3%, respectively). Disease duration was similar for CD and UC patients (17.1 vs. 15.0 years). Duration of follow up was also similar for CD and UC patients (3.2 vs. 3.1 years). CD patients most often had ileocolonic (34.4%), followed by ileal (28.8%), colonic (28.0%) and isolated upper (7.2%) disease. Most UC patients had pancolitis (63.3%), followed by proctitis (20.3%) and left-sided colitis (16.5%). CD behavior was most frequently non-stricturing (52.8%), followed by stricturing (29.6%) and penetrating (16.8%). Perianal disease was present in 32.8% of CD patients. Current immunomodulator and biologic use was more common in CD patients (35.2% vs. 13.9%, P<0.001; 62.4% vs. 27.8%, P<0.001; respectively). Prior biologic use was also more common in CD patients (55.2% vs. 26.6%, P<0.001). Prior corticosteroid use was similar amongst CD and UC patients (77.6% vs. 68.4%) (Supplementary Table 1). Further characterization of CD and UC patients by MND and age-specific outcomes was limited by the sample size and did not yield significant results.

While vitamin D (66.8%), iron (48.2%) and zinc (37.4%) deficiencies were common in the total population, folate (1.5%), and vitamin B12 (6.9%) deficiencies were less frequent. Vitamin D (61.5%), iron (46.4%), and zinc (40.5%) deficiencies were common in older adults, though the rates of occurrence were not greater than in younger adults (Table 2). The presence of multiple MNDs (37.7%) was common in the total population. Younger and older adults experienced similar rates of having multiple MNDs (Table 2). Additionally, we examined the co-occurrence of specific MNDs. In the total population, iron and zinc deficiency were associated with one another, and were present in 10.8% of patients (P=0.024). However, while vitamin D deficiency co-occurred with iron (25.9%) and zinc (15.2%) deficiencies, these associations were not statistically significant.

Table 1 Summary of demographics, medication history, and IBD diagnosis in younger adult (18-59 years) and older adult (≥60 years) cohorts

Variable	Younger (n=134)	Older (n=70)	P-value
Mean age (years)	39.2±10.2	71.6±6.9	<0.001
Female sex	75 (56.0%)	38 (54.3%)	0.88
Ethnicity			0.062
Caucasian	105 (78.4%)	64 (91.4%)	0.019
Hispanic	12 (9.0%)	5 (7.1%)	
Other	19 (14.2%)	3 (4.2%)	
Mean BMI (kg/m^2)	27.3±5.9	26.2±4.5	0.50
Smoking			
Never	105 (78.4%)	37 (52.9%)	0.038
Former	22 (16.4%)	31 (44.3%)	<0.001
Current	7 (5.2%)	2 (2.9%)	0.44
Crohn's disease	77 (57.5%)	43 (61.4%)	0.74
Mean disease duration (years)	12.7±7.8	23.1±15.8	<0.001
Mean follow up (years)	3.1±1.5	3.2±1.4	0.30
Current immunomodulator	41 (30.6%)	14 (20.0%)	0.13
Current biologic	68 (50.8%)	31 (44.3%)	0.46
Prior biologic	64 (47.8%)	24 (34.3%)	0.075
Prior corticosteroid	104 (77.6%)	46 (65.7%)	0.094

IBD, inflammatory bowel disease; BMI, body mass index

Table 2 MND rates in younger adult (18-59 years) and older adult (≥60 years) cohorts

Micronutrients	Younger (n=134)	Older (n=70)	P-value
Vitamin D	85 (69.7%)	40 (61.5%)	0.33
Iron	54 (49.1%)	26 (46.4%)	0.87
Zinc	29 (35.8%)	17 (40.5%)	0.70
Vitamin B12	10 (8.6%)	2 (3.5%)	0.34
Folate	2 (2.1%)	1 (2.1%)	>0.99
Number of MND			0.65
0	27 (20.2%)	13 (18.6%)	
1	53 (39.6%)	34 (48.6%)	
2	37 (27.6%)	18 (25.7%)	
3	15 (11.2%)	4 (5.7%)	
4	2 (1.5%)	1 (1.4%)	
>1	54 (40.3%)	23 (32.9%)	0.36

MND, micronutrient deficiency

In the total population, vitamin D deficiency was associated with combined intestinal complication (P=0.005), IBD-related surgery (P=0.043), and the composite clinical outcome (P<0.001). Iron deficiency was associated with a need for corticosteroids (P<0.001), combined intestinal complication (P<0.001), IBD-related surgery (P=0.012), IBD-related hospitalization (P<0.001), and the composite clinical outcome (P=0.006). Zinc deficiency was not associated with adverse

outcomes, though there was a trend towards associations with corticosteroid use, combined intestinal complications, and the composite clinical outcome (Table 3). Vitamin B12 and folate deficiencies occurred at rates insufficient for comparison and for micronutrient-specific outcome analyses.

When compared to older adults, younger adults were more frequently prescribed corticosteroids (36.6% vs. 18.6%, P=0.01), whereas older patients were less likely to have an adverse clinical outcome (25.7% vs. 48.5%, P=0.002) (Table 4). Younger adults with vitamin D deficiency had a worse composite clinical outcome (51.8% vs. 27.5%, P=0.012) (Supplementary Table 2). Younger adults with iron deficiency had more combined intestinal complications (31.5% vs. 7.7%, P=0.024) and a worse composite clinical outcome (64.8% vs. 26.9%, P=0.002) (Supplementary Table 3). Zinc deficiency was not associated with adverse clinical outcomes in the younger adult and older adult cohorts, but there was a trend towards a worse composite clinical outcome in younger adults (Supplementary Table 4).

In all patients, having multiple MNDs was associated with combined intestinal complication (27.3% vs. 7.1%, P<0.001), IBD-related surgery (15.6% vs. 2.4%, P=0.001), and IBD-related hospitalization (26.0% vs. 11.0%, P=0.007) (Table 5). Older adults with multiple MNDs had a better composite clinical outcome than younger adults with multiple MNDs (57.4% vs. 26.1%, P=0.005) (Table 6). Likewise, the remaining clinical outcomes did not occur at higher rates in older adults with multiple MNDs.

Table 3 Summary of clinical outcomes associated with vitamin D, iron and zinc deficiencies for all patients, depicted as P values

Outcome	Vitamin D	Iron	Zinc
Need for corticosteroids	0.522	<0.001	0.171
Combined intestinal complication	0.005	<0.001	0.136
IBD-related surgery	0.043	0.012	0.65
IBD-related hospitalization	0.429	<0.001	0.504
Composite clinical outcome	<0.001	0.006	0.122

IBD, inflammatory bowel disease

Table 4 Summary of clinical outcomes in the younger adult (18-59 years) and older adult (≥60 years) cohorts

Outcome	Younger (n=134)	Older (n=70)	P-value
Need for corticosteroids	49 (36.6%)	13 (18.6%)	0.01
Combined intestinal complication	24 (17.9%)	6 (8.6%)	0.10
IBD-related surgery	11 (8.2%)	4 (5.7%)	0.59
IBD-related hospitalization	23 (17.2%)	11 (15.7%)	0.68
Composite clinical outcome	65 (48.5%)	18 (25.7%)	0.002

IBD, inflammatory bowel disease

Discussion

In a retrospective examination of age-related outcomes in IBD patients with MNDs, vitamin and mineral deficiencies were common. Furthermore, advanced age was not associated with adverse clinical events. Younger adults with vitamin D or iron deficiency, or multiple MNDs, experienced higher rates of adverse clinical outcomes. However, vitamin D (61.5%), iron (46.4%) and zinc (40.5%) deficiencies were still common in older IBD patients. Importantly, our data further clarify the poorly defined epidemiology of MNDs in older IBD patients.

Vitamin D deficiency has been associated with increased disease activity, probably due to its regulation of the innate and adaptive immune system and the promotion of antibacterial proteins [7,18,24-28]. Our findings support vitamin D's association with greater disease activity, manifested by the higher rates of intestinal complications and IBD-related surgeries in vitamin D deficient patients [18-20]. Moreover, iron deficiency has been associated with increased disease activity due to mechanisms of blood loss and inflammatory sequestration [17]. In addition to simple blood loss, iron deficiency's association with all our study's adverse clinical outcomes probably reflects the pervasive mechanisms by which inflammation mediates iron metabolism in IBD.

While age was originally hypothesized to increase rates of adverse outcomes in IBD patients with MND, unique age-related risk factors related to nutritional deficiencies and the effect of immunosenescence may explain the discrepancy in adverse clinical outcomes experienced by the older cohort, despite similar rates of MNDs. The rates of MNDs in the older cohort may not be entirely reflective of IBD activity. Rather, MNDs in this cohort may in part be attributed to age-related risk factors that fell outside of our study's exclusion criteria, including catabolic comorbidities such as chronic cardiac, pulmonary and vascular diseases, and active malignancy. Furthermore, older adults are more prone to dysphagia, poor oral health, and disadvantageous social determinants of health [2,7]. Additionally, immunosenescence causes decreased phagocytic activity in macrophages and enteric dendritic cells,

Table 5 Summary of clinical outcomes by number of MNDs for all patients

Outcome	One or less MND (n=127)	Multiple MNDs (n=77)	P-value
Need for corticosteroids	36 (28.4%)	26 (33.8%)	0.44
Combined intestinal complication	9 (7.1%)	21 (27.3%)	<0.001
IBD-related surgery	3 (2.4%)	12 (15.6%)	0.001
IBD-related hospitalization	14 (11.0%)	20 (26.0%)	0.007
Composite clinical outcome	46 (36.2%)	37 (48.1%)	0.11

MND, micronutrient deficiency; IBD, inflammatory bowel disease

Table 6 Summary of clinical outcomes by number of MNDs for the younger adult (18-59 years) and older adult (≥60 years) cohorts

Outcome	Younger One or less MND (n=80)	Younger Multiple MNDs (n=54)	Older One or less MND (n=47)	Older Multiple MNDS (n=23)	P-value[a]	Int P-value
Need for corticosteroids	28 (35.0%)	21 (38.9%)	8 (17.0%)	5 (21.7%)	0.06	0.85
Combined intestinal complication	6 (7.5%)	18 (33.3%)	3 (6.4%)	3 (13.0%)	<0.001	0.30
IBD-related surgery	2 (2.5%)	9 (16.7%)	1 (2.1%)	3 (13.0%)	0.004	0.93
IBD-related hospitalization	8 (10.0%)	15 (27.8%)	6 (12.8%)	5 (21.7%)	0.04	0.47
Composite clinical outcome	34 (42.5%)	31 (57.4%)	12 (25.5%)	6 (26.1%)	0.005	0.40

[a]Comparisons across the 4 groups based on Fisher's exact test

[b]Testing the interaction effect between age (old vs. young) and total number of deficiencies (>1 vs. ≤1) based on logistic regression, in which fistula and abscess were dichotomized into (abnormal/perianal vs. not)

MND, micronutrient deficiency; IBD, inflammatory bowel disease

which initiate adverse IBD activity via enteric antigen sampling. Macrophages subsequently release less inflammatory TNF-α and interleukins 6, 12, and 23 locally. Impaired dendritic cell phagocytosis hinders antigen presenting activity to naïve T-cells, which is further compounded by decreases in naïve T-cell number, proliferation, and differentiation. The T-cell response is thereby attenuated in the systemic circulation and in its ability to target intestinal tissues, which could lead to less severe downstream IBD activity [29,30]. Older adults may therefore have lower baseline inflammatory disease activity and may not mount a maladaptive immune response with an intensity that would be captured by the adverse clinical outcomes examined in this study.

Provider practice patterns may have also contributed to more favorable rates of specific adverse clinical outcomes in the older IBD patient cohort. Prior exposure to corticosteroids was high in this patient population, irrespective of age, which is consistent with previous findings [13,31]. However, a subsequent need for corticosteroids occurred less often in the older cohort. This may in part reflect patient and provider caution due to corticosteroids' adverse relationship with hypertension, encephalopathy, osteoporosis, fragility fractures, infections, glycemic control, glaucoma and cataracts [11,32]. Additionally, the decision to pursue medical or surgical management for older patients with increased IBD activity is complex. Comorbidities associated with adverse surgical outcomes are more prevalent in older patients and can influence surgical candidacy [13,14,33]. However, the side-effects of medical management with small molecules and TNF-α inhibitors, including infection, heart failure, non-Hodgkin's lymphoma and drug–drug interactions, may also promote definitive surgical management [11,34,35]. Indeed, previously observed IBD-related surgical rates for older patients vary. Older data showed that older IBD patients experienced milder to similar clinical courses; however, a recent meta-analysis demonstrated similar and possibly higher rates of IBD-related surgeries, specifically for UC, in older patients [14,15]. Specific indications and procedures for the spectrum of inflammatory complications, including intra-abdominal abscesses, intestinal strictures, internal fistulae and perianal disease, may also explain the heterogeneous surgical rates observed in older IBD patients. Our observation of similar IBD-related surgical rates in the younger and older cohorts coincides with these previously mixed findings.

Older age also appeared to have a favorable association with IBD-related hospitalizations in this cohort, which reflects previously observed temporal trends associated with the increased use of biologic therapies. Previously, using the Nationwide Inpatient Sample data from 2004, Ananthakrishnan *et al* found in their cross-sectional study that older IBD patients were more likely to be hospitalized and that age was an independent risk factor for mortality. When hospitalized, these patients also experienced greater disease severity, malnourishment, hypovolemia, anemia, and comorbidity-adjusted mortality [14]. Moreover, using the same database, Malarcher *et al* showed that CD-related hospitalization rates for older patients significantly increased from 2003-2013 [36]. However, more recent data from the Center for Medicare and Medicaid, spanning 1997-2017, describe decreasing hospitalization rates for both CD and UC in the older IBD patient population, probably due to the increased utilization of a more diverse biologic therapy armamentarium [37]. Similarly, our older IBD cohort may not have experienced higher rates of IBD-related hospitalizations in part due to this trend, especially given that clinical outcomes were observed between 2015 and 2021.

The epidemiology of MNDs in the older IBD population is poorly defined, since rates of vitamin D, iron and zinc deficiencies have been seldom reported. Our study found vitamin D (61.5%), iron (46.4%) and zinc (40.5%) deficiencies were common in older IBD patients. The previously established rates of vitamin D and iron deficiencies are approximately 15.3-19.4% and 17.6%, respectively [10,20]. The prevalence of zinc deficiency in the older IBD population has yet to be established. Our older cohort's higher rates of vitamin D and iron deficiencies may be explained by less conservative micronutrient cutoff levels and a greater proportion of older IBD patients [10,20].

Our findings importantly shed further light on prevalence of MNDs and associated adverse clinical outcomes in the growing older IBD demographic [8,9]. While adverse

outcomes were present in the older cohort, age alone did not appear to increase their occurrence in the context of one or more MNDs. These observations could inform clinicians routinely monitoring for MND in older IBD patients. For all IBD patients, current guidance from the American Gastroenterological Association and the European Society for Clinical Nutrition and Metabolism suggest screening for MNDs, including vitamin B12, folate, iron, zinc, and vitamin D, at the time of diagnosis, and yearly monitoring thereafter based upon the consensus of expert opinions and common clinical practice [38,39]. With a similar level of evidence, the European Crohn's and Colitis Organization further recommends iron deficiency screening every 3 months for patients with active IBD, as well as folate and vitamin B12 deficiency screening every 3-6 months in high-risk patients with extensive small-bowel disease and/or resection [40]. Current guidelines do not comment on whether routine screening for MNDs improves adverse IBD-related clinical outcomes. Our retrospective results do not suggest that MNDs occur more frequently in older IBD patients, nor that adverse IBD-related outcomes occur more often in older patients with MNDs. Indeed, our findings suggest that older IBD patients do not require more frequent monitoring than the general IBD population for MNDs, and that current expert opinions about screening intervals probably also apply to the older IBD population. Moreover, our retrospective data suggest that monitoring for MNDs may not improve rates of adverse IBD-related outcomes in older patients. Prospective, randomized studies must be conducted to confirm these findings. Screening for MNDs in older IBD patients to mitigate non-IBD-related adverse outcomes is likely still warranted.

The limitations of this study include its retrospective nature, which led to varying rates of screening for specific MNDs, observation of outcomes and duration of disease, despite an equal duration of follow up. Given these variances, older age and presence of MND(s) did not correlate with a single adverse outcome, nor with the composite clinical outcome. Additionally, screening rates for vitamin D, iron and zinc deficiencies were similar between the age cohorts. The patients were also evaluated in a single institution located in the southwest United States of America, which may impact the generalizability of our results. However, the proportion of older IBD patients in our study reflects previously reported proportions [8,9]. Additionally, we did not directly account for disease activity between the 2 cohorts. However, prior corticosteroid and biologic use in our younger and older patients was similar. Lastly, our limited study size did not allow for examination of outcomes based on IBD subtype.

In conclusion, MNDs were present in a majority of IBD patients regardless of age. Deficiencies in vitamin D and iron, and having multiple MNDs, were specifically associated with worse outcomes. However, compared to younger adults, older adults with MNDs did not have higher rates of adverse clinical outcomes.

Summary Box

What is already known:

- Micronutrient deficiencies (MND) are common in patients with inflammatory bowel disease (IBD)
- The IBD population is aging, and 30% of patients are older than 60 years, either having aged with their diagnosis or being diagnosed after this age
- Age is an independent risk factor for MND, owing to comorbid conditions, social determinants of health, and the natural physiology of aging
- The relationship between age, MND, and IBD-related adverse clinical outcomes is currently poorly defined

What the new findings are:

- The majority of IBD patients experienced 1 or more MND, regardless of whether their age was less or greater than 60 years
- Despite similar rates of MNDs, older patients did not experience increased rates of adverse IBD-related outcomes
- The presence of multiple MNDs may be associated with IBD-related surgeries, IBD-related hospitalizations, and intestinal complications, including intra-abdominal abscess, intestinal stricture, internal fistula, and perianal disease

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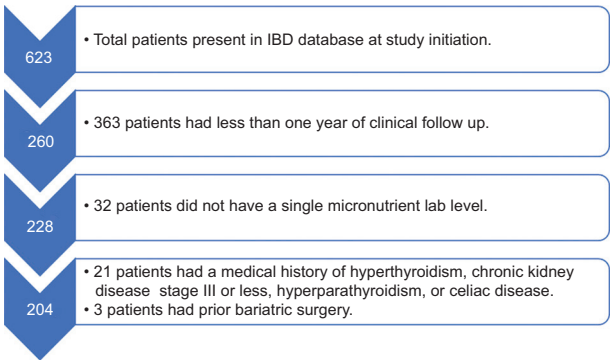
Supplementary material



Supplementary Figure 1 Selection of total patient population
IBD, inflammatory bowel disease

Supplementary Table 1 Summary of demographics, medication history, and IBD diagnosis in Crohn's disease and ulcerative colitis patients

Variable	Crohn's disease (n=125)	Ulcerative colitis (n=79)	P-value
Mean age	49.6±17.5	51.5±18.7	0.46
Female sex	74 (59.2%)	39 (49.4%)	0.88
Ethnicity			
Caucasian	104 (83.2%)	65 (82.3%)	0.86
Hispanic	7 (5.6%)	6 (7.6%)	0.56
Other	14 (12.7%)	10 (12.7%)	>0.99
Mean BMI (kg/m^2)	26.7±5.7	27.2±5.0	0.52
Smoking			
Never	82 (65.6%)	60 (75.9%)	0.12
Former	35 (28.0%)	18 (22.8%)	0.41
Current	8 (6.4%)	1 (1.3%)	0.08
Mean disease duration (years)	17.1±12.4	15.0±11.8	0.23
Mean follow up (years)	3.2±1.5	3.1±1.5	0.64
Disease location			
Ileal	36 (28.8%)		
Colonic	35 (28.0%)		
Ileocolonic	43 (34.4%)		
Isolated upper disease	9 (7.2%)		
Proctitis		16 (20.3%)	
Left-sided colitis		13 (16.5%)	
Pancolitis		50 (63.3%)	
Disease behavior			
Non-stricturing	66 (52.8%)		
Stricturing	37 (29.6%)		
Penetrating	21 (16.8%)		
Perianal disease	41 (32.8%)		
Current immunomodulator	44 (35.2%)	11 (13.9%)	<0.001
Current biologic	78 (62.4%)	22 (27.8%)	<0.001
Prior biologic	69 (55.2%)	21 (26.6%)	<0.001
Prior corticosteroid	97 (77.6%)	54 (68.4%)	0.15

IBD, inflammatory bowel disease; BMI, body mass index

Supplementary Table 2 Summary of clinical outcomes in vitamin D deficient younger adult (18-59 years) and older adult (≥60 years) patients

Outcome	Younger (n=85)	Older (n=40)	P-value
Need for corticosteroids	32 (37.7%)	8 (20.0%)	0.064
Combined intestinal complication	21 (24.7%)	5 (12.5%)	0.16
IBD-related surgery	9 (10.6%)	3 (7.5%)	0.75
IBD-related hospitalization	18 (21.2%)	6 (15.0%)	0.47
Composite clinical outcome	44 (51.8%)	11 (27.5%)	0.012

IBD, inflammatory bowel disease

Supplementary Table 3 Summary of clinical outcomes in iron deficient younger adult (18-59 years) and older adult (≥60 years) patients

Outcome	Younger (n=54)	Older (n=26)	P-value
Need for corticosteroids	24 (44.4%)	6 (23.1%)	0.086
Combined intestinal complication	17 (31.5%)	2 (7.7%)	0.024
IBD-related surgery	10 (18.5%)	2 (7.7%)	0.32
IBD-related hospitalization	17 (31.5%)	6 (23.1%)	0.60
Composite clinical outcome	35 (64.8%)	7 (26.9%)	0.002

IBD, inflammatory bowel disease

Supplementary Table 4 Summary of clinical outcomes in zinc deficient younger adult (18-59 years) and older adult (≥60 years) patients

Outcome	Younger (n=29)	Older (n=17)	P-value
Need for corticosteroids	12 (41.4%)	4 (23.5%)	0.34
Combined intestinal complication	9 (31.0%)	1 (5.9%)	0.067
IBD-related surgery	3 (10.3%)	1 (5.9%)	>0.99
IBD-related hospitalization	5 (17.2%)	3 (17.7%)	>0.99
Composite clinical outcome	17 (58.62%)	5 (29.41%)	0.072

IBD, inflammatory bowel disease