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Review Article

Review Article

The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

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Abstract

Background and Aims: Inflammatory bowel disease [IBD] is a chronic disease which affects up to 0.5% of the population. Various extraintestinal manifestations occur, among which are rheumatic manifestations, grouped together under the name spondyloarthritis. The objective of this systematic review and meta-analysis was to give a systematic overview of the prevalence and incidence of spondyloarthritis in patients with inflammatory bowel disease.

Methods: We systematically searched Embase, Pubmed, OvidSP, Scopus, and Web-of-Science databases from inception to August 2016. All articles that addressed the prevalence or incidence of the different features of spondyloarthritis in adult inflammatory bowel disease patients were included. Methodological quality was assessed using a modified quality assessment tool developed for prevalence studies.

Results: A total of 71 studies were included, reporting on the prevalence of sacroiliitis, ankylosing spondylitis, arthritis, enthesitis, and dactylitis. Pooled prevalences were calculated for sacroiliitis (10%; 95% confidence interval [CI] 8–12%), ankylosing spondylitis [3%; 95% CI 2–4%], and arthritis [13%; 95% CI 12–15%]. Geographical area, setting and use of different criteria contribute to the large heterogeneity. Few estimates were available for enthesitis [prevalence range from 1% to 54%] and dactylitis [prevalence range from 0% to 6%]. Only three incidence studies were identified, which report cumulative incidences from 5 to 30 years.

Conclusions: Spondyloarthritis occurs in up to 13% of patients with IBD. Ankylosing spondylitis is the least common [3%] followed by sacroiliitis [10%] and peripheral arthritis [13%].

Key Words: Extra-intestinal manifestations; spondyloarthritis; epidemiology

1. Introduction

Inflammatory bowel disease [IBD] is a common chronic inflammatory disease of the gastro-intestinal tract, which encompasses both Crohn's disease [CD] and ulcerative colitis [UC]. IBD can be accompanied by a number of extra-intestinal manifestations [EIM] in multiple organ systems, among which rheumatic manifestations

are grouped together under the name spondyloarthritis [SpA], which might affect 2–46% of IBD patients.[1–4] SpA can lead to a reduced quality of life as well as work disability, and is therefore a cause of significant burden on patients as well as on society as a whole.[5–8] Without treatment, severe joint deformations can occur, in both the peripheral joints and the spine. Detection of patients developing SpA is therefore important, as early and adequate treatment can prevent these complications.

In gastroenterology, a distinction is made between type 1 and type 2 arthritis. Type 1 arthritis parallels IBD activity, usually affects five joints or less, and tends to be self-limiting. Type 2 arthritis usually affects more than five joints and does not correlate with IBD activity.[3] Although this distinction is widely used in gastroenterology practice, it is not often used by rheumatologists. Rheumatologists tend to follow the recently developed Assessment in SpondyloArthritis International Society [ASAS] criteria, which make a distinction between axial and peripheral manifestations.[9,10] Both axial and peripheral manifestations can occur in patients with IBD.

With regard to the axial manifestations of SpA, the main symptom is chronic low back pain induced by inflammation of the sacroiliac joints, the so-called sacroiliitis [SI]. Ankylosing spondylitis [AS] is the best known subtype; however it is the least frequent manifestation. In peripheral SpA, arthritis, enthesitis, and dactylitis are the main symptoms. Arthritis can be observed in every peripheral joint, with a preference for the large joints. Enthesitis indicates inflammation of the tendon insertion to the bone. This can occur in every location of tendon insertions to bone, but best-known locations are the Achilles heel and the fascia plantaris. Dactylitis is a less common manifestation of SpA and indicates the presence of inflammation of an entire digit, the so-called sausage-fingers or toes. Patients with IBD are at increased risk for developing SpA but prevalence estimates based on the recently accepted definition of axial and peripheral joint manifestations are lacking. In this systematic review, we summarise the prevalence and incidence of the various axial and peripheral joint manifestations of SpA in patients with IBD. Secondly, we perform a meta-analysis to estimate the point prevalence of SI, AS and peripheral arthritis in patients with IBD.

2. Methods

This systematic review was reported in accordance with the PRISMA guidelines.[11]

2.1. Literature search

In collaboration with a medical librarian, a search strategy was developed. Medline, Embase, Web of Science, and Pubmed as publisher were searched to identify relevant studies from database inception to August 2016. Key words included terms and synonyms for all joint manifestations of spondylarthropathies, inflammatory bowel disease [including Crohn's disease and ulcerative colitis], incidence, and prevalence. The full search strategy is available in supplementary file S1, at *ECCO-JCC* online.

2.2. Selection of studies

Inclusion of studies was based on a two-stage process; first, titles and abstracts were screened for eligibility followed by retrieval of full-text articles to further check the eligibility criteria. One investigator [MK] screened all articles for eligibility on title and abstract and subsequently the full text of all articles that had passed the first eligibility screening. Studies were eligible if they: [i] were written in Dutch or English language; [ii] had an observational design; and [iii] described the prevalence of axial manifestations [SI, AS] or peripheral joint manifestations [arthritis, enthesitis, or dactylitis] in patients diagnosed with IBD. Studies were excluded if they were only published as conference abstracts or contained no original data. The reference section in review articles and original studies were searched for additional studies.

2.3. Data extraction

Data were extracted by one investigator [MK] according to a predefined data form. The following information was extracted: setting (population-based, secondary care, tertiary care [university hospital]), type of study, study population, number of IBD patients participating, mean age and percentage women of IBD patients, criteria for establishment of IBD, disease duration of IBD, case definition of axial and peripheral joint manifestations of SpA, outcome measurement, outcome assessor, and number of cases of different SpA manifestations.

2.4. Assessment of methodological quality

MK assessed all and AW or JL each assessed half of the papers for methods of data collection by a quality list, comprising six yes/no questions. The quality list was based on a recently developed quality assessment tool for prevalence studies, slightly adjusted for our situation.[12] We included the questions about representativeness of the sample for the target population, appropriate recruitment of the study participants, adequate sample size calculation, and whether the data analysis was conducted with sufficient coverage of the identified sample. With regard to case ascertainment, we included questions about whether objective, standard criteria were used for the establishment of a case and if the condition was measured reliably [meaning by a qualified outcome assessor]. The full quality assessment tool with instructions on how we applied the tool can be found in supplementary file S2, available at *ECCO-JCC* online. All papers were discussed between MK and AW or JL and disagreements were resolved by consensus.

2.5. Pooling of data

A meta-analysis was performed for the prevalence of the axial manifestations AS and SI and for the peripheral manifestation arthritis in patients with CD and UC. For the peripheral manifestations enthesitis and dactylitis, too few studies were available for pooling, so these were described narratively.

Meta-analysis was performed using the 'metaprop' command in Stata 13, using a random effects model.[13] I^2 was used to calculate the between-study heterogeneity. Meta-analysis according to different subgroups was performed to explore possible sources of heterogeneity.

3. Results

3.1. Search results

The search resulted in 4533 publications [Figure 1]. After removing duplicates, 2780 publications remained and were screened on title and abstract. Eventually 658 publications were found eligible for full-text review, after which 71 publications were included. These 71 publications reported on the prevalence of the different axial and peripheral joint manifestations of SpA in either CD or UC. Seven studies did not specify the type of inflammatory bowel disease and are described as unspecified IBD. The characteristics of the included studies are shown in Table 1.

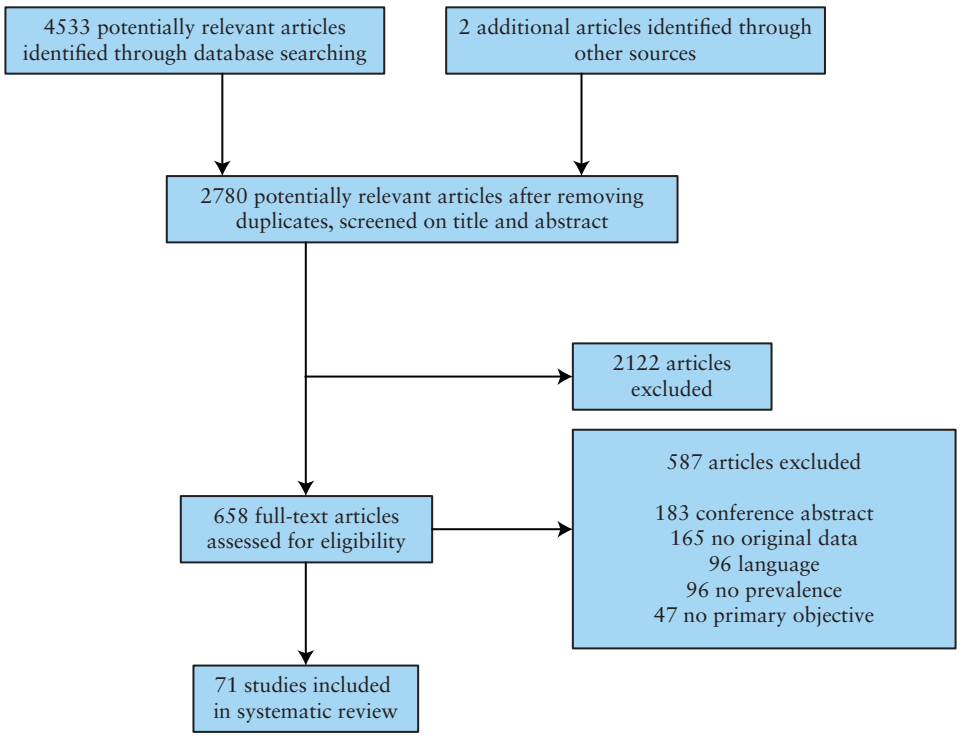

Figure 1. Flow diagram of study selection.

3.2. Risk of bias

A complete overview of the assessment of methodological quality can be found in supplementary file S2, available at *ECCO-JCC* online. In Table 2, the different items of the quality list are shown with the percentage of studies that scored positive on this item. The majority of studies had a sample representative of the target population [63.4%] and most studies recruited their patients in an appropriate way [90.1%], meaning consecutively, at random, or all patients being selected for the study. None of the studies reported a sample size calculation, but a slight majority did conduct an adequate data-analysis [59.2%]. With regard to case ascertainment, in 56.3% objective standard criteria were used and in 46.5% of the studies the condition, meaning SpA, was measured reliably.

3.3. Prevalence of axial involvement

In all, 59 studies [125 estimates] reported the prevalence of axial SpA in patients with IBD.[14–66]

3.3.1. Sacroiliitis

The prevalence of SI in patients with IBD was described in 41 studies [59 estimates][see supplementary file S3, available at *ECCO-JCC* online].[16–18,21–26,28,30–32,34,35,37–40,42,43,45–49,51,52,55,57–62,65,67–71] The pooled prevalence of SI in IBD patients is estimated to be 10% [95% CI 8–12%], with an I^2 of 94.3%. The prevalence of SI is higher in patients with CD [13%, 95% CI 1–17%] than in patients with UC [7%, 95% CI 4–11%].

As there was considerable heterogeneity in the observed prevalence between studies, we explored the variability by a meta-analysis of subgroups according to different demographical and study characteristics [Figure 2]. Higher prevalences were observed in European and studies [11%; 95% CI 8–15% and11%; 95% CI 7–16%], compared with North-America [7%; 95% CI 2–14%] and South-America [5%; 95% CI 2–9%]. With regard to mean age, the prevalence seemed highest in the three studies for age category 20–30 years of age, with 16% [95% CI 8–27%]. In the age group 30–40 years, the prevalence dropped towards 9% [95% CI 5–14%], to rise again slightly in the age groups of 40–50 years and 50–60 years. Studies were performed in different settings, resulting in higher prevalences of SI in tertiary care [15%; 95% CI 1–22%] compared with secondary care [7%; 95% CI 5–11%] and population-based studies [3%; 95% CI 1–7%]. The use of clinical evaluation also resulted in a higher prevalence [15%, 95% CI 10–21%] than studies using case records or a self-reported diagnosis as outcome. The use of different imaging techniques to establish an SI did not seem to have much influence on the prevalence estimates, with an estimate of 12% [95% CI 8–16%] when using X-ray, 15% [95% CI 5–29%] when using computed tomography [CT] and 10% [95% CI 6–14%] when using magnetic resonance imaging [MRI].

When making the distinction between subclinical SI [i.e. no pain or stiffness] and clinical SI, the prevalence differed slightly. The prevalence of subclinical SI was estimated to be 11% [95% CI 7–17%] in 12 studies [18 estimates].[21,24,31,32,34,35,38,40,45,46,51,62] The prevalence of clinical SI was estimated to be 8% [95% CI 6–10%].[16–18,22–26,28,30,32,34,37–40,42,43,47–49,52,55,57–62,65,67–71]

3.3.2. Ankylosing spondylitis

The prevalence of AS in IBD patients was described in 43 studies [64 estimates] [see supplementary file S3, available at *ECCO-JCC* online]. The pooled prevalence of AS was 3% [95% CI 2–4%] with considerable heterogeneity [I^2 = 81.9%]. Patients with CD had a slightly higher prevalence of AS than patients with UC: 4% [95% CI 3–5%] compared with 2% [95% CI 1–3%].

To look into potential explanations for the heterogeneity, the prevalence estimates for AS are shown in Figure 3 according to several demographical and study characteristics. For geographical area, the prevalence of AS in IBD patients was highest in Europe with 3% [95% CI 3–4%]and North America [3%; 95% CI 2–5%]. The prevalence was slightly lower in South America and Asia with 2% [95% CI 0–5% and 1–3%, respectively]. For the mean age of

Table 1. Study characteristics of included studies.

	Setting	Study design	No. of IBD patients	Mean age population [years]	% women	Disease duration [months]	Outcome	Case definition axial	Axial *n* [%]	AS *n* [%]	SI *n* [%]	Imaging SI	Arthritis *n* [%]	Enthesitis *n* [%]	Dactylitis *n* [%]
IBD															
Bernstein, 2001, Canada[19]	PB	RS	4454	NA	NA	NA	CR	Code		182 [4.1]					
Beslek, 2009, Turkey[20]	TC	CS	122	44.1	53.3	61	CR	[m]NY		10 [8.2]			19 [15.6]	24 [19.7]	
Gotler, 2015, Israel[68]	SC	RS	286	29.3	49	151.2	CR	ASAS			26 [9.1]	MRI			
Kamo, 2015, Japan[79]	SC	CS	137	45	40.9	122.4	SR								8 [5.8]
Nguyen, 2006, US/Canada[39]	SC	RS	1106	36.1	51.9	NA	CR	Clinical		14 [1.3]	23 [2.1]	NA			
Palm, 2001, Norway[44]	SC	CS	521	39	53.0	73	CE	[m]NY		7 [1.3]	[0]				
Palm, 2002, Norway[45]	SC	CS	406	NA	NA	NA	CE	[m]NY			5 [1.2]	NA	69 [17]	26 [6.4]	18 [4.4]
CD															
Al-Jarallah, 2012, Kuwait[14]	TC	CS	81	29.6	33.3	NA	CE	Clinical	8 [9.9]				29 [35.8]		
Al-Jarallah, 2013, Kuwait[15]	TC	CS	85	29.6	NA	NA	CE	Clinical	10 [11.8]				25 [29.4]	1 [1.2]	0 [0]
Ansell BM, 1964, Canada[16]	SC	CS	91	NA	59.3	94.8	CE	NA		5 [5.5]	18 [19.8]	X-ray	10 [11]		
Bandyopadhyay, 2015, India[67]	SC	CS	62	NA	34	NA	CE	ASAS	12 [19.4]		13 [21]	MRI	15 [24.2]		
Barreiro-De Acosta, 2007,Spain [18]	TC	CS	173	36	59	90	CE	Clinical		4 [2.3]	12 [6.9]	X-ray	31 [17.9]		
Bruining, 2008, USA[21]	SC	RS	357	NA	51	NA	CR	NA			8 [2.2]	CT			
Christodoulou, 2002, Greece[22]	TC	RS	37	40.2	40.5	7.8	SR	NA			6 [16.2]	NA	2 [5.4]		
Davis, 1978, Canada[23]	SC	CS	60	36	50	96	CE	[m]NY		3 [5]	7 [11.7]	Scinti-graphy	4 [6.7]		
De Vlam, 2000, Belgium[24]	TC	CS	78	NA	68	127.8	CE	[m]NY		7 [9]	27 [34.6]	X-ray	7 [9]	6 [7.7]	0 [0]
Dekker Saeys, 1978, The Netherlands[25]	TC	CS	51	37.2	58.8	NA	CE	[m]NY		2 [3.9]	8 [15.7]	X-ray	6 [11.8]		
D'Inca, 2009, Italy[26]	SC	CS	266	41	47.7	126	CE	[m]NY		5 [1.9]	15 [5.6]	MRI	9 [3.4]		
Fatemi, 2016, Iran[74]	TC	CS	96	40.6	52.1	80.4	CE	Clinical		2 [2.1]			5 [5.2]		
Fielding, 1986, Ireland[28]	SC	CS	72	30.5	51.4	NA	SR	NA			1 [1.4]	NA			
Greenstein, 1976, USA[29]	SC	RS	498	NA	NA	NA	CR	NA		19 [3.8]			84 [16.9]		
Haslock, 1973, UK[30]	TC	CS	116	NA	50	152.4	CE	[m]NY		8 [6.9]	19 [16.4]	X-ray	24 [20.7]		
Hwangbo, 2010, Korea[31]	SC	CS	81	28.8	27.2	32.1	CR	[m]NY			17 [21]	CT			
Indiveri, 2010, South-Africa[75]	TC	RS	43	NA	69.8	NA	CR						3 [7]		
Isene, 2015, Norway, Denmark, *et al.*[69]	PB	FU	364	42.4	NA	NA	CR	NA		6 [1.6]	8 [2.2]	NA	33 [9.1]		
Karmiris, 2016, Greece[70]	TC	CS	1001	NA	NA	NA	CR	Clinical		34 [3.4]	70 [7]	MRI	155 [15.5]		
Lakatos, 2003, Hungary [33]	SC	FU	254	NA	50.8	110.4	CE	Clinical	26 [10.2]				37 [14.6]		
Lanna, 2008, Brasil[34]	TC	CS	71	39.4	59.2	63.3	CE	[m]NY		8 [11.3]	10 [14.1]	X-ray	14 [19.7]	5 [7]	
Leclerc-Jacob, 2014, France[35]	TC	RS	131	NA	NA	NA	CR	Other			23 [17.6]	MRI			
Liu, 2016, China[92]	TC	RS	194	NA	NA	NA	CR	[m]NY		8 [4.1]					
Maeda, 1994, Japan[36]	SC	FU	203	NA	30	52.8	CE	NA	3 [1.5]				21 [10.3]		
Mocelin, 2015, Brasil[72]	TC	CS	100	41.9	60	NA	CE	ASAS	2 [2]	3 [3]			1 [1]		
Modena, 1988, Italy[37]	SC	CS	51	NA	47.1	NA	CE	[m]NY		5 [9.8]	6 [11.8]	X-ray	10 [19.6]		
Münch, 1986, Germany[38]	SC	FU	167	25	62.3	76.8	CE	[m]NY		15 [9]	35 [21]	X-ray	34 [20.4]		
Orchard, 1998, UK[41]	TC	CS	483	NA	58.2	NA	SR	[m]NY		6 [1.2]			49 [10.1]		
Orchard, 2009, UK[40]	TC	CS	44	36.2	75	96	CR	[m]NY		5 [11.4]	17 [38.6]	MRI			
Ott, 2014, Germany[71]	PB	FU	161	NA	55.9	NA	SR	Clinical			16 [9.9]	MRI	26 [16.1]		

Table 1. *Continued*

	Setting	Study design	No. of IBD patients	Mean age population [years]	% women	Disease duration [months]	Outcome	Case definition axial	Axial *n* [%]	AS *n* [%]	SI *n* [%]	Imaging SI	Arthritis *n* [%]	Enthesitis *n* [%]	Dactylitis *n* [%]
Ozdil, 2003, Turkey[42]	TC	RS	105	37.4	55.2	32.4	NA	NA		5 [4.8]	8 [7.6]	NA			
Palm, 2001, Norwa[44]	SC	CS	168	39	53.0	73	CE	[m]NY					24 [14.3]	6 [3.6]	9 [5.4]
Palm, 2002, Norway[45]	SC	CS	133	NA	NA	NA	CE	[m]NY		8 [6]					
Paparo, 2012, Italy[46]	SC	RS	221	50.2	48.4	NA	CR	Other			53 [24]	CT			
Peeters, 2008, Belgium[47]	TC	CS	251	35	40	NA	CE	[m]NY		16 [6.4]	49 [19.5]	X-ray	72 [28.7]		
Pezerovic, 2013, Croatia[48]	SC	RS	31	NA	NA	NA	CR	NA		4 [12.9]	3 [9.7]	NA	8 [25.8]		
Queiro, 2000, Spain[51]	SC	FU	35	35.9	57.1	81.6	CE	[m]NY		1 [2.9]	8 [22.9]	X-ray	10 [28.6]		
Repiso, 2006, Spain[53]	SC	RS	157	41.15	43.3	NA	CR	NA	9 [5.7]				9 [5.7]		
Ricart, 2004, USA[54]	SC	CS	243	NA	48	NA	SR	NA		9 [3.7]					
Salvarani, 2001, Italy + The Netherlands[55]	SC	CS	59	NA	NA	NA	CE	[m]NY		3 [5.1]	3 [5.1]	X-ray	6 [10.2]	9 [15.3]	1 [1.7]
Singh, 2015, India[93]	SC	FU	303	NA	NA	NA	NA	NA		10 [3.3]					
Steer, 2003, UK[57]	SC	CS	134	NA	52.9	NA	CE	[m]NY		9 [6.7]	31 [23.1]	CT			
Suh, 1998, Korea[58]	TC	RS	52	34	40.4	NA	CR	NA		1 [1.9]	4 [7.7]	X-ray	5 [9.6]		
Teh, 1987, Singapore[59]	SC	RS	9	30.5	44.4	NA	CR	NA			1 [11.1]	NA			
Torres, 2012, Puerto-Rico[60]	SC	CS	336	30.9	41	NA	CR	NA		1 [0.3]	13 [3.9]	NA	62 [18.5]		
Tozun, 2009, Turkey[61]	SC	CS	216	37.4	44	NA	SR	NA		3 [1.4]	5 [2.3]	NA	24 [11.1]		
Turkcapar, 2006, Turkey[62]	TC	CS	78	40.91	64.1	52.29	CE	[m]NY		9 [11.5]	48 [61.5]	NA	12 [15.4]	42 [53.8]	
Vavricka, 2011, Switzerland[63]	SC	CS	580	41	54	132	CE	Clinical		33 [5.7]			193 [33.3]		
Veloso, 1996, Portugal[64]	TC	FU	449	29.4	56.1	54	CE	Clinical		14 [3.1]			91 [20.3]		
Wagtmans, 2001, The Netherlands[65]	TC	RS	541	NA	50.8	NA	CR	Clinical		20 [3.7]	23 [4.3]	NA	77 [14.2]		
Yi, 2012, China[66]	SC	RS	153	33.64	62.1	20.67	CR	Clinical		1 [0.7]			7 [4.6]		
Yuksel, 2011, Turkey[77]	SC	CS	120	NA	43.3	6.22	CE						34 [28.3]		
Zippi, 2014, Italy[78]	SC	RS	216	NA	39.4	NA	CR	NA		5 [2.3]			66 [30.6]		
UC															
Al-Jarallah, 2012, Kuwait[14]	TC	CS	44	37.6	61.4	NA	CE	Clinical	7 [15.9]				22 [50]		
Al-Jarallah, 2013, Kuwait[15]	TC	CS	45	37.6	NA	NA	CE	Clinical	5 [11.1]				16 [35.6]	6 [13.3]	2 [4.4]
Al-Shamali, 2003, Kuwait[73]	TC	CS	90	NA	56	NA	SR	NA					8 [8.9]		
Bandyopadhyay, 2015, India[67]	SC	CS	58	NA	29	NA	CE	ASAS	9 [15.5]		11 [19]	MRI	12 [20.7]		
Bardazzi, 1997, Italy[17]	SC	CS	68	48.5	41.2	NA	CE	[m]NY			9 [13.2]	X-ray			
Christodoulou, 2002, Greece[22]	TC	RS	215	54.1	42.3	8.2	SR	NA			9 [4.2]	NA	5 [2.3]		
De Vlam, 2000, Belgium[24]	TC	CS	25	NA	52	107	CE	[m]NY		3 [12]	6 [24]	X-ray	3 [12]	1 [4]	1 [4]
Dekker Saeys, 1978, The Netherlands[25]	TC	CS	58	42.1	58.6	NA	CE	[m]NY		2 [3.4]	7 [12.1]	X-ray	8 [13.8]		
D'Inca, 2009, Italy[26]	SC	CS	385	44	44.2	138	CE	[m]NY		4 [1]	8 [2.1]	MRI	15 [3.9]		
Dorofeyev, 2009, Ukraine[27]	TC	CS	319	43.2	53.9	NA	NA	NA		8 [2.5]			48 [15]		
Fatemi, 2016, Iran[74]	TC	CS	177	41.4	56.5	94.8	CE	Clinical		0 [0]			7 [4]		
Greenstein, 1976, USA[29]	SC	RS	202	NA	NA	NA	CR	NA		8 [4]			27 [13.4]		
Hwangbo, 2010, Korea[31]	SC	CS	82	42.7	46.3	18.0	CR	[m]NY			10 [12.2]	CT			
Indiveri, 2010, South Africa[75]	TC	RS	80	NA	52.5	NA	CR						8 [10]		
Isene, 2015, Norway, Denmark, *et al.*[69]	PB	FU	781	47.7	NA	NA	CR	NA		8 [1]	12 [1.5]	NA	43 [5.5]		

Table 1. *Continued*

	Setting	Study design	No. of IBD patients	Mean age population [years]	% women	Disease duration [months]	Outcome	Case definition axial	Axial *n* [%]	AS *n* [%]	SI *n* [%]	Imaging SI	Arthritis *n* [%]	Enthesitis *n* [%]	Dactylitis *n* [%]
Karmiris, 2016, Greece[70]	TC	CS	859	NA	NA	NA	CR	Clinical		5 [0.6]	16 [1.9]	MRI	66 [7.7]		
Kochhar, 1991, India[32]	SC	CS	150	NA	47.3	NA	CE	[m]NY			21 [14]	Xray	16 [10.7]		
Lakatos, 2003, Hungary[33]	SC	FU	619	NA	48.8	134.4	CE	Clinical	20 [3.2]				30 [4.8]		
Lanna, 2008, Brasil[34]	TC	CS	59	40.9	59.3	54	CE	[m]NY		0 [0]	2 [3.4]	X-ray	7 [11.9]	2 [3.4]	
Leclerc-Jacob, 2014, France[35]	TC	RS	55	NA	NA	NA	CR	Other			8 [14.5]	MRI			
Orchard, 1998, UK[41]	TC	CS	976	NA	50.4	NA	SR	[m]NY		9 [0.9]			59 [6]		
Ott, 2014, Germany[71]	PB	FU	96	NA	47.9	NA	SR	Clinical			3 [3.125]	MRI	15 [15.6]		
Ozdil, 2004, Turkey[42]	TC	RS	116	36	55.2	51.8	NA	NA			14 [12.1]	NA	2 [1.7]		
Palm, 2001, Norway[44]	SC	CS	353	46	50.1	74	CE	[m]NY					38 [10.8]	17 [4.8]	9 [2.5]
Palm, 2002, Norway[45]	SC	CS	273	NA	NA	NA	CE	[m]NY		7 [2.6]					
Pezerovic, 2013, Croatia[48]	SC	RS	119	NA	NA	NA	CR	NA		4 [3.4]	3 [2.5]	NA	24 [20.2]		
Pokharna, 2004, India[49]	SC	CS	46	NA	37.0	57.6	CE	[m]NY			0 [0]	X-ray	1 [2.2]		
Pongprasobchai, 2001, Thailand[50]	TC	RS	40	NA	52.5	NA	CR	NA		1 [2.5]	[0]		2 [5]		
Queiro, 2000, Spain[51]	SC	FU	27	40.9	48.1	84	CE	[m]NY		1 [3.7]	7 [25.9]	X-ray	9 [33.3]		
Rajput, 1992, South Africa[52]	TC	NA	64	NA	50	NA	NA	NA			0 [0]	X-ray	4 [6.3]		
Salvarani, 2001, Italy + The Netherlands[55]	SC	CS	98	NA	NA	NA	CE	[m]NY		2 [2]	2 [2]	X-ray	11 [11.2]	6 [6.1]	2 [2]
Scarpa, 1992, Italy[56]	TC	CS	79	38.72	30.4	NA	CE	[m]NY		20 [25.3]			23 [29.1]		
Singh, 2015, India[93]	SC	FU	1146	NA	NA	NA	NA	NA		25 [2.2]					
Suh, 1998, Korea[58]	TC	RS	77	38.5	55.8	NA	CR	NA		0 [0]	4 [5.2]	X-ray	15 [19.5]		
Teh, 1987, Singapore[76]	SC	RS	61	38.2	50.8	NA	CR						4 [6.6]		
Torres, 2012, Puerto-Rico[60]	SC	CS	299	40.3	56	NA	CR	NA		2 [0.7]	8 [2.7]	NA	48 [16.1]		
Tozun, 2009, Turkey[61]	SC	CS	661	42.6	43	NA	SR	NA		6 [0.9]	4 [0.6]	NA	37 [5.6]		
Turkcapar, 2006, Turkey[62]	TC	CS	84	42	61.9	57.36	CE	[m]NY		7 [8.3]	48 [57.1]	NA	12 [14.3]	39 [46.4]	
Vavricka, 2011, Switzerland[63]	SC	CS	370	42	48	108	CE	Clinical		6 [1.6]			79 [21.4]		
Veloso, 1996, Portugal[64]	TC	FU	343	36.4	50.7	52.8	CE	NA		10 [2.9]			38 [11.1]		
Yuksel, 2011, Turkey[77]	SC	CS	237	NA	41.8	7.06	CE						32 [13.5]		
Zippi, 2014, Italy[78]	SC	RS	595	NA	48.6	NA	CR	NA		8 [1.3]			161 [27.1]		

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; NA, not available; PB, population-based; SC, secondary care; TC, tertiary care; RS, retrospective; CS, cross-sectional; FU, prospective follow-up; CR, case records; SR, self-reported; CE, clinical evaluation; [m]NY, [modified] New York Criteria; ASAS, Assessment of Spondyloarthritis International Society; AS, ankylosing spondylitis; SI, sacroiliitis; CT, computed tomography; MRI, magnetic resonance imaging.

the study population, patients of younger age [age group 20–30] had a slightly higher prevalence of AS, based on two estimates [4%; 95% CI 3–6%], compared with older age groups [3%; 95% CI 1-5%]. Study characteristics like setting, outcome measurement, and case ascertainment seemed to influence the reported prevalences. The differences are small, with slightly higher prevalences in tertiary care setting, diagnoses based on clinical evaluation, and the use of the recommended [modified] New York criteria to diagnose AS.

Table 2. Risk of bias assessment.

Query	% positive
Was the sample representative of the target population?	63.4
Were study participants recruited in an appropriate way?	90.1
Was the sample size adequate?	0
Was the data analysis conducted with sufficient coverage of the identified sample?	59.2
Were objective standard criteria used for the measurement of the condition?	56.3
Was the condition measured reliably?	46.5

3.3.3. Unspecified axial involvement

Six studies [nine estimates] did not specify the type of axial involvement; in these studies the prevalence ranged from 1 to 16%.[14,15,33,36,53,72] One recent study [two estimates] used the new ASAS criteria to diagnose axial spondyloarthritis. Since axial spondyloarthritis can be diagnosed without abnormalities on imaging [which are required for diagnosing AS], these estimates are higher at 18% for UC and 19% for CD.

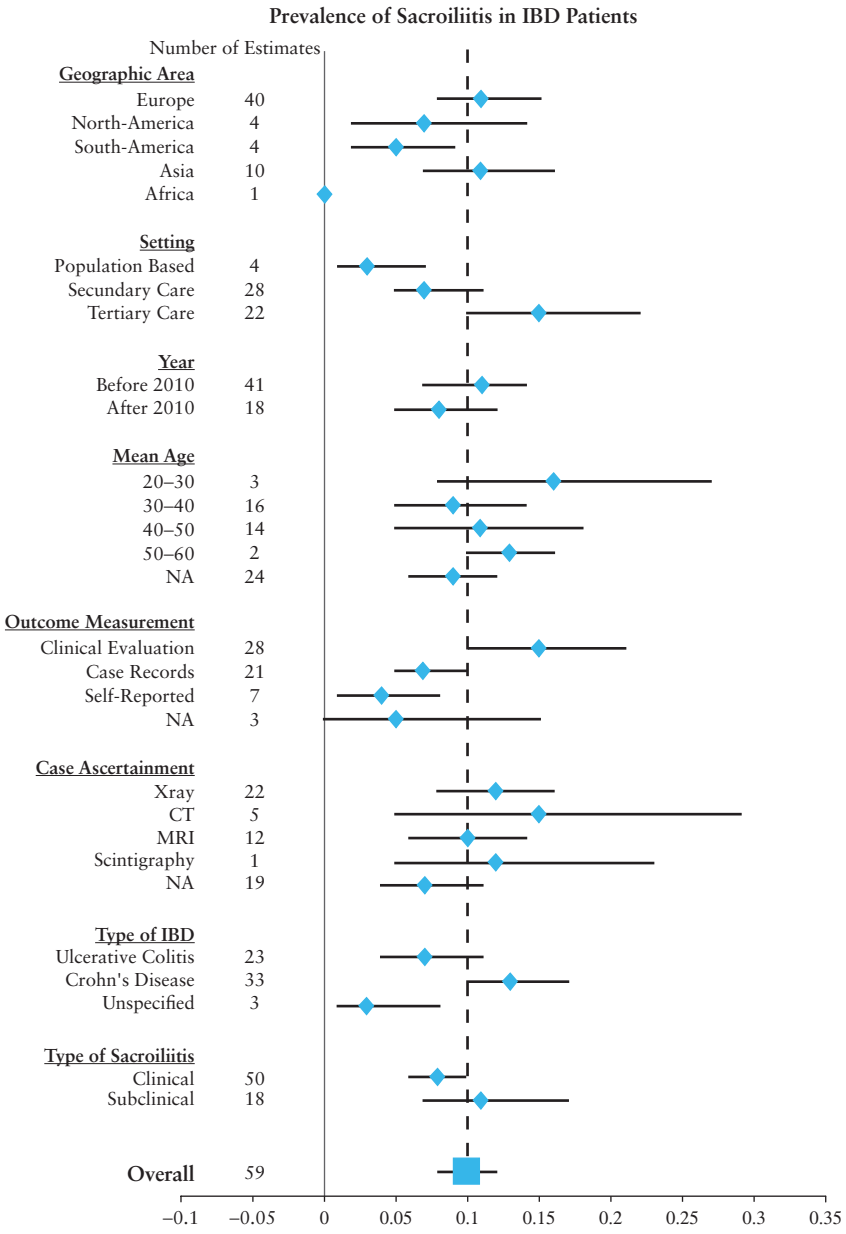

Figure 2. Meta-analysis of the prevalence of sacroiliitis in inflammatory bowel disease [IBD] patients.

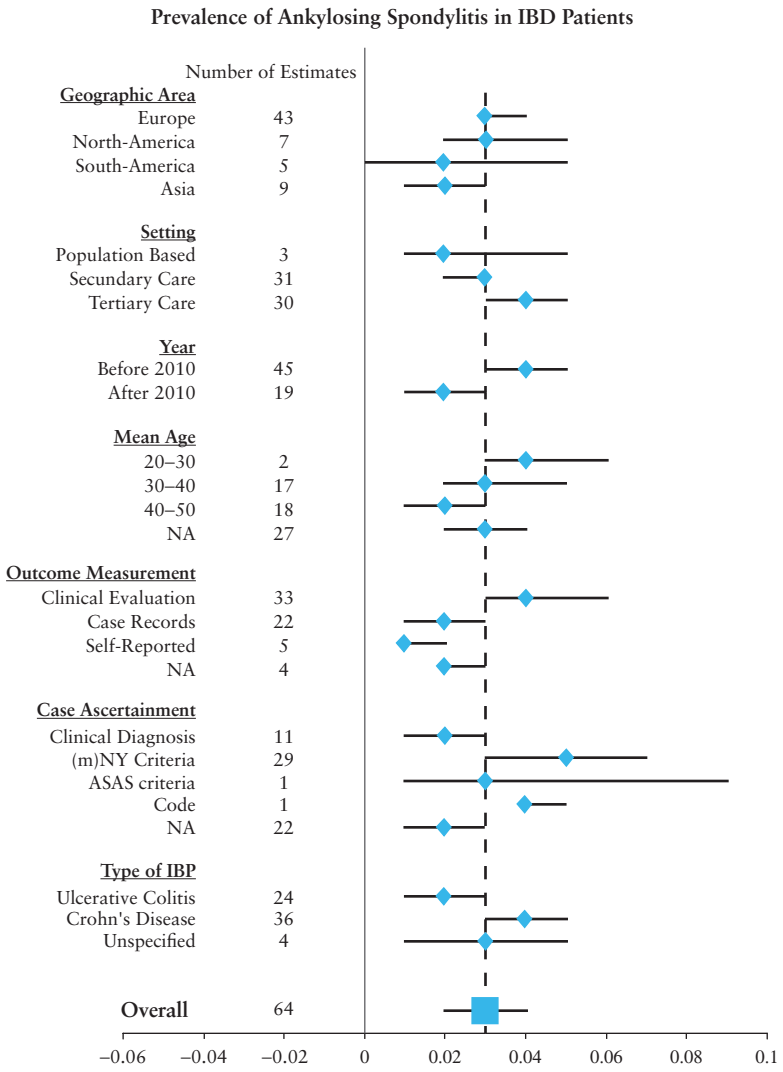

Figure 3. Meta-analysis of the prevalence of ankylosing spondylitis in inflammatory bowel disease [IBD] patients.

3.4. Prevalence of peripheral involvement

A total of 103 estimates from 52 studies were available for the prevalence of peripheral joint manifestations of SpA in IBD patients[see supplementary file S3].

3.4.1. Arthritis

The pooled prevalence of peripheral arthritis [79 estimates] was 13% [95% CI 12–15%] with a high heterogeneity [I^2 = 92.3%].[14–16,18,20,22–27,29,30,32–34,36–38,41,42,44,45,47–53,55,56,58,60–67,69–78] Forty estimates were available for CD and 37 for UC, and two studies did not specify the type of IBD. The prevalence was highest in this unspecified IBD with 17% [95% CI 14–20%], followed by CD [15%; 95% CI 12–18%] and UC [12%; 95% CI 9–15%].

Figure 4 shows the estimates according to several subgroups, which might explain the heterogeneity. With regard to geographical area, the prevalence seemed comparable among the different continents. Most studies were available from Europe [14%; 95% CI 11–16%] and Asia [14%; 95% CI 9–20%], followed by North and South America [13%; 95% CI 9–17% and 12%; 95% CI 6–20%, respectively]. The prevalence of arthritis in IBD seemed to be decreasing with increasing age. The prevalence in the youngest age group of 20–30 years was 25% [95% CI 19–32%], whereas the prevalence in the age group of 50–60 years was 2% [95% CI 1–5%]. Estimates from tertiary care were slightly higher compared with secondary care and population-based studies, but the difference is negligible. In the majority of studies, clinical evaluation was used as an outcome measurement and this led to the highest prevalence estimate at 15% [95% CI 13–19%].

3.4.2. Enthesitis

The prevalence of enthesitis was reported in eight studies [14 estimates]: six from Europe,[20,24,44,45,55,62] one from South-America,[34] and one from Asia.[15] The reported prevalence ranged from 1% [95% CI 0–6%] to 54% [95% CI 42–65%]. Three estimates were available from Turkey, and these were considerably higher than the other estimates at 20% [95% CI 13–28%], 46% [95% CI 35–58%], and 54% [95% CI 42–65%].[20,62] The estimates from the other countries ranged from 1% [95% CI 0–6%] in Kuwait to 0.15% [95% CI 7–27%] in a combined study from Italy and The Netherlands.[15,55] With regard to setting or type of IBD, the differences in prevalence were negligible.

3.4.3. Dactylitis

For the prevalence of dactylitis, 10 estimates from six studies were available.[15,24,44,45,55,79] The reported prevalences were all quite low, with a range from 0 in CD patients in Kuwait[15] and Belgium[24] to

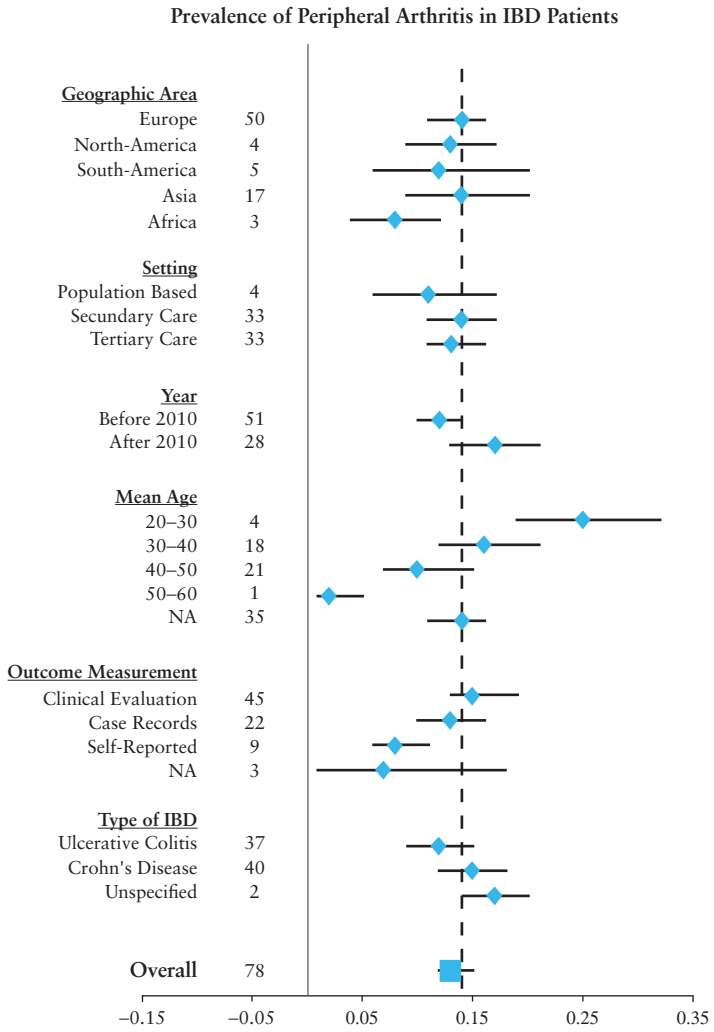

Figure 4. Meta-analysis of peripheral arthritis in inflammatory bowel disease [IBD] patients.

5% [95% CI 2–10%] in CD patients in Norway.[44] The range in UC patients was reported to be from 2% [95% CI 0–7%] to 4% [95% CI 1–15%]. Two studies did not specify the type of IBD and reported prevalences of 4% [95% CI 3–7%][45] and 6% [95% CI 3–11%], respectively.[79] Geographical area or setting did not seem to influence the prevalence when looking at the available estimates.

3.5. Incidence

Three studies that report incidence figures were identified.[80–82] All were performed in North America and used database records.

In CD patients, the cumulative incidence of SpA according to the ASAS criteria increased from 0.67 [95% CI 0.35–0.97] at age 10 years towards 0.19 [95% CI 0.11–0.26%] at age 30 years. The 5-year cumulative incidence of AS was 0.02 and of peripheral arthritis 0.009.

In UC patients, the cumulative incidence at age 10 years according to the ASAS criteria was 0.48 [95% CI 0.02–0.07] increasing towards 0.22 [95% CI 0.04–0.29] at 30 years. The 5-year cumulative incidence for AS was 0.03 and for peripheral arthritis was 0.05.

4. Discussion

In this systematic review, we calculated the pooled prevalences of SpA manifestations in IBD patients. The pooled prevalence of SI was 10% [95% CI 8–12%] and for its subtype AS was 3% [95% CI 3–4%]. The pooled prevalence of peripheral arthritis was 13% [95% CI 12–15%]. The prevalence of AS, SI, and peripheral arthritis was higher in patients with CD than in patients with UC. This difference in prevalence estimates has been described before.[2,4,83] For the prevalence of enthesitis and dactylitis, fewer estimates were available. The prevalence of enthesitis had a wide range from 1% [95% CI 0–6%] to 54% [95% CI 42–65%] with outliers in two studies from Turkey. The prevalence of dactylitis was relatively low between 0 and 5% [95% CI 2–10%]. Only three studies reported the cumulative incidence of SpA in IBD patients.

As the heterogeneity between the different studies was high, these estimates should be interpreted with caution. Geographical area, setting, and case ascertainment seemed to contribute to this large heterogeneity in prevalence estimates.

Prevalence estimates of AS were higher if case ascertainment was done by using validated criteria. As only a slight majority [60%] of studies used validated criteria for diagnosing AS, a lot of studies will underestimate the prevalence of AS in IBD. The same applies for studies performed in secondary care, which seem to estimate a lower prevalence of the different SpA manifestations than studies in tertiary care. This could imply that tertiary care centres are more focused on joined care between gastroenterologists and rheumatologists,

to enhance recognition of SpA in IBD patients. Geographical area also contributes to the heterogeneity and prevalences for axial manifestations [SI and AS], which are highest in Europe and North America. This is in line with the estimates for SpA in general.[84,85] Clinical evaluation as an outcome measurement led to higher prevalence estimates compared with self-reported diagnosis or case records. This might suggest that our estimates are an underestimation, as in other types of arthritis it has been shown that the prevalence of self-reported diagnosis is higher than could be objectified via case records or specialists.[86,87]

As shown, there was large variety in methodological quality of studies. Most studies included their participants adequately, but only 65% selected a sample representative of the target population. The results of these studies therefore have poor external validity. Even though the quality of the included studies differed widely, we chose not to pool on the quality in the meta-analysis as it has been shown before that the quality is highly dependent on the quality assessment tool chosen.[88]

When discussing the results of our study, several strengths and limitations should be taken into account. Although some narrative reviews about the prevalence of rheumatic manifestations in IBD patients have been published,[2–4,83,89] the strength of this study is that it is the first systematically performed review and it includes a meta-analysis. We set up an extensive search strategy in collaboration with an experienced librarian in order to identify as many relevant studies as possible. We also included a risk of bias assessment to give an indication of the methodological quality of the included studies. Furthermore, we are the first to make the distinction between axial and peripheral manifestations of SpA, as recommended by the widely used ASAS criteria.[9,10] Regarding the limitations, we only included studies that were available in the English language, so we cannot rule out missing certain studies. Second, only one author performed the screening of the papers and the data extraction. Ideally, this would have been done independently by two authors. However, we discussed beforehand with all authors which papers to include and which not. In addition, the author who performed the screening was very liberal and in case of any doubt, the paper was discussed with one of the other authors until consensus was reached. Third, we used a risk of bias tool especially developed for prevalence studies, but left some items out as these did not seem to apply to our selected studies. We left out items about the description of study subjects and setting, as we gathered this information in the data extraction. Items about the definition of subgroups and differences between subgroups were also left out, as we only looked at prevalence in the complete groups. As we do not take the quality into account when pooling the results, we do not think leaving out these items will influence our results. For the pooled estimates of SI and AS, we cannot rule out that a certain overlap between these two manifestations occurred. Some papers described very accurately if patients only suffered from SI or AS, but in the majority of studies it was unclear whether the patients with AS were a subset of the patients with SI or if they were completely separated in establishing the cases. It is therefore possible that the prevalence of SI is slightly overestimated.

Based on this meta-analysis, the prevalence of peripheral arthritis is around 13%. This means that one in every eight patients will develop SpA. The prevalence for axial involvement in slightly lower, with 10% for SI [i.e. one in every 10 patients] and 3% for AS [i.e. one in every 33 patients]. Gastroenterologists, especially in secondary care, should pay attention to their IBD patients with musculoskeletal complaints since they are common and might cause significant impact on quality of life, even in the absence of inflammation.[8] IBD patients are prone to develop SpA and should be recognised early, as the benefits of early treatment are well established.[90,91]

In conclusion, we calculated pooled prevalences for SI [10%], its subtype AS [3%], and peripheral arthritis[13%] in patients with IBD. It seems that there is room for improvement in gastroenterology, especially in secondary care, with regard to recognition of SpA manifestations in IBD patients.

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Conflict of Interest

No conflicts of interest to declare.

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Author Contributions

MK: study design, literature search, data collection, data analysis, data interpretation, writing. JL: study design, data collection, data analysis, data interpretation, writing. JH: study design, data interpretation, writing. AW: study design, data collection, data analysis, data interpretation, writing.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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