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Incidence and natural history of ulcerative colitis in the Uppsala Region of Sweden 2005–2009 — Results from the IBD Cohort of the Uppsala Region (ICURE)

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Abstract

Background and aims: The incidence of ulcerative colitis (UC) increased during the 20th century in Western Europe and the North America, but there are conflicting reports whether the incidence has declined, stabilized or continued to increase. The aim of this study was to evaluate the incidence of UC in the Uppsala Region, Sweden.
Methods: All new UC patients in Uppsala County (305,381 inhabitants) were prospectively registered during 2005–2006 and the same for all new UC patients in the Uppsala Region (642,117 inhabitants) during 2007–2009. The extent and severity of disease according to the Montreal classification, relapse rates and surgery were assessed.
Results: 526 UC patients were included. The mean overall incidence for the time period was 20.0 (95% CI: 16.1–23.9) cases per 100,000 inhabitants. The incidence among children <17 years of age was 8.9 per 100,000. The extent at diagnosis was evenly distributed (E1: n=167, 32%, E2: n=161, 31%, E3: n=163, 31%). Half of the cases had moderate to severe symptoms (S1: n=269, 51%, S2: n=209, 40%, S3: n=45, 8.6%). 228 (43%) relapsed and 13 (2.5%) required colectomy during the first year. Children had a higher proportion of extensive disease vs adults (27/42 vs 136/484), but no increased risk for severe symptoms or colectomy.
Conclusion: In this prospective population-based study we found one of the highest incidences of UC in the world. The proportion of severe cases is comparable with historical data. The conclusion is that the nature of UC has not changed, only the incidence.

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1. Introduction

The incidence of Ulcerative Colitis (UC) has continuously been increasing during the past half century in Western European and North American countries. During the past decade conflicting reports have been published whether the incidence has stabilized, continued to increase or even declined in these parts of the world.[1–3] However, a recent review of 50 published articles, studying temporal trends of incidence over at last 10 years, found an increased incidence in 30 and a decreased incidence in 3 of these studies.[4]

In Sweden the latest published incidence for UC with partial data from the current study pointed out an increase from 2/100,000 in 1945 to 19.2 in 2007.[5] A prior Swedish report from the Uppsala Region found an incidence of 10.4 per 100,000 for the years 1965–1983.[6] Another study from the neighboring county of Örebro estimated the incidence to 11.1 per 100,000 inhabitants during 1983–1987.[7]

The aim of this study was to evaluate the current UC incidence in the Uppsala Region of Sweden, to determine extension as well as severity of disease at diagnosis, according to the Montreal classification, and to determine the colectomy rate during the first 12 months after diagnosis.

2. Materials and methods

A total of six hospitals in the Uppsala Health Care Region participated in the study (one university hospital, four county hospitals and one county district hospital). Swedish hospitals almost exclusively recruit their patients by the place of residence and not by preferences. Thus, the general practitioners refer patients in their catchment area only to these hospitals. In case of emergency care at a hospital outside the region, all follow-up must occur at the hospital in the area where the patient is resident.

In Uppsala County data collecting began on the 1st of January 2005 and in the remaining counties on the 1st of January 2007. The study was closed for inclusion on the 31st of December 2009.

During 2005–2006 the mean population in the study area was 305,381 individuals and during 2007–2009, when the geographic area of the study expanded, the mean population was 642,117. Eighty-one percent of the population in the expanded region lived in urban areas (compared to the whole of Sweden: 85%) and the population density was 37.7 inhabitants per km^2 (Sweden: 22.8). Thirteen percent were born in another country (Sweden: 14.3%).[8]

All probable new cases of inflammatory bowel disease (IBD) during the time period were reported prospectively to the local investigators. Furthermore all colonoscopies and patient records at the clinics were reviewed by the local investigators to ensure that cases not reported by colleagues were identified. Every case was thereafter assessed by at least two gastroenterologists to ensure certainty of diagnosis. In applicable cases the histological samples were reviewed together with experienced pathologists. The cases were classified as UC, Crohn's Disease (CD), IBD unknown (IBDU), observational cases or were excluded. 165 patients with UC diagnosed 2005–2007 in Uppsala County were presented in a previous study[5] and also included in the present study.

The diagnosis of UC was based on established appraisal of patient history together with endoscopic, laboratory and histological findings.[9] An endoscopy was required in order to include the patient, but in 25% of the cases only sigmodeoscopy was performed at the initial visit. The first endoscopy with inflammatory findings interpreted as probable IBD marked the date of diagnosis.

We did not apply a time limit on duration of symptoms, but evaluated other parts of patient history including previous episodes of diarrhea as well as relapses after first diagnosis in order to avoid including patients with undiagnosed infectious colitis. Cases with positive fecal cultures but with chronic histological changes compatible with UC were regarded as observational cases, but later included as UC if they relapsed during follow up with negative cultures. Most patients were diagnosed in an outpatient care setting, but some were diagnosed during an admission to one of the hospital wards.

Registration of data was performed at diagnosis and continuously during the follow up period by scrutinizing patient records. Basic demographic data including gender, age, heredity and symptom duration were recorded. Smoking habits were assessed from patient records at the time of diagnosis. Remission was defined as normalization of daily bowel movements and absence of blood in stools. Time to first relapse during the first 12 months after diagnosis was estimated. The definition of relapse was recurrence of diarrhea or stools with blood requiring changes in current therapy.

Extension and severity of disease according to the Montreal classification were recorded at time of diagnosis.[10] Extension was divided into proctitis (E1), left-sided colitis (E2) and extensive colitis (E3). Only endoscopic and not histological extension was accounted for. If the endoscopy was incomplete and did not reach the upper border of inflammation, it was registered separately as uncertain extent (E2 or E3). Severity was divided into mild (S1), moderate (S2) and severe UC (S3) according to the Montreal classification.[10]

2.1. Statistics

All data were analyzed using the software STATISTICA (data analysis software system), version 10 (2011), StatSoft Inc. Oklahoma, USA (http://www.statsoft.com). Population data were obtained from the governmental Swedish agency Statistics Sweden (http://www.scb.se). Age adjusted incidences were calculated by weighting the incidence in the study area (divided into 5-year age intervals) with the proportion of Swedish population in the same age group each corresponding year. The 95% confidence intervals (CI) of incidence were calculated assuming a Poisson distribution.

Non-parametric continuous variables are presented as median and inter-quartile range (IQR). Non-parametric independent samples by groups were tested for significance with Mann–Whitney two sample rank sum test. Contingency tables were tested with the chi-square test. Survival plots of relapse and colectomy were constructed using Kaplan–Meier analysis. A Cox proportional hazards regression was performed with age, gender, extension and severity at diagnosis as factors. Parameters estimates are presented as hazard ratios (HR) with 95% CI. P-values<0.05 were considered statistically significant.

2.2. Ethical considerations

The study was approved by the local Ethics Committee at Uppsala University.

3. Results

We initially identified 527 UC patients applicable for the study. Twenty-four patients were not domiciled in the study area and thus excluded. Eleven patients were excluded due to change in diagnosis from UC to CD. Twenty-five patients originally classified as IBDU and nine patients as CD were later diagnosed as UC and therefore included. In most cases the change in diagnosis was made in the first few months of disease. Thus, the total number of UC cases in this study was 526. Nine of these patients moved outside the region and were lost to follow up.

3.1. Basic epidemiology

The mean overall incidence for the time period was 20.0 (95% CI: 16.1–23.9) cases per 100,000 inhabitants/year, age adjusted for the Swedish population (Fig. 1). Separate incidence for men and women distributed in 10-years age groups are presented in Fig. 2. There is a noticeable peak in incidence between the ages of 20 and 39 and a second peak among men in the 60–79 age groups. The crude incidence among children under 10 years of age was 2.6 per 100,000/year and for children under 17 years 8.9 per 100,000/year.

3.2. Disease phenotype

Demographic data as well as extent and severity of inflammation according to the Montreal classification are shown in Table 1. The variation in age at diagnosis was considerable with the youngest patient only 3 years old and the eldest patient 88 years old. There was a slight male preponderance with a male vs. female ratio of 1.24. Fifty-five (10%) had a relative with IBD.

Women had a significantly higher proportion of proctitis and mild symptoms compared to men, but there was no gender difference in the small subgroup of extensive as well as severe cases.

Patients presenting with extensive colitis (E3) were significantly younger ($P=.0023$) than patients with a more limited disease (E1 or E2) with a median age of 28.5 (IQR: 19.0–52.0) compared to 38.0 (IQR: 26.0–56.0). There was, however, no difference in age between patients with mild, moderate or severe symptoms. Patients with severe symptoms had a shorter disease history compared to patients with mild and moderate symptoms (1.0 vs. 3.0 months, $P<.0001$).

Children (<17 years of age, n=42) had a similar proportion of severe disease at diagnosis compared to adults (11.9% vs 8.3%, $P=.3931$). Twenty-seven (64%) of the children had an extensive colitis (adults: 28%, $P<.0001$).

3.3. Early disease course

All patients had symptoms at the time of diagnosis. 228 patients (43.3%) had a relapsing course during the first 12 months after diagnosis (Fig. 3). The median time before recurring symptoms was 133 (IQR: 67.0–204.0) days. Twenty-three patients (4.4%) had chronic symptoms with absence of remission. 266 patients (50.6%) remained in remission during the first year. In nine patients (1.7%) it was not possible to assess remission or relapse due to insufficient journal records.

Factors affecting risk of relapse was female gender (HR: 1.37, 95% CI: 1.10–1.71, $P=.0053$) and age under 40 years (HR: 1.29, 95% CI: 1.03–1.61, $P=.0287$). Neither extension nor severity at the time of diagnosis was associated with risk of relapse.

Only 13 patients (2.5%) required colectomy during the first 12 months of follow up, all due to severe inflammation (Fig. 3). All 13 patients received high-dose corticosteroids and five patients (38%) were treated with infliximab as rescue therapy prior to colectomy. Six patients had left-sided colitis (E2) and seven patients had extensive colitis (E3). The colectomy rate did not differ between adults and children (12/484 vs. 1/42, $P=.9686$). One additional patient with a previously known primary sclerosing cholangitis was colectomized due to colonic cancer, but also had an extensive colitis at colonoscopy with mild symptoms. The median time from diagnosis to surgery was short (14.5 days, IQR: 9.0–122.0), with eight patients colectomized within 30 days from diagnosis (Fig. 4).

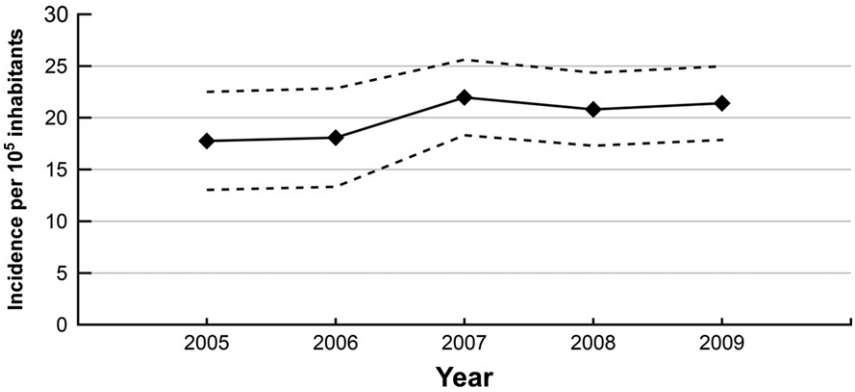

Figure 1 Age adjusted incidence. Dotted lines: upper and lower limits of 95% confidence interval assuming a Poisson distribution.

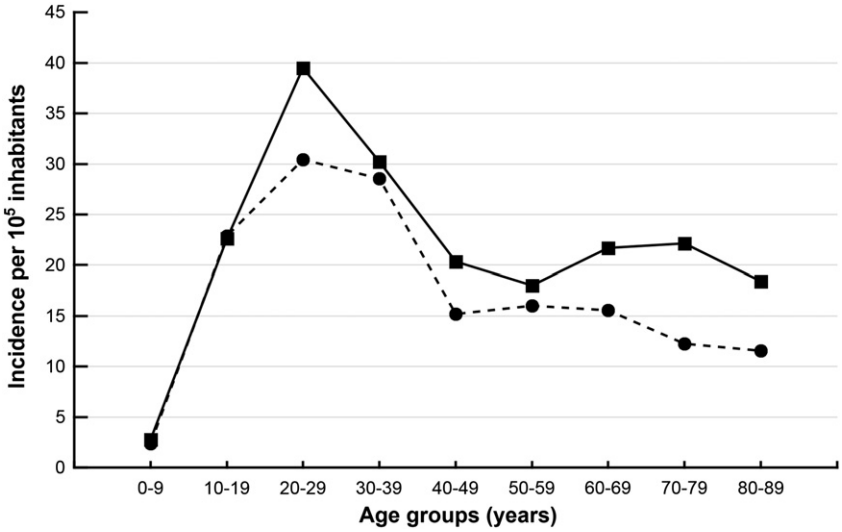

Figure 2 Crude incidence in different age groups. Men (–■–); women (--●--).

3.4. Medication

512 of the patients (97%) were prescribed 5-ASA, steroids or a combination of 5-ASA and steroids during the first year. Mono-therapy with either 5-ASA or steroids was used in only 11%. In 14 patients (3%) no medication was prescribed and all these patients had mild and transient symptoms. Within the first year 61 patients (12%) were treated with immunosuppressive drugs (azathioprine, mercaptopurine or methotrexate) and 25 patients (5%) with anti-TNF-alpha antibodies. Introduction of systemic steroids, immunosuppressive drugs and anti-TNF-alpha antibodies during the first 12 months are presented in Fig. 5.

3.5. Smoking

Smoking habits were documented in 342 patient records. 130 (38%) of these patients were ex-smokers, 41 (12%) were current smokers and 171 (50%) had never smoked. The non-smokers had a significantly higher proportion of extensive colitis compared to current or ex-smokers (38%, 23% and 22% respectively, $P = .0005$), but this difference was confounded by the lower age of the first group and when stratifying for age there was no difference. The smoking habits did not affect the severity of the disease.

4. Discussion

In this population based study we found one of the highest incidences of UC in the world (Table 2), to the best of our knowledge only surpassed by incidence rates generated from a recent register study in Finland.[11] The second highest reported incidence, presented by the EC-IBD workgroup,[12] was 24.3 among the Icelandic population in the age group 15–64 years. Our calculated crude incidence in the same age group was 24.5.

Table 1 Demographics, extent and severity of disease at diagnosis.

	All (n = 526)		Men (n = 291)		Women (n = 235)		*P* value [a]
Median age, years (IQR)	36.0 (23.0–54.0)		36.0 (24.0–55.0)		35.0 (23.0–54.0)		
Mean age, years (SD)	39.2 (19.3)		39.5 (19.3)		38.9 (19.4)		0.6252
Symptom duration before diagnosis, median months (IQR)	3.0 (1.0–7.0)		2.5 (1.0–6.0)		4.0 (1.5–8.0)		0.0042
	n	(%)	n	(%)	n	(%)	
Extent							
Proctitis (E1)	167	(31.7)	75	(25.8)	92	(39.1)	0.0011
Left sided colitis (E2)	161	(30.6)	99	(34.0)	62	(26.4)	0.0588
Extensive colitis (E3)	163	(31.0)	98	(33.7)	65	(27.7)	0.1379
Uncertain extent (E2 or E3)	35	(6.7)	19	(6.5)	16	(6.8)	0.8983
Severity							
Mild (S1)	269	(51.1)	132	(45.4)	137	(58.3)	0.0025
Moderate (S2)	209	(39.7)	132	(45.4)	77	(32.8)	0.0038
Severe (S3)	45	(8.6)	26	(8.9)	19	(8.1)	0.7291
Missing	3	(0.6)	1	(0.3)	2	(0.9)	0.4027

[a] Men vs women, Mann–Whitney *U*-test or χ^2-test.

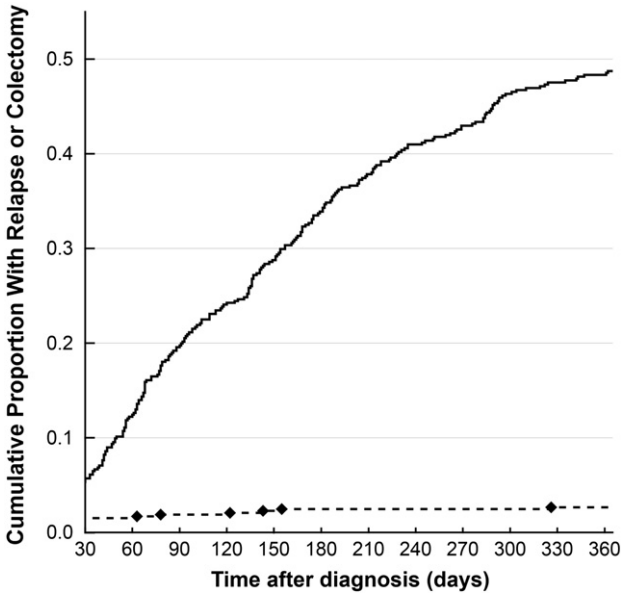

Figure 3 Kaplan–Meier plot of patients with relapse (–) and colectomy (---) during follow-up after 12 months. Relapse was defined as recurrence of diarrhea or stools with blood requiring changes in current therapy.

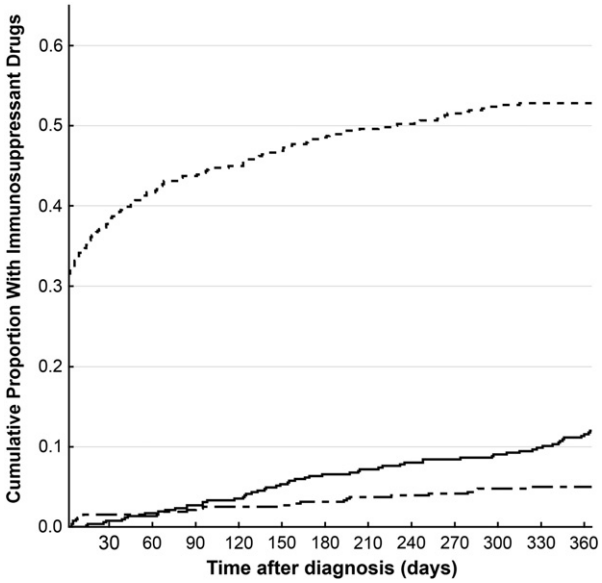

Figure 5 Kaplan–Meier plot of patients introduced to anti-TNF-alpha antibodies (– - –), azathioprine/puri-nethol/methotrexate (–) and systemic steroids (---).

Studies from northern France[13] and USA[14] have reported a low incidence, kept constant over several decades. In contrast the incidence in Uppsala County has increased markedly from 10.4 during 1945–1983[5] to 20.0 during 2005–2009 (present study). UC remained uncommon among children under the age of 10 in our study population, which corresponds well to several previous studies.[5,7,15,16] However, incidence was rather high in the 0–15 year group, especially compared to data from the neighboring county of Stockholm with a crude incidence of 2.2 during 1990–2001[17] and 3.6 during 2002–2007.[18]

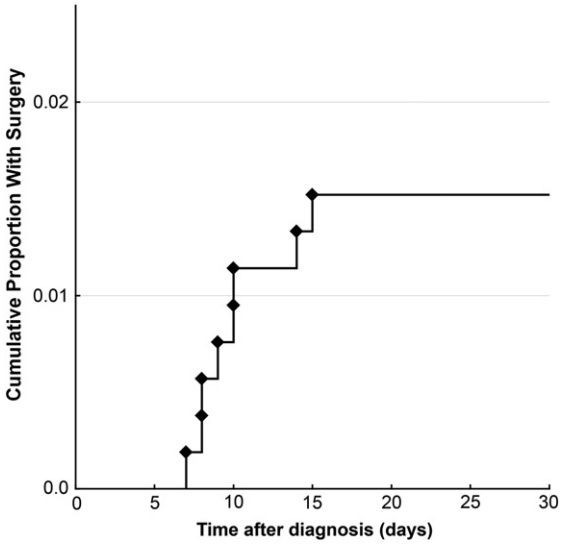

Figure 4 Kaplan–Meier plot of patients with colectomy days 0–30 after diagnosis.

In order to explain the observed increase in UC in our region, exposition to environmental factors is of importance. High intake of total fat, mono-unsaturated fatty acids (MUFA), poly-unsaturated fatty acids (PUFA) and omega-6 fatty acids have been associated with increased UC risk.[19–22] There has been an increased intake of omega-6 fatty acids in Sweden until the 1990s.[24] The Swedish consumption of MUFA and PUFA is however lower than in southern European countries[23] and saturated fatty acids constitute the main proportion of fat intake in Sweden.[24]

A previously identified risk factor for developing UC is cessation of smoking.[25] There has been a prominent decline in smoking in Sweden during the past decade, with only 14.5% of the population smoking compared to the OECD average of 23.6%.[26]

The extent of disease was in line with previous studies[7,15,27,28] suggesting that there has not been an over-inclusion of more benign proctitis cases. The finding that young patients had a more extensive inflammation was previously reported in a population-based study from France.[29]

In one of the first studies of the natural history of UC from Oxford,[30] the proportion of severe cases was 10.7% in the years 1958–1962. The corresponding proportion in Uppsala County was 7% during 1945–1964.[5] When compared with our results of 8.6% severe cases almost 50 years later, it could be stated that the nature of UC has not changed, only the incidence.

Only 2.5% of the patients were subjected to colectomy within the first 12 months after diagnosis. This was similar to data from the IBSEN group with a colectomy rate of 3.5% after one year,[31] but was considerably lower than the 6% reported from Denmark.[27] However, in the latter study no patient received IV treatment with steroids, which may explain the higher colectomy rates. The colectomy rate after one year was only 0.5% in a study from Hungary,[28] but no data regarding severity was presented which makes a comparison difficult.

Table 2 Incidence rates of ulcerative colitis in selected population based studies.

Country		Time period	Incidence	Population	Author
Finland	Nationwide	2000–2007	24.8	5,240,000	Jussila[11]
Iceland	Nationwide	1990–1994	16.5	260,000	Björnsson[35]
Norway	South-Western	1990–1993	13.6	966,427	Moum[15]
Denmark	Copenhagen	2003–2005	13.4	1,211,634	Vind[27]
Hungary	Veszprem	2002–2006	11.9	364,500	Lakatos[28]
Canada	5 provinces	1998–2000	11.8	5,500,000	Bernstein[36]
Australia	Geelong	2007–2008	11.2	259,015	Wilson[37]
USA	Olmsted County	1990–2000	8.8	124,000	Loftus[14]
Germany	Oberpfalz	2004–2006	3.9	1,090,000	Ott[38]
France	Northern	2006–2007	3.4	5,790,526	Chouraki[13]
South Korea	Songpa-Kangdong	2001–2005	3.1	1,069,899	Yang[39]

Whether these differences in colectomy frequency could be related to heterogeneity in patient materials, phenotypes or treatment traditions in different countries is still unclear. The relapse rate was in line with a previous report.[32]

There has been a discussion whether UC in young patients are prone to a more severe disease. In this rather large material with the same inclusion criteria and background population, the children more often had an extensive disease. We could, however, not find any differences in severity at diagnosis between children and adults. Neither was there any elevated risk for colectomy among children. One interpretation to this could be that genetic factors predispose to early onset of extensive disease, but that the severity of the disease has other causes, i.e. environmental factors.

Taking into account that UC patients develop their disease in early adulthood without decreased life expectancy,[33,34] it is crucial to acknowledge that this will result in a markedly elevated prevalence. More health care resources need to be assigned to this patient group in the future.

One of the strengths with the current study was the recruitment process with thorough evaluation of each case, compared to relying on data from a disease registry. Some potential cases may have eluded identification, including cases diagnosed and treated exclusively by general practitioners. It is however our experience that very few IBD patients are handled in the primary health care and they are usually referred to specialist units. There was also a very low variation of incidence between the different parts of the region, suggesting that inclusion was uniform.

In conclusion, the UC incidence reported in this study is one of the highest in the world. The proportion of severe cases is similar to historical data from the same region. This indicates that it is a true increase and not attributed to better diagnostics. The nature of UC has not changed, only the incidence.

Conflict of interest

None.

Acknowledgments

DS and AR carried out the studies and data analyses and drafted the manuscript. AE, LH, AN, ML and TH conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Dr Steven Lucas and Dr Lars Åkerberg have contributed in finding patients for the study. Dr Erika Björs and Dr Maria Hårdstedt contributed with valuable comments regarding the manuscript.

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