

Supplementary Table 1 Search algorithms

Explanation	ID	Search terms
Search syntax applied in Ovid for MEDLINE, Embase, and EMB Reviews		
Disease and synonyms	#1	exp crohn disease/ or (colitis, granulomatous or crohn disease or crohn's disease or crohn's enteritis or crohns disease or enteritis, granulomatous or enteritis, regional or granulomatous colitis or granulomatous enteritis or ileitis, regional or ileitis, terminal or ileocolitis or inflammatory bowel disease 1 or regional enteritis or regional ileitides or regional ileitis or terminal ileitis).mp.
Syntax for perianal fistulas	#2	((anal adj5 fistul\$) or (perianal adj5 fistul\$) or (rectal adj5 fistul\$)).ti,ab.
Combine studies of CD with mention of fistulae	#3	1 and 2
Exclude other languages	#4	limit 3 to English language
Time limitations for only recent treatment options	#5	limit 4 to yr="2015-Current"
Unique entries only	#6	remove duplicates from 5
Search Syntax applied on Ovid for EconLit		
Syntax for disease and perianal fistulas	#1	Crohn disease and fistul* (Including Limited Related Terms)
Exclude other languages	#2	limit 1 to English language

Time limitations for only
recent treatment options

#3 limit 1 to yr="2015 -Current"

CD: Crohn's disease.

Supplementary Table 2 Study characteristics (N = 140). Please see supplementary Excel file for further details on what was reported in each study

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Abraham_2020 ¹	AB	US	CS	Yes	Epidemiology	774	N/A	NR [N/A]
Adegbola_2018c ₂	AB	Europe (UK)	Cohort, retrosp.	No	Treatment	236	NR	NR [N/A]
Adler_2015 ³	AB	US, UK	Cohort, retrosp.	Yes	Epidemiology Risk	6679	max. 60	Yes [1]
Adler_2019a ⁴	FT	US	CS	No	Epidemiology	274	N/A	NR [N/A]
Adler_2020a ⁵	FT	US	Cohort, retrosp.	Yes	Epidemiology Risk	CD: 2, 214 CPF: 384	45 (range: 24.3-182.4)	NR [N/A]
Al-Saddah_2019 ⁶	AB	Kuwait	Cohort, retrosp.	No	Epidemiology	132	23.6 (IQR: 2.6-60.3)	NR [N/A]
Alina_2018 ⁷	AB	Europe (Romania)	Cohort, retrosp. prosp.	No	Epidemiology	16	NR	NR [N/A]
Alli-Akintade_2015 ⁸	FT	US	CS	No	Epidemiology	333	N/A	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Angiolini_2018 ⁹	AB	Europe (Italy)	Cohort, retrosp.	No	Epidemiology Treatment	165	146 ^b	NR [N/ A]
Angriman_2020 ¹⁰	AB	Europe (Italy)	CS	No	Treatment	66	N/ A	NR [N/ A]
Arai_2021 ¹¹	AB	Japan	Cohort, retrosp.	No	Epidemiology	53	NR	NR [N/ A]
Ashton_2015 ¹²	FT	Europe (UK)	CS	No	Epidemiology	106	N/ A	NR [N/ A]
Assa_2017a ¹³	AB	Israel/ Multicountry	Cohort, prosp.	Yes	Epidemiology	234	NR	NR [N/ A]
<i>Azzam_2020¹⁴</i>	<i>AB</i>	<i>Saudi Arabia</i>	<i>Cohort, retrosp.</i>	<i>No</i>	<i>Risk Treatment</i>	<i>61</i>	<i>≥ 12</i>	Yes [3]
Balint_2018 ¹⁵	FT	Europe (Hungary)	Cohort, retrosp.	No	Epidemiology Risk	CD: 517 CPF: 134	NR	NR [N/ A]
Battat_2017a ¹⁶	AB	Canada	Cohort, prosp.	No	Epidemiology	62	NR	NR [N/ A]
Biemans_2020 ¹⁷	AB	Europe (Netherlands)	Cohort, prosp.	Yes	Epidemiology	221	13 (IQR: 12.3 - 14.6)	NR [N/ A]
Black_2017a ¹⁸	FT	Multicountry	Cohort,	Yes	Morbidity	253	NR	Yes [3]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
			retrosp.		Risk Treatment			
Bokemeyer_2019 ¹⁹	AB	Europe (Germany)	Cohort, prosp.	Yes	Epidemiology	334	4	NR [N/ A]
Boucher_2016b ²⁰	AB	Europe (France)	Cohort, retrosp.	No	Epidemiology	161	≥ 6	NR [N/ A]
Bounab_2015 ²¹	FT	Algeria	Cohort, prosp.	No	Epidemiology	169	82.8 ^b	NR [N/ A]
Brochard_2018 ²²	AB	Europe (France)	Cohort, retrosp.	No	Morbidity Risk, Treatment	70	70 (IQR: 48-96)	NR [N/ A]
Brochard_2022 ²³	FT	Europe (France)	Cohort, prosp.	Yes	Epidemiology Risk	CD: 272 CPF: 53	153.6 (SD: 74.4) ^b	NR [N/ A]
Bruckner_2018 ²⁴	FT	Europe (Germany, Austria)	Cohort, retrosp.	Yes	Epidemiology Risk	742	14.4 (range: 1.2-87.6)	NR [N/ A]
Chen_2021a ²⁵	FT	US	Cohort, retrosp.	Yes	Epidemiology	81862	12	NR [N/ A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Chun_2018 ²⁶	FT	South Korea	Cohort, retrosp.	Yes	Epidemiology Morbidity Risk	CD: 1193 CPF: 465	105.2 (range: 12-309.6) ^b	NR [N/A]
Cyranka_2022 ²⁷	FT	NR	CS	No	Epidemiology	169	N/A	NR [N/A]
Danielou_2020 ²⁸	FT	Europe (France)	Cohort, prosp.	Yes	Epidemiology Risk	CD: 907 CPF: 59	68.4 (range: 24-127.2)	Yes [10]
De Gregorio_2021b ²⁹	FT	Australia, New Zealand	CS	Yes	Treatment	193	N/A	Yes [4]
Deng_2021 ³⁰	FT	China	Cohort, retrosp.	No	Morbidity Risk, Treatment	130	62 (IQR: 28-117)	Yes [5]
Dhaliwal_2021 ³¹	FT	Canada	Cohort, prosp.	Yes	Epidemiology	451	18	NR [N/A]
Diaz Hernandez_2016	FT	Europe (Spain)	Cohort, retrosp.	No	Epidemiology	62	6	NR [N/A]
El-Matary_2019 ³³	AB	Canada	Cohort, prosp.	Yes	Epidemiology Risk	CD: 667 CPF: 52	6	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
<i>Erzin_2015</i> ³⁴	<i>FT</i>	<i>Europe (Turkey)</i>	<i>Cohort, retrosp.</i>	<i>No</i>	<i>Epidemiology Risk Treatment</i>	<i>60</i>	<i>NR</i>	NR [N/ A]
Fan_2020 ³⁵	AB	US	CS	Yes	Epidemiology	878	N/ A	NR [N/ A]
Felton_2020 ³⁶	AB	US	Cohort, retrosp.	No	Risk Treatment	53	NR	NR [N/ A]
<i>Ferrante_2020b</i> ³⁷	<i>AB</i>	<i>Multicountry^c</i>	<i>CS</i>	<i>Yes</i>	<i>Treatment</i>	<i>498</i>	<i>N/A</i>	NR [N/ A]
Francois_2019 ³⁸	AB	Europe (France)	Cohort, retrosp.	No	Morbidity Risk Treatment	200	NR	NR [N/ A]
<i>Georgiadou_2019</i> ³⁹	<i>FT</i>	<i>Europe (Germany)</i>	<i>CS</i>	<i>Yes</i>	<i>Epidemiology Risk Treatment</i>	<i>CD: 13 346 CPF: 451</i>	<i>N/A</i>	Yes [1]
Gklavas_2021 ⁴⁰	FT	Europe (Greece)	CS	No	Treatment	95	36	NR [N/ A]
Gold_2018a ⁴¹	AB	NR	Cohort, retrosp.	No	Treatment	100	NR	NR [N/ A]
Gomes_2021 ⁴²	FT	Brazil	CS	Yes	Epidemiology	303	N/ A	NR [N/ A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Goren_2021 ⁴³	AB	Israel	CS	No	Epidemiology	97	N/A	NR [N/A]
Gottgens_2017 ⁴⁴	FT	Europe (Netherlands)	Cohort, retrosp.	Yes	Epidemiology Risk Treatment	1162	133.2 (SD: 69.6)	Yes [4]
Graf_2016 ⁴⁵	FT	Europe (Sweden)	Cohort, retrosp.	No	Morbidity Risk Treatment	119	85.2 (range: 12- 210)	NR [N/A]
Gu_2020 ⁴⁶	AB	Australia	CS	Yes	Risk Treatment	123	N/A	NR [N/A]
Gubatan_2021 ⁴⁷	AB	US	Cohort, retrosp.	No	Risk Treatment	311	60	NR [N/A]
Haennig_2015 ⁴⁸	FT	Europe (France)	Cohort, retrosp.	No	Epidemiology , Risk Treatment	81	63.8 (range: 2- 263)	Yes [10]
Herissay_2021 ⁴⁹	FT	Europe (France)	Cohort, retrosp.	Yes	Morbidity Risk Treatment	169	48 (IQR: 15.6- 86.4)	Yes [5]
Herman_2017a ⁵⁰	FT	Europe (Israel)	Cohort,	No	Epidemiology	296	102 (IQR:	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
			retrosp.				62.4- 140.4)	
Hong_2020 ⁵¹	FT	China	Cohort, retrosp.	No	Epidemiology Treatment	CD: 301 CPF: 91	6-12 (after diagnosis)	NR [N/ A]
Hsu_2017 ⁵²	FT	Taiwan	Cohort, retrosp.	Yes	Epidemiology	611	64.3 (range: 0.07 -167.2)	NR [N/ A]
<i>Jeon_2019⁵³</i>	<i>FT</i>	<i>South Korea</i>	<i>Cohort, retrosp.</i>	<i>No</i>	<i>Treatment</i>	<i>76</i>	<i>25.8 (SD: 13.7)</i>	NR [N/ A]
Jiang_2021a ⁵⁴	AB	US	CS	No	Epidemiology Morbidity Risk	CD: 403 CPF: 103	N/ A	NR [N/ A]
Jung_2015b ⁵⁵	FT	South Korea	Cohort, retrosp.	Yes	Epidemiology	1002	NR	NR [N/ A]
Kang_2020 ⁵⁶	FT	South Korea	CS	Yes	Epidemiology Risk	CD: 241 CPF: 108	N/ A	NR [N/ A]
Kaur_2016 ⁵⁷	FT	US	CC	No	Epidemiology Risk	CD: 1721 CPF: 524	NR	NR [N/ A]
Kim_2015 ⁵⁸	AB	South Korea	Cohort, retrosp.	No	Epidemiology	600	NR	NR [N/ A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Kim_2017b ⁵⁹	FT	South Korea	CS	Yes	Risk	CD: 734	NR	NR [N/A]
Kim_2020a ⁶⁰	AB	South Korea	Cohort, prosp.	No	Epidemiology	440	21 (range: 1- 78; IQR: 14 - 33)	NR [N/A]
Lawrence_2021 ⁶¹	FT	US	Cohort, retrosp.	No	Epidemiology Risk	150	76.8 (SD: 34.8) ^b	NR [N/A]
Lee_2015 ⁶²	FT	South Korea	Cohort, retrosp.	No	Epidemiology	2414	88.8 ^b	NR [N/A]
Lee_2017a ⁶³	FT	South Korea	Cohort, prosp.	No	Mortality Risk	1065	103.2 ^b	NR [N/A]
Lee_2018c ⁶⁴	FT	Europe (UK)	Cohort, retrosp.	No	Treatment	79	6.8	NR [N/A]
Lee_2020b ⁶⁵	AB	NR	CS	No	Treatment Risk	99	N/A	NR [N/A]
Lee_2021 ⁶⁶	FT	Australia	Cohort, retrosp.	No	Treatment	93	57.6 (IQR: 28.8-72)	Yes [1]
Lian_2018a ⁶⁷	AB	China	CS	No	Epidemiology	248	N/A	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Lightner_2021 ⁶⁸	FT	US, Canada	Cohort, retrosp.	No	Epidemiology	63	17.7 (IQR: 4.72- 38.7)	NR [N/ A]
Lima Martins_2018 ⁶⁹	FT	Brazil	CS	Yes	Epidemiology	352	N/ A	NR [N/ A]
Lin_2016 ⁷⁰	FT	China	Cohort, retrosp.	No	Morbidity Risk Treatment	65	25.3 (range: 3-84; SD: 17.9) ^b	Yes [10]
Longworth_2019 ⁷¹	FT	Europe (UK)	CS	No	Epidemiology	162	N/ A	NR [N/ A]
Lovasz_2017 ⁷²	AB	Europe (Hungary)	Cohort, retrosp.	No	Epidemiology	75	NR	NR [N/ A]
Mak_2018b ⁷³	FT	China	Cohort, retrosp.	Yes	Epidemiology Treatment	CD: 981 CPF: 242	106 (IQR: 65- 161)	Yes [7]
Malian_2020a ⁷⁴	FT	Europe (France)	Cohort, retrosp.	No	Mortality Risk Treatment	157	43 (IQR: 26-64)	NR [N/ A]
Mansoor_2020c ⁷⁵	AB	US	CS	Yes	Epidemiology	139 070	N/ A	NR [N/ A]
Martinez	FT	Europe (Spain)	CS	No	Epidemiology	430	N/ A	Yes [3]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Sanchez_2021 ⁷⁶					Morbidity			
Mizushima_2021 ⁷⁷	FT	Japan	Cohort, retrosp.	Yes	Epidemiology	2 932 854 - 5 123 077 (not all CD patients)	NR	NR [N/ A]
Moon_2015a ⁷⁸	FT	South Korea	Cohort, retrosp.	Yes	Epidemiology Risk	1047	89.5 (range: 6-173.3; SD: 36.1) ^b	NR [N/ A]
Motamedi_2021 ⁷⁹	FT	Canada	Cohort, retrosp.	No	Morbidity Risk Treatment	83	31 (IQR: 15-54)	Yes [5]
<i>Mujukian_2020a⁸⁰</i>	<i>FT</i>	<i>US</i>	<i>Cohort, retrosp.</i>	<i>No</i>	<i>Morbidity Risk Treatment</i>	<i>60</i>	<i>36 (6-192)</i>	NR [N/ A]
Naffouj_2018 ⁸¹	AB	US	Cohort, retrosp.	No	Risk Treatment	79	NR	NR [N/ A]
Nam_2021 ⁸²	FT	South Korea	Cohort, retrosp.	No	Risk Treatment	51	26 (range: 2-89)	NR [N/ A]
Nordholm-Carstensen_2019	AB	Europe	Cohort,	Yes	Epidemiology	CD: 17 789	NR	NR [N/ A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
⁸³		(Denmark)	retrosp.		Treatment	CPF: 1773		
Ota_2020 ⁸⁴	AB	Japan	Cohort, retrosp.	Yes	Epidemiology	1135	NR	NR [N/A]
Papaconstantinou_2017 ⁸⁵	FT	Europe (Greece)	Cohort, retrosp.	No	Morbidity Risk Treatment	59	19.2 (SD: 13.2)	NR [N/A]
Park_2021b ⁸⁶	FT	South Korea	Cohort, retrosp.	No	Risk Treatment	209	29	Yes [8]
Park_2021c ⁸⁷	FT	South Korea	Cohort, retrosp.	No	Morbidity Risk Treatment	69	46 (IQR: 30- 52.5)	NR [N/A]
Park_2019b ⁸⁸	FT	South Korea	Cohort, retrosp.	Yes	Epidemiology	418	NR	NR [N/A]
Parlow_2018b ⁸⁹	AB	NR	Cohort, retrosp.	No	Morbidity Risk Treatment	77	3; 6	NR [N/A]
Pestour_2018 ⁹⁰	AB	Europe (France)	Cohort, retrosp.	No	Epidemiology	133	NR	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Pires_2019 ⁹¹	AB	Europe (Portugal)	Cohort, prosp.	No	Epidemiology	298	120	NR [N/A]
Plevris_2020 ⁹²	FT	Europe (UK)	CS	No	Risk Treatment	64	N/A	NR [N/A]
Qari_2022 ⁹³	FT	Saudi Arabia	CS	No	Epidemiology	245	N/A	NR [N/A]
Rabilloud_2016a ⁹⁴	AB	Europe (France)	Cohort, retrosp.	Yes	Epidemiology Morbidity Risk	CD: 272 CPF: 87	153.6	Yes [9]
Radford-Smith_2015 ⁹⁵	AB	Australia	Cohort, retrosp.	No	Epidemiology	257	123 (IQR: 88.7-165.4)	NR [N/A]
Rayen_2017 ⁹⁶	FT	New Zealand	Cohort, retrosp.	No	Treatment	57	32 (IQR: 16-48)	Yes [9]
<i>Reddy_2016⁹⁷</i>	<i>AB</i>	<i>US</i>	<i>Cohort, retrosp.</i>	<i>No</i>	<i>Morbidity Mortality Risk Treatment</i>	<i>57</i>	<i>NR</i>	NR [N/A]
Reid_2020 ⁹⁸	AB	Canada	Cohort, retrosp.	No	Treatment	50	80.4 (SD: 76.8) ^b	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Rencz_2019b ⁹⁹	FT	Europe (Hungary)	CS	No	Epidemiology	206	N/A	NR [N/A]
Rinawi_2017 ¹⁰⁰	FT	Europe (Israel)	CS	No	Epidemiology	275	N/A	NR [N/A]
Rodriguez-Lago_2020 ¹⁰¹	FT	Europe (Spain)	Cohort, retrosp.	No	Epidemiology	85	24	NR [N/A]
Rubin de Celix Vargas_2018 ¹⁰²	FT	Europe (Spain)	Cohort, retrosp.	No	Epidemiology Morbidity Mortality Treatment	CD: 300 CPF: 65	NR	Yes [8]
Sahnan_2017b ¹⁰³	AB	Europe (UK)	Cohort, retrosp.	Yes	Risk	3623	NR	NR [N/A]
Schaad_2021 ¹⁰⁴	AB	Europe (Switzerland)	Cohort, prosp.	No	Risk Treatment	365	90 (range: 0- 151.2)	NR [N/A]
Schoepfer_2019 ¹⁰⁵	FT	Europe (Switzerland)	Cohort, prosp.	Yes	Risk	1550	90 (range: 0- 151.2)	NR [N/A]
Sebastian_2018 ¹⁰⁶	AB	Multinational ^d	Cohort, retrosp.	Yes	Morbidity Risk Treatment	253	NR	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Sebastian_2017e ¹⁰⁷	FT	Multinational ^d	Cohort, retrosp.	Yes	Morbidity Risk Treatment	116	NR	NR [N/A]
Seifarth_2021 ¹⁰⁸	FT	Europe (Germany)	Cohort, retrosp.	No	Treatment	55	7	NR [N/A]
Sheriff_2019 ¹⁰⁹	AB	US	CS	Yes	Epidemiology	187 070	N/A	NR [N/A]
Sibio_2018 ¹¹⁰	FT	Europe (Italy)	Cohort, prosp.	No	Treatment	61	≥ 12	NR [N/A]
Singer_2016a ¹¹¹	AB	US	Cohort, retrosp.	No	Epidemiology Risk Treatment	CD: 363 CPF: 57	NR	NR [N/A]
<i>Solina_2016¹¹²</i>	<i>AB</i>	<i>Europe (Italy)</i>	<i>Cohort, prosp.</i>	<i>No</i>	<i>Treatment</i>	<i>58</i>	<i>NR</i>	NR [N/A]
Song_2016 ¹¹³	FT	South Korea	Cohort, retrosp.	No	Epidemiology	178	≥ 3	NR [N/A]
Song_2018 ¹¹⁴	AB	South Korea	Cohort, retrosp.	No	Epidemiology	2989	86 (IQR: 44.9- 138.8)	NR [N/A]
Song_2020 ¹¹⁵	FT	South Korea	Cohort,	Yes	Epidemiology	CD:9188	86 (IQR:	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
			retrosp.		Risk Treatment	CPF: 2456 / 1639	44.9- 138.8)	
Strik_2019b ¹¹⁶	FT	Europe (Netherlands)	CS	No	Epidemiology Risk Treatment	CD: 352 CPF: 66	N/A	NR [N/A]
Sugrue_2017a ¹¹⁷	AB	US	Cohort, retrosp.	No	Treatment	56	48 (range: 0-144)	NR [N/A]
Toruner_2017 ¹¹⁸	AB	Turkey	Cohort, prosp.	No	Epidemiology	106	12	NR [N/A]
Trad_2019 ¹¹⁹	AB	Tunisia	Cohort, retrosp.	No	Epidemiology	79	NR	NR [N/A]
Vidon_2021 ¹²⁰	FT	Europe (France)	Cohort, retrosp.	No	Risk Treatment	119	18.3	Yes [6]
Vuyyuru_2020 ¹²¹	FT	India	Cohort, retrosp.	No	Epidemiology Mortality Risk Treatment	65	45 (IQR: 24-66)	Yes [6]
Wallenhorst_2016 ¹²²	FT	Europe (France)	Cohort, retrosp.	No	Epidemiology	282	Approx. 60	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Walters_2016a ¹²³	AB	Canada	CS	Yes	Epidemiology	305	N/A	NR [N/A]
Wang_2021 ¹²⁴	FT	China	Cohort, retrosp.	No	Epidemiology	293	72 (IQR: 36-108)	Yes [9]
Watadani_2015 ¹²⁵	AB	Japan	CS	No	Morbidity Risk Treatment	84	N/A	NR [N/A]
Watadani_2020 ¹²⁶	AB	Japan	Cohort, prosp.	No	Morbidity Risk Treatment	59	40 (IQR: 16-91)	NR [N/A]
Wewer_2021 ¹²⁷	FT	Europe (Denmark)	Cohort, retrosp.	Yes	Epidemiology Risk Treatment	CD: 9739 CPF: 943	98.4 (IQR: 49.2-159.6)	NR [N/A]
Xu_2020 ¹²⁸	FT	China	CS	No	Morbidity Risk	139	N/A	Yes [7]
Yarur_2017 ¹²⁹	FT	US	CS	No	Risk Treatment	117	N/A	NR [N/A]
Yassin_2015e ¹³⁰	AB	NR	Cohort, retrosp.	No	Risk Treatment	270	72 (range: 1-163)	NR [N/A]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
Yewale_2021 ¹³¹	FT	India	CS	Yes	Epidemiology	654	N/A	NR [N/A]
Zaharie_2016 ¹³²	FT	Europe (Romania)	CS	Yes	Risk	44	N/A	NR [N/A]
Zarrar Khan_2021 ¹³³	AB	US	Cohort, retrosp.	Yes	Epidemiology	23 860	NR	NR [N/A]
Zeitz_2015 ¹³⁴	AB	Europe (Switzerland)	CS	Yes	Risk	CD: 1600	N/A	NR [N/A]
Zhang_2016 ¹³⁵	AB	China	Cohort, retrosp.	No	Epidemiology	152	NR	NR [N/A]
Zhao_2020a ¹³⁶	FT	Europe (Denmark)	Cohort, prosp.	Yes	Epidemiology	95	NR	NR [N/A]
Zhao_2019 ¹³⁷	AB	Europe (Denmark)	Cohort, prosp.	No	Epidemiology	213	120 (IQR: 99.6-134.4)	NR [N/A]
Zhi_2019 ¹³⁸	AB	China	Cohort, retrosp.	No	Epidemiology Risk Treatment	CD: 274 CPF: 158	12-24 months	NR [N/A]
Zhu_2021 ¹³⁹	FT	China	Cohort, retrosp.	No	Epidemiology Risk	CD: 471 CPF: 178	7.8-33.8 months	Yes [10]

Study name	FT or AB	Country	Study design	Population-based?	Outcomes	Sample size ^a	Follow-up (months)	Complex CPF % study pop [# defining characteristics]
					Treatment			
Zhu_2022 ¹⁴⁰	FT	China	Cohort, retrosp.	No	Morbidity Risk Treatment	117	36 (IQR: 23.5-58.5)	Yes [10]

^aSample size refers to number of patients with CD for epidemiology outcomes and number of patients with CPF for other outcomes.

^bMean value reported, otherwise median value reported.

^cBelgium, France, Germany, Italy, Spain.

^d11 centres across Europe.

Blue text: calculated values. Bold and italicized text: studies including 100% complex CPF.

AB: abstract; CC: case-control; CD: Crohn's disease; CPF: Crohn's perianal fistulas; CS: cross-sectional; IQR: interquartile range; NR: not reported; prosp.: prospective; retrosp.: retrospective; SD: standard deviation.

Supplementary Table 3 Prevalence of complex Crohn's perianal fistulas among patients with Crohn's disease

Time point ^a	Number of studies	Median, range (IQR)
Before diagnosis ^b	1	14.1%, N/ A
Past history of fistula at any time ^c	3	18.6%, 12.4-19.2% (15.5-18.9%)
Presence of fistula at cross-sectional time points ^d	11	16.3%, 3.4-48.2% (6.1-28.8%)
Fistula documented by MRI/MRE scan	3	4.1%, 3.6-54.6% (3.9-29.4%)

^aStudies were included more than once if they described prevalence at multiple time points.

^bIncludes time points before CD diagnosis, before or at CD diagnosis, and at CD diagnosis.

^cIncludes time points before enrolment, before and/or at time of survey, before and/or after CD diagnosis, after CD diagnosis, and throughout follow-up.

^dIncludes time points at enrolment, at baseline, at time of survey, at end of follow-up, at hospital/surgery admission.

CD: Crohn's disease; CPF: Crohn's perianal fistulas; IQR: interquartile range; MRE: magnetic resonance elastography; MRI: magnetic resonance imaging.

Supplementary Table 4 Incidence of Crohn's perianal fistulas among patients with Crohn's disease

Time after CD diagnosis (number of studies)	Cumulative incidence (%)		
	Median	Range	IQR
1 year (<i>n</i> = 8)	11.0	3.5-50.1	8.1-20.1
2 years (<i>n</i> = 1)	18.7	N/A	N/A
3 years (<i>n</i> = 3)	11.0	7.5-37.9	9.3-24.5
5 years (<i>n</i> = 6)	16.0	11.6-54.7	16.0-34.8
10 years (<i>n</i> = 5)	19.0	15.8-57.4	19.0-25.0
15 years (<i>n</i> = 2)	20.0%	20.0%	20.0%
20 years (<i>n</i> = 1)	21.5%	N/A	N/A
25 years (<i>n</i> = 1)	23.9%	N/A	N/A

CD: Crohn's disease; CPF: Crohn's perianal fistulas; IQR: interquartile range.

Supplementary Table 5 Intervention categories

Intervention category	Interventions	
Antibiotics ^{a,b}	• Antibiotics • Ciprofloxacin and/or metronidazole	
Biologics ^{a,b}	• Adalimumab • Anti-TNF • Biologics • Certolizumab • Infliximab • Monoclonal antibody treatment • Ustekinumab • Vedolizumab	
Immunomodulators/Immunosuppressants ^{a,b}	• 5-ASA • Azathioprine • Immunosuppressants • Methotrexate • Thalidomide • Thiopurines	
Cell therapy ^{a,b}	• Stem cell therapy	
Steroids ^a	• Steroids • Systemic corticosteroids	
Colectomy/-ostomy ^a	• Bowel diversion • Colectomy • Colostomy • Permanent colostomy	
Cutting seton ^b	• Cutting seton • Cutting seton fistulotomy • Long-term seton • Permanent seton	

Fistulectomy/-otomy^{a,b}

Flap^{a,b}

Glue^{a,b}

Loose seton^{a,b}

Plug^{a,b}

Surgery^{a,b}

Surgery (without seton)^{a,b}

- Fistulectomy
- Advancement flap
- Fibrin glue injection
- Loose seton
- Anal fistula plug
- Surgery
- Local proctological surgery (including seton drainage)
- Abdominoperineal resection
- Colon deviation and/or extirpation operations
- External drainage
- Faecal diversion
- Ileal and/or colonic resection
- IPAA
- Ileostomy
- Incision and drainage
- Intestinal diversion
- LIFT
- Fistulotomy
- Seton (indwelling seton)
- Minor surgery
- Surgery (unspecified)
- Obturation
- Luminal resection
- Permanent stoma
- Proctectomy
- Proctocolectomy
- Sphincter-sparing techniques
- Stoma
- Surgical drainage
- Surgical fistula closure
- Video-assisted anal fistula treatment

Multimodal approach	• Multimodality treatment (combination of medical treatments [antibiotics, immunosuppressants, and biologics] along with surgical approach [examination under anaesthesia +/- seton drainage])
Other ^a	• Medical treatment (not further specified) • Traditional treatment (neither biologics nor surgery) • Non-biological treatment • NSAID • Prior repair attempts • Salicylates • Triple MedTx

^aIntervention-specific healing data available.

^bIntervention-specific treatment failure data available.

ASA: amino salicylic acid; IPAA: ileal pouch-anal anastomosis; LIFT: ligation of the intersphincteric fistula tract; NSAID: non-steroidal anti-inflammatory drugs; SCT: stem cell therapy; TNF: tumour necrosis factor; Tx: treatment.

Supplementary Table 6 Proportion of patients with morbidities of interest across multiple time points

Time point	Proportion of patients (no. of studies)				
	Abscess (<i>n</i> = 16)	Anal stricture/stenosis (<i>n</i> = 14)	Faecal incontinence (<i>n</i> = 6)	Proctitis and/or continuous pain in the anal area ^a (<i>n</i> = 13)	Sepsis (<i>n</i> = 4)
At CPF diagnosis	79.0-87.7 (<i>n</i> = 2)	9.5-27.2 (<i>n</i> = 2)	NA (<i>n</i> = 0)	41.0-80.2 (<i>n</i> = 3)	NA (<i>n</i> = 0)
Baseline	22.5-53.0 (<i>n</i> = 6)	4.3-30.8 (<i>n</i> = 6)	57.0 (<i>n</i> = 1)	25.6-58.5 (<i>n</i> = 8)	NA (<i>n</i> = 0)
Enrolment (cross-sectional)	23.7-67.2 (<i>n</i> = 3)	31.7 (<i>n</i> = 1)	3.4-72.8 (<i>n</i> = 3)	NA (<i>n</i> = 0)	NA (<i>n</i> = 0)
Surgery	14.5-78.3 (<i>n</i> = 3)	18.0-22.6 (<i>n</i> = 2)	6.7 (<i>n</i> = 1)	27.0-40.5 (<i>n</i> = 2)	NA (<i>n</i> = 0)
After surgery	14.5 (<i>n</i> = 1)	15.4-15.4 (<i>n</i> = 1)	4.6-16.3 (<i>n</i> = 3)	NA (<i>n</i> = 0)	13.3 (<i>n</i> = 1)
During follow-up	16.6-66.0 (<i>n</i> = 2)	14.9-30.1 (<i>n</i> = 2)	NA (<i>n</i> = 0)	NA (<i>n</i> = 0)	1.5-1.8 ^b (<i>n</i> = 2)
Other specific time point	41.6 ^c (<i>n</i> = 1)	NA (<i>n</i> = 0)	NA (<i>n</i> = 0)	NA (<i>n</i> = 0)	43.7 ^d (<i>n</i> = 1)

Studies may report rates at multiple time points.

^aOnly one study reported pain in anal area; all other studies in this category reported proctitis.

^bStudies only report patients who died from sepsis.

^cAt 3 months.

^d5 years post-surgery.

CPF: Crohn's perianal fistulas; NA: not applicable.

Supplementary Table 7 Risk factors associated with developing Crohn's perianal fistulas

Risk factors for developing CPF	Number of studies	References	Countries
Male sex ^a	7	3,5,15,24,26,56,115	US, Hungary, Germany/ Austria, South Korea
Colonic CD location (L2)	5	28,57,115,134,138	China, France, South Korea, Switzerland, US
Younger age at CD diagnosis ^b	5	26,59,76,115,134	South Korea, Spain, Switzerland
Rectal involvement	4	23,28,57,76	France, Spain, US
Stricturing CD behaviour (B2)	3	28,57,134	France, Switzerland, US
Antibiotics	1	134	Switzerland, US
Anti-TNF/biologics ^b	2	127,134	Denmark, Switzerland, US
Extraintestinal manifestations	2	23,76	France, Spain
Higher C-reactive protein levels ^a	2	15,111	Hungary, US
Ileocolonic location (L3)	2	26,134	South Korea, Switzerland
Long diagnostic delay of CD (≥ 18 months; delay > 75th percentile)	2	78,105	South Korea, Switzerland

Risk factors for developing CPF	Number of studies	References	Countries
Ulcerations	2	23,94	France
Corticosteroids ^a	1	24	Austria / Germany
African American ethnicity <i>vs</i> Caucasian ethnicity	1	75	US
CD diagnosis before 2005	1	115	South Korea
CD diagnosis between 6-10 years old (<i>vs</i> < 6, 10-13, 14-17, ≥ 17 years) ^a	1	3	US
CD diagnosis in 2009-2014 (<i>vs</i> in 2001-2005)	1	5	US
Diagnosis of CD at primary care clinics	1	26	South Korea
Each additional year of age at CD diagnosis	1	5	US
Ethnic group other than Romanian	1	132	Romania
Family history of IBD among first-degree relatives	1	57	US
Female sex	1	103	United Kingdom
Gastrointestinal bleeding	1	5	US
Genetic associations	1	57	US
Higher antimicrobial antibody levels (ASCA IgG, ASCA Ig A, I2, Omp C), and ANCA positivity	1	57	US

Risk factors for developing CPF	Number of studies	References	Countries
Higher weight/BMI z-score ^a	1	56	South Korea
Internal fistulas	1	5	US
Ischiorectal abscess (<i>vs</i> perianal abscess)	1	103	United Kingdom
Non-white race	1	111	US
Northeast US region (<i>vs</i> other US regions) ^a	1	3	US
Penetrating CD behaviour	1	28	France
Presence of granulomas on diagnostic biopsies ^a	1	61	US
Presence of non-penetrating perianal lesions ^a	1	111	US
Procedures before CD diagnosis: Perianal lesion (skin tag, haemorrhoid) removal, fistulotomy, incision, and drainage of a perianal abscess ^{a111}	1	111	US
Rectal location at diagnosis	1	23	France
Shorter diagnostic delay of CD (≤ 6 months)	1	115	South Korea
Smoking at time of CD diagnosis	1	134	Switzerland
Upper GI tract location ^a	1	56	South Korea

^aIncluded in at least one paediatric-only study.

^bIncluded in at least one adult-only study.

Montreal Classification for Crohn's Disease was used to describe some clinical characteristics (*e.g.* A1-A3, L1-L4, B1-B3).

ANCA: anti-neutrophil cytoplasmic antibody; ASCA: anti-Saccharomyces cerevisiae antibodies; BMI: body mass index; CD: Crohn's disease; GI: gastrointestinal; IBD: inflammatory bowel disease; Ig: immunoglobulin; OMP C: outer membrane porin C; TNF: tumour necrosis factor.

Supplementary Table 8 Protective factors associated with developing Crohn's perianal fistulas

Factors associated with a lower likelihood for developing CPF	Number of studies	References	Countries
Anti-TNF/biologics ^a	3	5,61,111	US
Female sex ^b	2	127,134	Denmark, Switzerland
Immunosuppressants use <i>vs</i> non-use ^a	2	5,61	US
Older age at CD diagnosis (> 60 years) ^b	2	44,134	Netherlands, Switzerland
Antibiotics	1	5	US
Corticosteroids	1	5	US
Diagnosed with CD in later years (2012-2014) <i>vs</i> 2001-2011	1	5	US
Higher education level of primary insurance policy holder	1	5	US
Ileal CD location (L1)	1	134	Switzerland
Isolated small bowel CD	1	57	US
Non-stricturing and non-penetrating CD behaviour (B1)	1	57	US
<i>Perianal EUA with drainage performed within 12 months prior to MRI</i>	1	29	<i>Australia/New Zealand</i>

Factors associated with a lower likelihood for developing CPF	Number of studies	References	Countries
Steroid-sparing therapy (immunosuppressants and/or anti-TNF) to treat CD <i>vs</i> no SST use, early use of SST <i>vs</i> later use of SST	1	⁵	US

^aIncluded in at least one paediatric-only study.

^bIncluded in at least one adult-only study.

Bolded and italicized text indicates factors for complex CPF population.

CD: Crohn's disease; CPF: Crohn's perianal fistulas; EUA: examination under anaesthesia; MRI: magnetic resonance imaging; SST: steroid-sparing therapy; TNF: tumour necrosis factor.

Supplementary Table 9 Risk factors associated with treatment failure

Risk factors for the failure of advanced therapies	Number of studies	References	Countries
Complex perianal fistula (<i>vs</i> simple perianal fistula) ^b	5	29,30,48,102,125	Australia/New Zealand, China, France, Japan, Spain
Stricturing behaviour (B2) ^b	4	47,48,74,125	France, Japan, US
<i>Higher number of fistulas/tracts^b</i>	3	29,34,89	Australia/New Zealand, <i>Turkey</i>
<i>Longer duration of CD since diagnosis</i>	3	29,34,116	Australia/New Zealand, Netherlands, <i>Turkey</i>
<i>Perianal abscess at baseline^b</i>	3	14,44,140	China, Netherlands, <i>Saudi Arabia</i>
Prior or concomitant proctitis	3	116,125,139	China, Japan, Netherlands
Anti-TNF use (<i>vs</i> no anti-TNF use) ^a	1	70	China, US
Discontinuation of anti-TNF therapy	2	30,74	China, France
<i>Female sex</i>	2	34,48	<i>France</i> , Turkey
Fistulotomy (<i>vs</i> seton) ^a	2	86,111	South Korea, US
Higher BMI at baseline ^a	2	29,111	Australia/New Zealand, US
<i>Higher C-reactive protein at baseline</i>	2	14,29	Australia/New Zealand, <i>Saudi Arabia</i>

Risk factors for the failure of advanced therapies	Number of studies	References	Countries
<i>Luminal CD</i>	2	34,130	<i>Turkey</i> , Not reported
<i>Rectal involvement</i>	2	14,34	<i>Saudi Arabia, Turkey</i>
Absence/discontinuation of immunosuppressant after start of fistula tract management ^b	1	49	France
Active smoking	1	129	US
Anterior fistula ^b	1	49	France
Anti-TNF dose escalation	1	29	Australia/New Zealand
History of perianal surgery	1	139	China
Ileocolonic CD location (L3)	1	130	Not reported
<i>Longer perianal fistula duration</i>	1	34	<i>Turkey</i>
<i>Longer time spent under seton</i>	1	34	<i>Turkey</i>
<i>Low BMI at baseline</i>	1	14	<i>Saudi Arabia</i>
Lower infliximab levels	1	129	US
Mucosal inflammation	1	129	US
Need for ≥ 2 fistula drainages ^b	1	49	France

Risk factors for the failure of advanced therapies	Number of studies	References	Countries
Older age (at least 40)	1	125	Japan
Penetrating CD (B3) ^b	1	30	China
Presence of antibodies to infliximab	1	129	US
Presence of rectovaginal fistula	1	48	France
Sphincter-sparing techniques/ seton <i>vs</i> fistulotomy ^b	1	49	France
<i>Suprasphincteric perianal fistula</i>	1	14	<i>Saudi Arabia</i>
Surgical treatment for PF <i>vs</i> medical treatment only ^b	1	44	Netherlands
Vedolizumab (<i>vs</i> ustekinumab among patients for whom anti-TNF treatment failed)	1	47	US

^aIncluded in at least one paediatric-only study.

^bIncluded in at least one adult-only study.

Bolded and italicized text indicates factors for complex CPF population.

BMI: body mass index; CD: Crohn's disease; PF: perianal fistula; TNF: tumour necrosis factor.

Supplementary Table 10 Protective factors associated with treatment failure

Factors associated with the success of advanced therapies	Number of studies	References	Countries
Higher median anti-TNF drug levels ^a	7	29,33,46,65,92,116,129	Australia, Australia/New Zealand, Canada, Netherlands, United Kingdom, US
Anti-TNF + immunosuppressant	4	38,116,120,130	France, Netherlands, Not Reported
Lower CD severity/lower median HBI	2	92,129	United Kingdom, US
Lower C-reactive protein level	2	92,129	United Kingdom, US
Initial control with seton ^{a,b}	2	79,111	Canada, US
<i>Longer anti-TNF treatment time</i>	2	34,116	Netherlands, <i>Turkey</i>
Non-inflamed rectal mucosa ^b	2	45,129	Sweden, US
Shorter duration of CD ^b	2	45,130	Sweden, Not reported
Stem cell therapy	2	86,87	South Korea
< 2 secondary tracts	1	22	France
Among patients for whom anti-TNF treatment failed, switching to another anti-TNF (compared with switching to ustekinumab)	1	47	US
Anal ulceration as first CD manifestation	1	22	France

Factors associated with the success of advanced therapies	Number of studies	References	Countries
Anti-TNF (<i>vs</i> no anti-TNF)	1	130	Not Reported
Anti-TNF naïve (before starting IFX therapy)	1	116	Netherlands
Fistula closure as the last surgical procedure	1	22	France
Fistulotomy	1	86	South Korea
Ileal CD location (L1)	1	139	China
Initial curative operation (fistulotomy or advancement flap) ^b	1	45	Sweden
<i>LIFT procedure vs AF</i>	1	80	US
<i>Longer azathioprine treatment time</i>	1	34	Turkey
Longer duration on continuous anti-TNF drug therapy	1	29	Australia/New Zealand
Lower levels of detectable antibodies to infliximab	1	129	US
Lower/superficial fistula (F1 Cardiff Hughes classification)	1	22	France
Luminal CD	1	22	France
Male sex	1	129	US
No perianal abscess	1	121	India

Factors associated with the success of advanced therapies	Number of studies	References	Countries
No proctitis	1	130	Not reported
No suprasphincteric fistula tract	1	22	France
Older age	1	29	Australia/New Zealand
Presence of proctitis	1	38	France
Seton + anti-TNF	1	116	Netherlands
Seton drainage + additional surgery + anti-TNF	1	38	France
Shorter fistula duration	1	130	Not reported
Simple fistula (<i>vs</i> complex fistula)	1	130	Not reported
Treatment with surgery alone or surgery + biologics (<i>vs</i> treatment with biologics alone or traditional medical treatment) ^b	1	81	US
Ustekinumab use at time of diagnosis (<i>vs</i> no biologic)	1	47	US
Van Assche score < 15	1	22	France
Younger age at CD diagnosis (Montreal classification A1 [16 years or younger])	1	139	China
<i>Younger age at surgery</i>	1	80	<i>US</i>

^aIncluded in at least one paediatric-only study.

^bIncluded in at least one adult-only study.

Bolded and italicized text indicates factors for complex CPF population.

AF: advancement flap; CD: Crohn's disease; HBI: Harvey Bradshaw index; IFX: infliximab; LIFT: ligation of the intersphincteric fistula tract; TNF: tumour necrosis factor.

Supplementary Table 11 Risk factors associated with patients undergoing multiple surgeries for Crohn's perianal fistulas

Risk factors for undergoing multiple surgeries for CPF	Number of studies	References	Countries
Complex fistula ^{a,b}	4	18,102,106,107	Multicountry (Europe, Israel), Multinational, Spain
Presence of proctitis ^{a,b}	3	18,106,107	Multicountry (Europe, Israel), Multinational
Need of abscess drainage ^a , presence of abscess	2	107,140	China, Multicountry (Europe, Israel)
Absence of multidisciplinary treatment approach (medical treatments + surgery)	1	18	Multinational
Anal stenosis ^b	1	106	Multicountry (Europe), Israel
Concomitant therapy with steroids ^b	1	106	Multicountry (Europe, Israel)
Infliximab maintenance therapy more than 3 infusions	1	140	China
Lack of imaging (MRI or TRUS) before seton removal	1	36	US
Low haemoglobin level	1	82	South Korea
Multiple fistulas	1	82	South Korea
Perianal fistula of the ileocolitis or colitis type	1	82	South Korea

^aIncluded in at least one paediatric-only study.

^bIncluded in at least one adult-only study.

CPF: Crohn's perianal fistulas; MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.

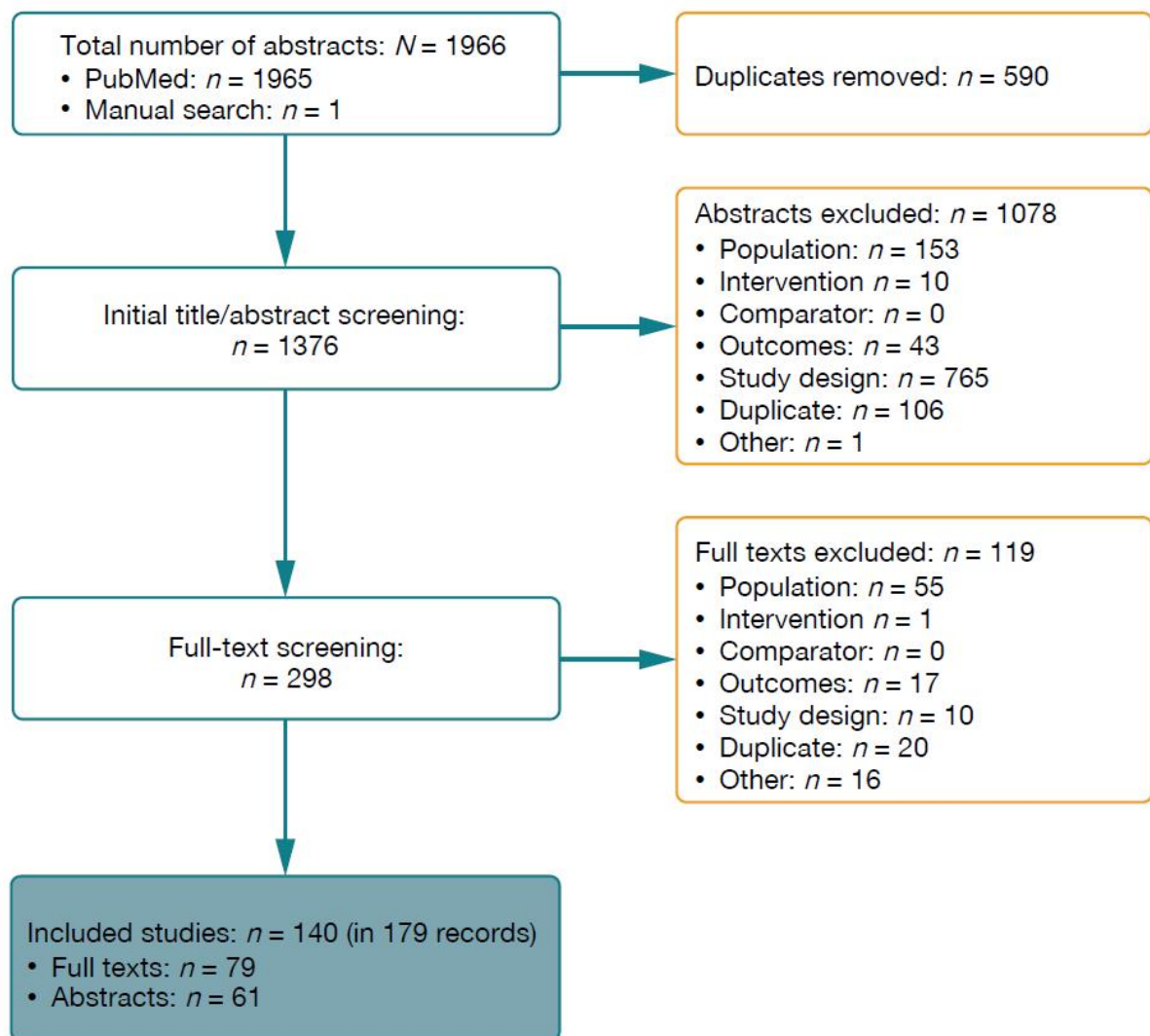
Supplementary Table 12 Protective factors associated with patients undergoing multiple surgeries for Crohn's perianal fistulas

Factors associated with a lower risk of undergoing multiple surgeries for CPF	Number of studies	References	Countries
Anti-TNF therapy ^{a,b}	2	106,107	Multicountry (Europe, Israel)
Biological treatment	1	15	Hungary
Drug escalation therapy (from 5-aminosalicylic acid [5-ASA] to thiopurine or from 5-ASA or thiopurine to anti-TNF agents)	1	82	South Korea
EUA at presentation ^b	1	106	Multicountry (Europe, Israel)
Multimodality treatment ^b	1	106	Multicountry (Europe, Israel)
Removal of seton after multimodality treatment ^b	1	106	Multicountry (Europe, Israel)

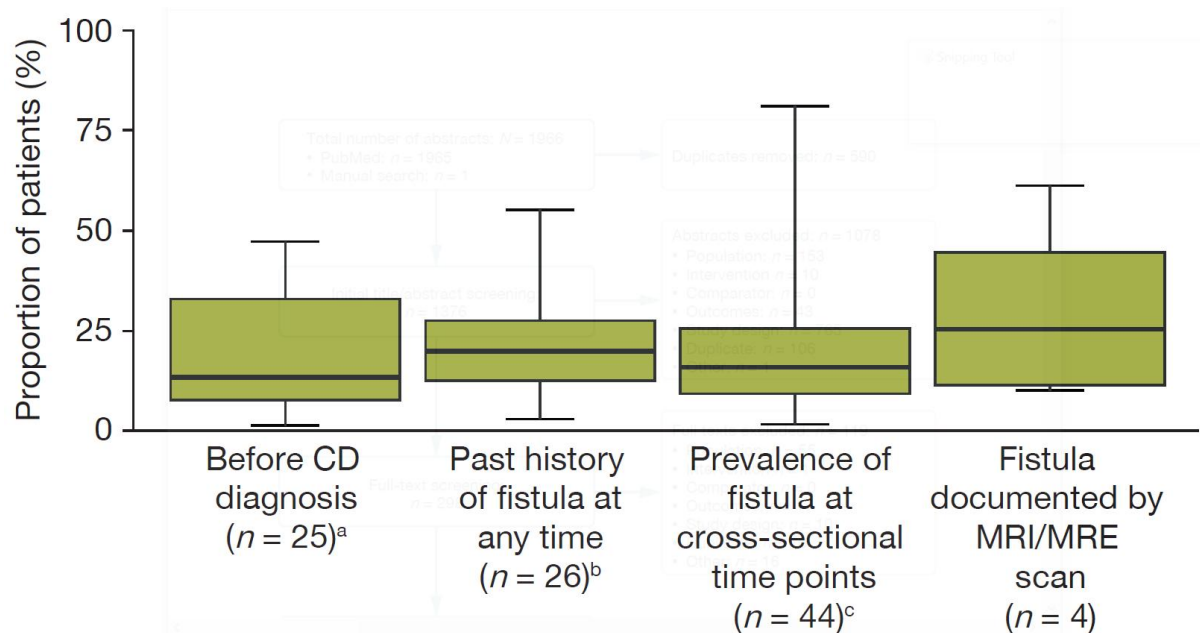
^aIncluded in at least one paediatric-only study.

^bIncluded in at least one adult-only study.

CPF: Crohn's perianal fistulas; EUA: examination under anaesthesia; TNF: tumour necrosis factor.



Supplementary Figure 1 PRISMA flow diagram.



Supplementary Figure 2 CPF prevalence was varied across all time points ($n = 84$ studies).

One study may have contained multiple time points and therefore may be counted more than once.

Boxes indicate the first and third quartile ranges; horizontal lines indicate medians; whiskers indicate minimums and maximums.

^aIncludes time points before CD diagnosis, before or at CD diagnosis, and at CD diagnosis.

^bIncludes time points before enrolment, before and/or at time of survey, before and/or after CD diagnosis, after CD diagnosis, and throughout follow-up.

^cIncludes time points at enrolment, at baseline, at time of survey, at end of follow-up, and at hospital/surgery admission.

CD: Crohn's disease; CPF: Crohn's perianal fistulas; IQR: interquartile range; Max: maximum of reported prevalence; Min: minimum of reported prevalence; MRE: magnetic resonance elastography; MRI: magnetic resonance imaging.