Anal fistulas: a global review on sociodemographic and clinicopathological risk factors

Abstract:

Anal fistulas are a disturbing condition for individuals worldwide. Existing literature primarily focuses on demographics and clinical pathological risk factors in specific areas, rather than providing comparisons of epidemiological trends between regions. This literature review aims to identify the sociodemographics and clinical pathological risk factors for both primary and recurrent anal fistula and how these factors differ across regions. Findings indicated that most risk factors, such as certain comorbidities and prior surgeries, showed consistency in individuals across regions, including Asia, Europe and the Americas. However, regional variations were found in other factors, such as the effect of Crohn's disease and recurrent rate following different surgical procedures. Notably, some regions were omitted from literature due to lack of research on anal fistula-related topics, suggesting future research should be conducted with larger and more representative samples to address the gaps of healthcare challenges in anal fistulas among these regions.

Introduction

An anal fistula is a common colorectal condition that affects the anus and rectum. It is an abnormal inflammatory tunnel connecting the skin near the anus and the bowel. Anal fistulas can be both acute and chronic. The condition typically occurs when an anal abscess develops due to an infection of the anal gland.[1] This anal abscess is the acute phase that usually triggers the development of an anal fistula.[2] An anal fistula can be associated with other diseases as well, including inflammatory bowel disease (Crohn's Disease (CD)), tuberculosis infection, cancer, etc.[3] It is difficult to eradicate an anal fistula because it can recur after having a history of anal abscess or fistula.[4][5]

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[1] Jeremy Sugrue et al., "Pathogenesis and Persistence of Cryptoglandular Anal Fistula: A Systematic Review," *Techniques in Coloproctology* 21, no. 6 (2017): 425–30, https://doi.org/10.1007/s10151-017-1645-5.
[2] A. G. Parks et al., "A Classification of Fistula-in-Ano," *British Journal of Surgery* 63, no. 1 (1976): 1–12, https://doi.org/10.1002/bjs.1800630102.
[3] Cleveland Clinic, "Anal Fistula: Causes, Symptoms, Diagnosis & Treatment," 2023, https://my.clevelandclinic.org/health/diseases/14466-anal-fistula.
[4] Sherif H. Emile, "Recurrent Anal Fistulas: When, Why, and How to Manage?" *World Journal of Clinical Cases* 8, no. 9 (2020): 1586–91, https://doi.org/10.12998/wjcc.v8.i9.1586.
[5] D. M. Skovgaards et al., "Fistula Development after Anal Abscess Drainage—A Multicentre Retrospective Cohort Study," *International Journal of Colorectal Disease* 39, no. 1 (2023), https://doi.org/10.1007/s00384-023-04576-6.

The actual global prevalence of anal fistula is unknown. However, the mean prevalence of anal fistula is estimated to be 8-23 per 100,000 cases based on European studies.[6][7][8][9][10][11] Given these data, it is inferred that thousands of people are affected by anal fistula globally.

Different regions have shown various incidence rates of having both primary and recurrent anal fistula, indicating a difference in the level of risk patients are exposed to based on where they reside. In Asia, specifically in China, anal fistula is commonly seen in men in their second to fourth decade and the overall incidence is 1.67%-3.6% [12] In the United States, the number of new cases per year that underwent primary anal fistula treatment was 20,000 to 25,000 and 96,000 cases per year underwent recurrent treatment after a perianal abscess.[13] Whereas in Europe, a study analysed 16 studies from 1984 to 2019 among seven countries and suggested the overall prevalence rate of anal fistula is 16.9 per 100,000 people.[14]

Anal fistula often causes serious discomfort, highly interfering with patients' overall quality of life.[15] People can feel intense pain and fluids such as pus or blood may emerge around their anus. All levels of complexity of the fistulas would result in different inconveniences, impairing patients' routine activities. Additionally, patients would have to set restrictions on their daily entertainment to manage symptoms, which interfere with patients' relationships with their partners and families and their perceptions of themselves, resulting in psychological distress and insecurity.[16]

In recent years, there have been many studies evaluating the efficiency and improving the procedures for anal fistula repair. Treatment such as endorectal advancement flap, novel

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[6] K. Adamo et al., "Prevalence and Recurrence Rate of Perianal Abscess—A Population-Based Study, Sweden 1997–2009," *International Journal of Colorectal Disease* 31, no. 3 (2016): 669–73, https://doi.org/10.1007/s00384-015-2500-7.

[7] A. Bondurri, "Epidemiology of Anal Fistula and Abscess," *Coloproctology* (2021): 1–10, https://doi.org/10.1007/978-3-030-30902-2_1-1.

[8] D. García-Olmo et al., "Prevalence of Anal Fistulas in Europe: Systematic Literature Reviews and Population-Based Database Analysis," *Advances in Therapy* 36, no. 12 (2019): 3503–18, https://doi.org/10.1007/s12325-019-01117-y.

[9] S. R. Hokkanen et al., "Prevalence of Anal Fistula in the United Kingdom," *World Journal of Clinical Cases* 7, no. 14 (2019): 1795–1804, https://doi.org/10.12998/wjcc.v7.i14.1795.

[10] K. Sahnan et al., "Natural History of Anorectal Sepsis," *British Journal of Surgery* 104, no. 13 (2017): 1857–65, https://doi.org/10.1002/bjs.10614.

[11] C. Zanotti et al., "An Assessment of the Incidence of Fistula-in-Ano in Four Countries of the European Union," *International Journal of Colorectal Disease* 22, no. 12 (2007): 1459–62, https://doi.org/10.1007/s00384-007-0334-7.

[12] W. Yang, "My Views on the Diagnosis and Treatment of Anal Fistula," *Chinese Medical Journal* 47, no. 1 (2012): 18–20, https://doi.org/10.3969/j.issn.1008-1070.2012.01.007.

[13] R. L. Nelson, "Anorectal Abscess Fistula: What Do We Know?" *Surgical Clinics of North America* 82, no. 6 (2002): 1139–51, https://doi.org/10.1016/s0039-6109(02)00063-4.

[14] García-Olmo et al., "Prevalence of Anal Fistulas,"

[15] W. Chadbunchachai et al., "Long-Term Outcomes after Anal Fistula Surgery: Results from Two University Hospitals in Thailand," *Annals of Coloproctology* (2021), https://doi.org/10.3393/ac.2021.01.06.

[16] N. Iqbal et al., "Living with Cryptoglandular Anal Fistula: A Qualitative Investigation of the Patient's Experience through Semi-Structured Patient Interviews," *Quality of Life Research* (2022), https://doi.org/10.1007/s11136-022-03098-y.

approaches such as ligation of the intersphincteric fistula tract (LIFT), or using biological material as an alternative can provide a vast range of options for complex anal fistula cases. [17]

Even with these various treatment options, anal fistula recurrence remains high. These conditions are usually developed due to the failure of complete healing of the surgical wound which underlines the significance of post-operative care of the wound. Both recurrent and primary anal fistulas can be severe and require complex treatment. However, with recurrent anal fistulas health professionals face new challenges such as the possibility of re-recurrence and impairment of bowel continence, making treatments more complex.[18] Globally the anal fistula rate of recurrence ranges from 2.5% to 57.1%.[19] A study in Spain found the anal fistula recurrence rate to be 48.2% within an average follow-up time of 119.7 months, whereas, a study in China found a 13.3% recurrent rate of anal fistula with a median time of recurrence of 7.5 months. [20]

Scientists have focused their efforts on developing new procedures for treating complex anal fistulas, leaving much unknown regarding the epidemiological trends in anal fistulas. Although there are various treatment options, it can be difficult for providers and patients to evaluate which options can best solve the patients' problems as the sociodemographics and medical history of each patient can be different based on the regions they live in and their culture. Previous reviews have stratified the risk factors for anal fistula by pathogenesis and demographic causes. To my knowledge, there has not been a study conducted globally that has identified the trends and risk factors that contribute to anal fistula development. Therefore, this literature review aims to identify the sociodemographics and clinical pathological risk factors for both primary and recurrent anal fistula and how these factors differ across regions.

Methods

A thorough search of the literature was conducted using PubMed and Google Scholar databases. Keyword combinations used in the search included "primary anal fistula," "recurrent anal fistula," "risk factors," and "epidemiology." Studies from all regions related to primary and recurrent anal fistula were included during the initial search. After a general search of the databases, 216 articles were found.

Further selection was then determined based on eligibility criteria. Only empirical research on primary and recurrent anal fistula of adult populations after 1950 was included. These inclusion criteria were applied because research before 1950 may be outdated considering the

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[17] E. Limura, "Modern Management of Anal Fistula," *World Journal of Gastroenterology* 21, no. 1 (2015): 12, https://doi.org/10.3748/wjg.v21.i1.12.

[18] Emile, S. H, "Recurrent anal fistulas," 1586.

[19] Z. Mei et al., "Risk Factors for Recurrence after Anal Fistula Surgery: A Meta-Analysis," *International Journal of Surgery (London, England)* 69 (2019): 153–64, https://doi.org/10.1016/j.ijsu.2019.08.003.

[20] Chi-Ming Poon et al., "Recurrence Pattern of Fistula-in-Ano in a Chinese Population," *Journal of Gastrointestinal and Liver Diseases* 17, no. 1 (2025): 53–57, https://www.jgld.ro/jgld/index.php/jgld/article/view/2008.1.9.

rapid improvements in medical technologies and adult populations are more prevalent to anal fistula than child and adolescent populations. [21]

All review articles were excluded. Empirical research that solely reported the incidence or prevalence rate were excluded as they did not report the epidemiological profile of its sample population. Studies that focused on the anatomical and pathological aspects of anal fistula formation were excluded as they did not identify the risk factors that triggered the pathological changes. The assessment of different surgical approaches and their outcomes were excluded as they were interested in the improvements of patients' symptoms after treatments rather than factors that contribute to the formation of anal fistula. Studies on innovations in treatment options such as novel surgical approaches or medications and improvements in perioperative management were excluded as they did not analyse the potential risk factors. Studies that analysed the surveys of patients' reflections on the changes in their quality of life were excluded as they focused on the effect of anal fistulas on patients' daily lives, not the associations between risk factors and anal fistulas. Lastly, articles focusing on improving surgical wound healing and postoperative patient care were excluded as they suggested new ways to enhance patients' recovery instead of identifying risk factors.

A total of 25 articles were identified once most of the eligibility criteria were applied. However, seven articles were review articles, thus, omitted from the inclusion, leaving 18 eligible articles. After reading through the seven ineligible review articles, 14 eligible empirical studies were found from the embedded references. Once all eligibility criteria were applied, there were a total of 32 articles included in the review with 22 studies investigating primary anal fistulas and ten studies examining recurrent anal fistulas (Figure 1).

[21] J. Deodhar, "Pediatric Fistula-in-Ano: Practice Essentials, Anatomy, Pathophysiology," Medscape (2023), https://emedicine.medscape.com/article/935312-overview#a7?form=fpf.

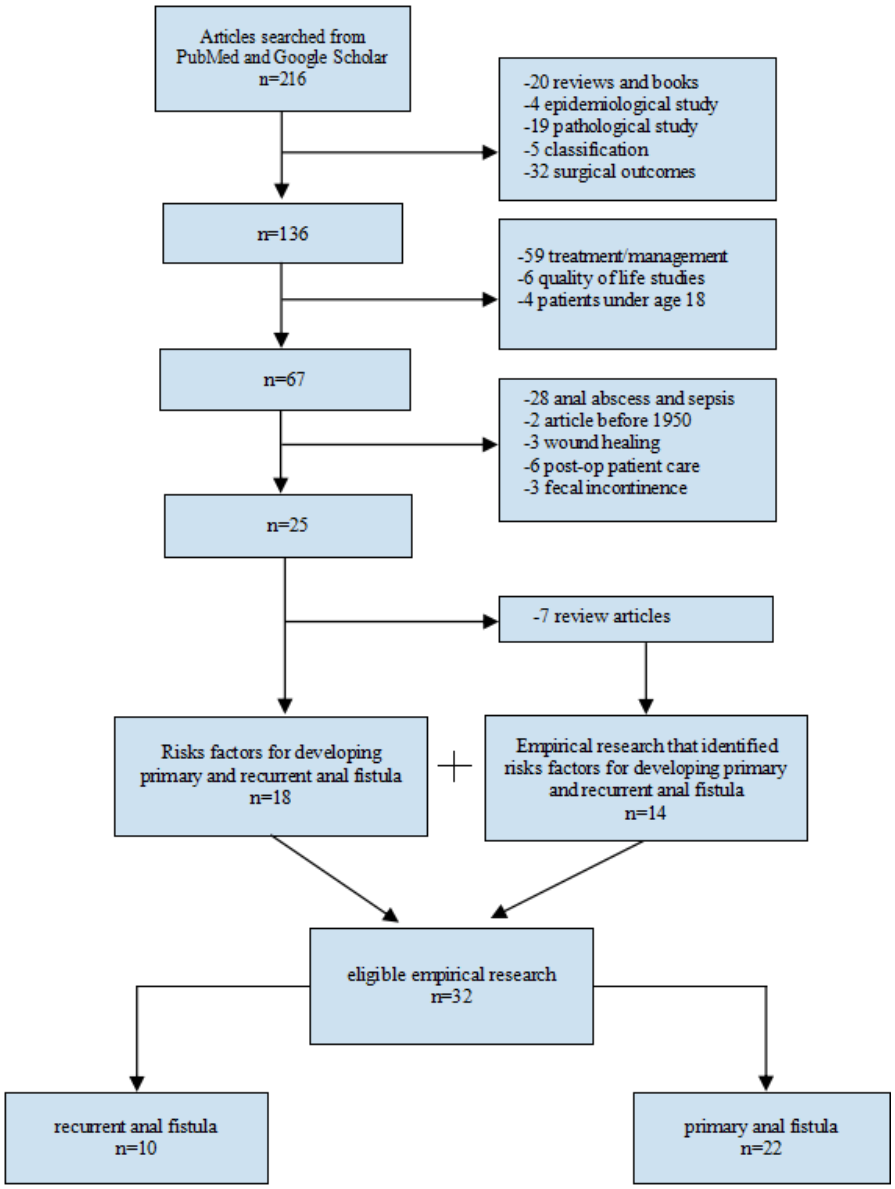

Figure 1. Flowchart of literature included in review

Primary anal fistula

Sociodemographic factors

Age and gender

Most studies in Asia have reported that primary anal fistulas are more prevalent in males than females. A study in Japan assessed 514 patients to evaluate the role of microbiological analysis in anorectal sepsis patients who developed anal fistula and approximately 90% were

male.[22] Gender was found to be a significant risk factor.[23] In this same study, age was not found to be statistically significantly associated with primary anal fistula. However, age was measured as a continuous variable, but the results may have been different if it was measured categorically.[24] Another study in India analysed the modalities of anal fistulas in 150 patients with various demographic features and nearly 71% were males, which may indicate that in Asia anal fistula most commonly occurred in males or there was bias in the sample selection process.[25] The authors of this study found that both gender and age were not statistically significantly associated with primary anal fistulas.[26] Although the Japanese study contradicts the Indian study regarding gender, both studies present consistent evidence that age was not a statistically significant risk factor of anal fistula; however, both studies reported that people in their third to fifth decades were more prone to anal fistula. A study in China that assessed the clinical risk factors for patients with anal fistula found that age and gender were not significantly associated with anal fistula formation even though there was a clear trend of developing anal fistula in middle-aged males.[27] Researchers from a study in Thailand that aimed to determine factors influencing anal fistula formation after acute perianal abscess drainage also found that gender was not predictive of fistula formation.[28] However, results from the study indicated that individuals with age under 40 years had a higher risk of developing anal fistula compared to those over 40 years.[29] Another group of researchers from the USA aimed to investigate the potential risk factors that might contribute to the development of chronic anal fistula and recurrent perianal sepsis.[30] They found that individuals younger than 40 years had a higher risk of developing chronic anal fistulas compared to those over 40 years of age.[31]

Studies in the Americas also calculated the distribution of individuals with anal fistula in different gender and age groups. Results from a study in Brazil that aimed to draw the epidemiological profile of adult patients with anal fistulas revealed that two-thirds of the 117 patients were males and the predominant age group was 18 to 60 years old and both factors were

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[22] T. Toyonaga et al., "Microbiological Analysis and Endoanal Ultrasonography for Diagnosis of Anal Fistula in Acute Anorectal Sepsis," *International Journal of Colorectal Disease* 22, no. 2 (2007): 209–13, https://doi.org/10.1007/s00384-006-0121-x.
[23] Toyonaga et al., "Microbiological Analysis,"
[24] Toyonaga et al., "Microbiological Analysis,"
[25] N. T. B., "An Observational Study on Clinico-Pathological Analysis of Fistula-in-Ano in a Tertiary Care Hospital," *Journal of Medical Science and Clinical Research* 8, no. 5 (2020), https://doi.org/10.18535/jmscr/v8i5.67.
[26] T. B., "Clinico-Pathological Analysis,"
[27] Ping Cai et al., "The Potential Roles of Gut Microbiome in Anal Fistula," *AMB Express* 13, no. 1 (2023): 1–12, https://doi.org/10.1186/s13568-023-01560-9.
[28] V. Lohsiriwat et al., "Incidence and Factors Influencing the Development of Fistula-in-Ano after Incision and Drainage of Perianal Abscesses," *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet* 93, no. 1 (2010): 61–65, https://pubmed.ncbi.nlm.nih.gov/20196412/.
[29] Lohsiriwat et al., "Incidence and Factors,"
[30] A. Hamadani et al., "Who Is at Risk for Developing Chronic Anal Fistula or Recurrent Anal Sepsis after Initial Perianal Abscess?" *Diseases of the Colon & Rectum* 52, no. 2 (2009): 217–21, https://doi.org/10.1007/DCR.0b013e31819a5c52.
[31] Hamadani et al., "Who Is at Risk,"

found to be statistically significant risk factors for primary anal fistula.[32] However, not all findings in the Americas are consistent with those in Asian studies. For example, a study in the USA aimed to determine the prevalence of benign anorectal disease (BAD) in a large population. In this study, 102 adults between the ages 21 to 65 for both genders and all races who had a history of benign anorectal diseases including anal fistulas, haemorrhoids, etc. were interviewed. They found that 53% of the interviewers were female with an average age of 39 years.[33] The authors also found that the female gender was statistically significantly associated with BAD symptoms.[34]

An European study found that males in their middle age (nearly 40 to 50 years old) were more prone to anal fistula just like other studies from other regions, but the reason behind this is unclear.[35] A study in the United Kingdom (U.K.) aimed to determine the factors that lead to a higher prevalence in males than females from an endocrinological perspective. In the study, although it was not statistically significant, they found that male individuals with anal fistula had an overall higher androgen level than male controls, which were individuals without anal fistula.[36] Whereas in females, those with anal fistula had higher levels of estrogen and lower progesterone compared to controls.[37] Based on those results, researchers further hypothesised that it was possible that local endocrinological factors also led to anal fistula formation.[38]

Generally, all three regions, Asia, the Americas, and Europe have shown similar trends in terms of the age and gender of individuals most at risk for anal fistula . Anal fistula is most likely to occur in males in their 40s and 50s. The reasons for a higher prevalence in males are still unclear, yet scientists believe that hormonal factors might play a role in the mechanisms of anal fistula formation.

Lifestyles and behaviours

Lifestyles and behaviours are also deemed as important factors that contribute to anal fistula development. Scientists in China examined 1342 patients and found that sedentary lifestyles with rare participation in sports, eating habits such as regular intake of high salt or spicy food and alcohol, plus prolonged sitting on the toilet for defecation could all increase the risk of developing an anal fistula.[39]

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[32] F. R. Fugita et al., "Epidemiological Profile of Patients with Fistula-in-Ano," *Journal of Coloproctology* 40, no. 1 (2020): 1–7, https://doi.org/10.1016/j.jcol.2019.09.009.
[33] R. L. Nelson et al., "Prevalence of Benign Anorectal Disease in a Randomly Selected Population," *Diseases of the Colon & Rectum* 38, no. 4 (1995): 341–44, https://doi.org/10.1007/bf02054218.
[34] Nelson, R. L. et al., "Prevalence of benign anorectal disease in a randomly selected population."
[35] P. Sainio, "Fistula-in-Ano in a Defined Population: Incidence and Epidemiological Aspects," *Annales Chirurgiae et Gynaecologiae* 73, no. 4 (1984): 219–24, https://pubmed.ncbi.nlm.nih.gov/6508203/.
[36] P. J. Lunniss et al., "Gender Differences in Incidence of Idiopathic Fistula-in-Ano Are Not Explained by Circulating Sex Hormones," *International Journal of Colorectal Disease* 10, no. 1 (1995): 25–28, https://doi.org/10.1007/bf00337582.
[37] Lunniss et al., "Gender Differences,"
[38] Lunniss et al., "Gender Differences,"
[39] D. Wang et al., "Risk Factors for Anal Fistula: A Case-Control Study," *Techniques in Coloproctology* 18, no. 7 (2014): 635–39, https://doi.org/10.1007/s10151-013-1111-y.

The USA study that evaluated the benign anorectal disease population found that fibre consumption and reading materials in the bathroom were positively correlated with BAD symptoms whereas time spent during defecation was negatively correlated; however, these findings were not statistically significant due to inadequate sample size.[40] These results are quite different from those of the Chinese study and these differences may be due to the fact that the USA study focused on a range of benign anorectal diseases, not just on anal fistula. A majority of this population tended to seek and adopt healthy lifestyles as they paid close attention to the choice of bread and fibre supplements, indicating that certain unhealthy eating habits would trigger such types of diseases.[41]

Smoking is another behavioural factor that researchers assessed to determine whether it was associated with anal fistula. Smoking was found to be significantly associated with the development of anal fistulas in a study in China.[42] Researchers in the USA found a similar relationship by asking 1,070 patients to complete a questionnaire about their smoking status and history during their visits to the General Surgery Clinic at the Department of Veterans Affairs (VA) in San Diego.[43] The study aimed to test the hypothesis that recent smoking is a significant risk factor for developing anal fistula.[44] Results showed a significant relationship between the development of anal abscess and fistula with recent smoking behaviours.[45] Additionally, research revealed a trend that individuals' risk of developing anal fistulas decreased as their exposure to smoking shortened over time, which indicated that constant smoking would lead to an increased risk of developing anal fistulas.[46] However, another study from the USA found that smoking was not a risk factor for chronic anal fistulas.[47] Additionally, researchers from Thailand reported that smoking and alcohol consumption were not significant risk factors for developing anal fistula. [48]

Socioeconomic status

Socioeconomic status was evaluated to determine how and if they were associated with anal fistulas. For example, authors from a study in China found that people with higher education levels were more prone to the disease and these same individuals mostly belonged to the middle and upper class.[49] Researchers in India studied the socioeconomic status of patients and found that 70% of 150 anal fistula patients belonged to the middle class; however, this result was not statistically significantly associated with developing anal fistula. [50]

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[40] Nelson et al., "Prevalence of Benign Anorectal Disease,"
[41] Nelson et al., "Prevalence of Benign Anorectal Disease,"
[42] Wang et al., "Risk Factors,"
[43] B. Devaraj et al., "Recent Smoking Is a Risk Factor for Anal Abscess and Fistula," *Diseases of the Colon & Rectum* 54, no. 6 (2011): 681–85, https://doi.org/10.1007/DCR.0b013e31820e7c7a.
[44] Devaraj et al., "Recent Smoking,"
[45]Devaraj et al., "Recent Smoking,"
[46] Devaraj et al., "Recent Smoking,"
[47] Hamadani et al., "Who Is at Risk,"
[48] Lohsiriwat et al., "Incidence and Factors,"
[49] Wang et al., "Risk Factors,"
[50] T. B., "Clinico-Pathological Analysis,"

The study in the USA that interviewed 102 adults found that 73% of the interviewees were married and 93% of them were white.[51] Additionally, 91% had completed either high school or university and 72% of all interviewees had an annual income greater than $25,000, indicating that people in the middle class are more prevalent to develop anal fistula, which is similar to the findings from the China and India studies.[52]

Few studies in Europe have assessed behavioural factors such as lifestyles and habits or socioeconomic statuses of individuals with anal fistulas. A possible explanation is that Europeans have relatively healthier eating habits and are generally more physically active than people in other countries (i.e., the USA). Southern European cultures are known for their Mediterranean diet which was found to reduce the risk of diabetes, certain types of cancers and cardiovascular diseases.[5354] The Mediterranean diet was also related to anti-inflammatory and antioxidant properties which could improve the overall quality of life, which would ultimately strengthen the countries' public health.[55] Additionally, European cities were notable for pedestrian and cyclist-friendly infrastructures that encouraged physical activity among citizens, which further reduced the prevalence of sedentary lifestyles[5657]

Clinicopathological factors

Bacteriology and microbiology

Gut microbiomes have been shown to be associated with the formation of anal fistula. Researchers conducted a study in China that aimed to identify whether gut microbiome of patients with anal fistula contributed to anal fistula formation. They found that a much richer and more diverse gut microbiome culture was seen in individuals without anal fistulas compared to those with anal fistula.[58] More specifically, these researchers found that individuals with anal fistula were enriched in bacteria such as *Blautia, Faecalibacterium, Ruminococcus, Coprococcus, Bacteroides, Clostridium, Megamonas,* and *Anaerotruncus*, while individuals without anal fistula were higher in *Peptoniphilus* and *Corynebacterium.*[59] *Faecalibacterium* was found in both groups, those with and without anal fistula. However, *Faecalibacterium* might influence the progression of anal

[51] Nelson et al., "Prevalence of Benign Anorectal Disease,"
[52] Nelson et al., "Prevalence of Benign Anorectal Disease,"
[53] Francesco Sofi et al., "Adherence to Mediterranean Diet and Health Status: Meta-analysis," *BMJ* 337 (September 11, 2008): a1344, https://doi.org/10.1136/bmj.a1344.
[54] T. Milenkovic et al., "Mediterranean Diet and Type 2 Diabetes Mellitus: A Perpetual Inspiration for the Scientific World. A Review," *Nutrients* 13, no. 4 (2021): 1307, https://doi.org/10.3390/nu13041307.
[55]M. Finicelli et al., "The Mediterranean Diet: An Update of the Clinical Trials," *Nutrients* 14, no. 14 (2022): 2956, https://doi.org/10.3390/nu14142956.
[56] World Health Organization, *Promoting Healthy Active Mobility*, 2021, accessed December 18, 2024, https://www.who.int/europe/activities/promoting-healthy-active-mobility.
[57] European Commission, *Active Mobility: Walking and Cycling*, 2021, https://transport.ec.europa.eu/transport-themes/urban-transport/active-mobility-walking-and-cycling_en.
[58] Cai et al., "Gut Microbiome in Anal Fistula,"
[59] Cai et al., "Gut Microbiome in Anal Fistula,"

fistula when combined with *Butyricicoccus, Coprococcus* and *Gemmiger.*[60] Researchers evaluated 514 patients in Japan who were treated for a clinical diagnosis of acute anorectal sepsis and had undergone microbiological analysis to improve the diagnosis of anal fistulas following anorectal sepsis.[61] They found that aerobic organisms were much greater in individuals with anal fistulas than in individuals without.[62] Gut-derived organisms such as *E. coli, Bacteroides,* and *Klebsiella* species are more frequently seen in individuals with anal fistula, whereas skin-derived organisms such as coagulase-negative *Staphylococci* and *Peptostreptococcus* species tend to be seen more often in individuals without anal fistula.[63]

European researchers were also interested in the bacterium culture of anal fistula patients. Researchers found that gut bacteria are related to the formation of acute anal fistulas. A study in the U.K. evaluated the bacteriology of anal fistula and confirmed that similar organisms were found in the pus of individuals with anal fistula and acute abscesses, indicating acute anal gland infection is associated with anal fistula formation.[64] *E. coli* was the predominant gram-negative aerobic organism and *B. fragilis* was the main gram-negative anaerobic organism, similar to those that grow from acute anal abscess.[65] Both bacteria were considered to be derived from the mucous membrane of the bowel, indicating they are gut- (bowel-) derived organisms.[66] Another study in the U.K. investigated the incidence of anal fistula and the original predominant microorganisms in acute anorectal sepsis reported similar results.[67] Among the 165 participants, most anal fistula patients started with a perianal abscess, others were triggered by Crohn's, anal carcinoma, etc.[68] Individuals with anal fistula were those who grew bowel-derived organisms from their pus, whereas, individuals without further developing anal fistula were those who grew skin-derived organisms from their pus.[69] These results are in alignment with the results of the Japanese study. Furthermore, a study in Denmark aimed to establish the true incidence of anal fistula in anal sepsis patients. Findings from this study aligned with the findings from other studies in which an anal fistula developed after an anorectal sepsis when intestinal microorganisms existed but an anal fistula did not develop after an anorectal sepsis when skin-derived organisms were present.[70] Another group of researchers in Denmark aimed to identify the clinical risk factors for developing anal fistulas following anal abscess treatments. They reported that *E. coli* pus cultures were statistically significantly associated with anal fistula

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[60] Cai et al., "Gut Microbiome in Anal Fistula,"
[61] Toyonaga et al., "Microbiological Analysis,"
[62] Toyonaga et al., "Microbiological Analysis,"
[63] Toyonaga et al., "Microbiological Analysis,"
[64] F. Seow-Choen, A. J. Hay, S. Heard, and R. K. S. Phillips, "Bacteriology of Anal Fistulae," British Journal of Surgery 79, no. 1 (1992): 27–28, https://doi.org/10.1002/bjs.1800790107.
[65] Seow-Choen et al., "Bacteriology of Anal Fistulae,"
[66] Seow-Choen et al., "Bacteriology of Anal Fistulae,"
[67] R. H. Grace, I. A. Harper, and R. G. Thompson, "Anorectal Sepsis: Microbiology in Relation to Fistula-in-Ano," British Journal of Surgery 69, no. 7 (1982): 401–403, https://doi.org/10.1002/bjs.1800690715.
[68] Grace, Harper, and Thompson, "Anorectal Sepsis,"
[69] Grace, Harper, and Thompson, "Anorectal Sepsis,"
[70] S. Henrichsen and J. Christiansen, "Incidence of Fistula-in-Ano Complicating Anorectal Sepsis: A Prospective Study," *British Journal of Surgery* 73, no. 5 (1986): 371–372, https://doi.org/10.1002/bjs.1800730515.

formation.[71] Additionally, scientists from Finland aimed to assess the incidence of anal fistulas and related risk factors after acute anorectal abscess treatment. They reported findings similarly to the study in Denmark, indicating that abscesses with *E. coli* cultures were significantly more prone to fistula formation than those growing other bacteria.[72]

Although gut microbiomes were closely related to acute anal fistulas, studies suggested that the persistence of anal fistulas might be associated with factors other than bacteria. A study in the U.K. aimed to assess the role of microorganisms in chronic anal fistula, reported that there was little evidence to support the role of infection in fistula persistence.[73] Moreover, scientists from Spain who focused on whether the presence of permanent infections was related to chronic anal fistula from a bacteriological perspective also resulted in similar findings.[74] They analysed 27 patients with anal fistula and reported that nearly 80% of samples had a polymicrobial growth, with *E. coli, B. fragilis, S. aureus* and *Viridans streptococci* as the predominant species.[75] However, they found no significant relationship between the number and types of microbiomes and the chronicity of anal fistulas.[76] This result was confirmed by another study from the U.K. in which scientists aimed to identify mucosa-associated bacteria in Crohn's and idiopathic anal fistula tracts.[77] They found little to no bacteria on the luminal surfaces of fistula tracts from individuals with both idiopathic and Crohn's-related anal fistulas, which suggested that bacteria may not play a significant role in the persistence of anal fistula.[78] As both types of fistulas lacked significant bacterial colonisation, it suggested that the role of other factors such as genetic, immunological, or tissue repair could also play a role in fistula persistence.[79] This study suggested that researchers should further investigate the non-bacterial factors that could lead to the chronicity of anal fistulas.

Overall, studies from Asia and Europe reported similar results related to the role of bacteria and microbiomes in the formation of anal fistulas . Gut-derived organisms were widely found in individuals who developed anal fistula from anal abscesses, whereas skin-derived organisms are rarely found in these individuals. Specifically, *E. coli* and *B. fragilis* were reported to be the two predominant bacteria in anal fistula patients. Additionally, scientists implied that the persistence of anal fistula may be associated with non-bacterial factors based on findings that revealed bacteria was not significantly associated with the chronicity of anal fistulas.

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[71] Skovgaards et al., "Fistula Development,"
[72] K.-P. J. Hämäläinen and P. A. Sainio, "Incidence of Fistulas after Drainage of Acute Anorectal Abscesses," Diseases of the Colon & Rectum 41, no. 11 (1998): 1357–1361, https://doi.org/10.1007/bf02237048.
[73] Lunniss et al., "Gender Differences,"
[74] A. De San Ildefonso et al., "Bacteriology of Anal Fistulae," Revista Española de Enfermedades Digestivas 94, no. 9 (2002): 533–536, https://www.researchgate.net/publication/10900311_Bacteriology_of_anal_fistulae.
[75] De San Ildefonso et al., "Bacteriology of Anal Fistulae,"
[76] De San Ildefonso et al., "Bacteriology of Anal Fistulae,"
[77] P. J. Tozer et al., "What Role Do Bacteria Play in Persisting Fistula Formation in Idiopathic and Crohn's Anal Fistula?" Colorectal Disease 17, no. 3 (2015): 235–241, https://doi.org/10.1111/codi.12810.
[78] Tozer et al., "Role of Bacteria in Persisting Fistula Formation,"
[79] Tozer et al., "Role of Bacteria in Persisting Fistula Formation,"

Comorbidities

There are several comorbidities correlated with anal fistula formation. For example, researchers from China found that obesity (body mass index (BMI) exceeding 25 kg/m2 in a Chinese population), prior diabetes, hyperlipidemia, dermatosis, and a previous history of enteritis were independently associated with anal fistula development.[80] A study in India reported that some individuals with anal fistulas had a history of inflammatory bowel disease (IBD) or carcinoma, which indicated the link between anal fistula formation and other intestinal diseases.[81] Specific inflammation such as tuberculosis infection were two of the 150 cases, with the majority of remaining cases being non-specific inflammation.[82] Tuberculosis endemic countries in sub-Saharan Africa and Asia should be aware of this specific infection because it was a risk factor for an anal fistula.[83] Whereas, in Western countries, tubercular anal fistulas were rarely seen in individuals with anal fistulas.[84] Findings from the Thailand study showed that non-diabetic individuals had a higher risk of anal fistula formation, which was contradictory to the study in China.[85] Additionally, researchers from the USA reported that the non-diabetic individuals were more likely to develop chronic anal fistula; however it did not reach statistical significance on multivariate analysis.[86] Thailand researchers also found that fever, leukocytosis, and location of abscess were not statistically significantly related to fistula formation.[87]

Crohn's disease is another risk factor associated with anal fistulas. Researchers conducted standardised calculations using data from The Health Improvement Network (THIN) to assess the point prevalence of anal fistulas and relevant comorbidities in individuals with and without Crohn's disease (CD) in the U.K. and European population.[88] Researchers estimated that the prevalence of anal fistula in the U.K. and European population were 1.80 and 1.83 per 10,000 individuals, implying that anal fistulas were infrequent in the general population. Additionally, they suggested that 25% of individuals with anal fistulas also had CD, whereas the associations with other comorbidities were relatively rare, highlighting the importance of CD as a complication associated with anal fistula.[89] Researchers found that, in the U.K., among those with anal fistula, those without CD were more prone to develop anal fistula-related comorbidities than those with CD, suggesting that CD might act as a protective factor in these cases. In the U.K. population, the majority of individuals without CD and over the age of 65 had at least one comorbidity.The most common comorbidity among individuals both with and without CD was

[80] Wang et al., "Risk Factors,"
[81] T. B., "Clinico-Pathological Analysis,"
[82] T. B., "Clinico-Pathological Analysis,"
[83] J. Jereb, "Tuberculosis," in CDC Yellow Book 2024, 2023, accessed December 18, 2024, https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/tuberculosis.
[84] Y.-W. Choi et al., "Clinical Features of Tuberculous Versus Crohn's Anal Fistulas in Korea," Journal of Crohn's and Colitis 9, no. 12 (2015): 1132–1137, https://doi.org/10.1093/ecco-jcc/jjv164.
[85] Lohsiriwat et al., "Incidence and Factors,"
[86] Hamadani et al., "Who Is at Risk,"
[87] Lohsiriwat et al., "Incidence and Factors,"
[88] Hokkanen et al., "Prevalence in the UK,"
[89] Hokkanen et al., "Prevalence in the UK,"

diabetes mellitus.[90] Apart from diabetes mellitus, diverticulosis and hidradenitis suppurativa were the second most common comorbidities of anal fistula patients with and without CD respectively. Other comorbidities reported in the study were rectal infectious diseases, anal carcinoma and systemic diseases.[91] Moreover, a study from Denmark also revealed that CD and a C-reactive protein level of more than 100 mg/L were found to be statistically significantly associated with anal fistula.[92] Given CD was not a common disease among Asian countries, it was not a main risk factor among Asian individuals with anal fistula.[93]

Anal abscess and sepsis are usually the direct triggers of an anal fistula formation. Authors from a study in India found that approximately 65% of the 150 patients had perianal abscess before developing an anal fistula.[94] A study conducted in Turkey aimed to examine the prognostic factors for recurrence of anorectal abscess and anal fistula formations[95] Results indicated that the duration of time from disease onset to incision was the only statistically significant risk factor for anal fistula formation. Researchers hypothesised that over time, abscesses would lead to fistula formation and/or the establishment of infections in the surrounding tissue, which will facilitate fistula formation.[96] Another study, conducted in Canada, aimed to determine the number of patients who developed anal fistulas after having anal abscess treatments.[97] The authors found that 87% of patients who developed anal fistula had ischiorectal abscesses, whereas none of the patients with intersphincteric abscesses developed any further conditions. Generally, having a history of ischiorectal abscesses increased the likelihood of developing anal fistulas.[98] The study from Denmark found that low intersphincteric and ischioanal abscesses were risk factors for anal fistula formation, which are in alignment with the study from Canada.[99] Additionally, researchers from Finland identified that female individuals had a higher risk of developing fistulas originating from anterior abscesses.[100] They also reported that a history of repeat surgeries for treating anal abscesses was statistically significantly correlated with primary anal fistulas.[101] Furthermore, a study in Spain analysed the incidence of anal fistula after urgent drainage for anal abscess and found that the existence of an undiagnosed

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[90] Hokkanen et al., "Prevalence in the UK,"
[91] Hokkanen et al., "Prevalence in the UK,"
[92] Skovgaards et al., "Fistula Development,"
[93] S. C. Ng et al., "Worldwide Incidence and Prevalence of Inflammatory Bowel Disease in the 21st Century: A Systematic Review of Population-Based Studies," *The Lancet* 390, no. 10114 (2017): 2769–2778, https://doi.org/10.1016/s0140-6736(17)32448-0.
[94] T. B., "Clinico-Pathological Analysis,"
[95] T. Yano et al., "Prognostic Factors for Recurrence Following the Initial Drainage of an Anorectal Abscess," International Journal of Colorectal Disease 25, no. 12 (2010): 1495–1498, https://doi.org/10.1007/s00384-010-1011-9.
[96] Yano et al., "Prognostic Factors for Recurrence,"
[97] C.-A. Vasilevsky and P. H. Gordon, "The Incidence of Recurrent Abscesses or Fistula-in-Ano Following Anorectal Suppuration," *Diseases of the Colon & Rectum* 27, no. 2 (1984): 126–130, https://doi.org/10.1007/bf02553995.
[98] Vasilevsky and Gordon, "Incidence of Recurrent Abscesses or Fistula-in-Ano,"
[99] Skovgaards et al., "Fistula Development,"
[100] Hämäläinen and Sainio, "Incidence of Fistulas,"
[101] Skovgaards et al., "Fistula Development,"

fistula during the acute moment of anal abscess was statistically significantly associated with anal fistula formation.[102]

Recurrent anal fistula

There has been less literature investigating the risk factors for recurrent anal fistulas compared to primary anal fistulas . Researchers may not have prioritised examining risk factors for recurrent anal fistulas because recurrent anal fistulas are less prevalent typically than primary anal fistulas. The overall recurrence rates of anal fistulas varied across regions, ranging from 7% to 50%.[103] In Europe, a nationwide study in Spain reported a recurrence rate of 6.8% following surgical treatments for primary anal fistulas.[104] Whereas, a study in the USA showed a higher recurrent rate of approximately 12.5% after primary anal fistula treatments.[105] Findings in Asia appeared to have the highest recurrence rate of all, with a general study from Malaysia reporting a recurrence rate of 22.86% following laser ablation procedures.[106]

Sociodemographic factors

Age and gender

Certain ages and gender may be more prone to developing recurrent anal fistulas than others, but these differences may not all be statistically significant. For example, a study in China investigated the clinical characteristics and other risk factors for 1,783 patients with recurrent anal fistulas treated at Shuguang Hospital between 2013 and 2015. The sample consisted of 1,526 male patients with a median age of 36 years.[107] Thus, recurrent anal fistulas were mostly seen in male individuals under the age of 40; however, the study did not identify gender or age as significant risk factors.[108] Another group of researchers in China performed a meta-analysis to

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[102] C. Chaveli Díaz et al., "Recurrence and Incidence of Fistula after Urgent Drainage of an Anal Abscess. Long-term Results. Recidiva e Incidencia de Fístula tras el Drenaje Urgente de un Absceso Anal. Resultados a Largo Plazo," Cirugía Española, S0009-739X(20)30384-5 (2020), advance online publication, https://doi.org/10.1016/j.ciresp.2020.11.010.

[103] N. Bakhtawar and M. Usman, "Factors Increasing the Risk of Recurrence in Fistula-in-Ano," *Cureus* (2019), https://doi.org/10.7759/cureus.4200.

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[105] S. Khan et al., "Predictors of Recurrence and Long-Term Patient-Reported Outcomes Following Surgical Repair of Anal Fistula: A Retrospective Analysis," *International Journal of Colorectal Disease* 39, no. 1 (2024), https://doi.org/10.1007/s00384-024-04602-1.

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[107] J. Li et al., "Clinical Characteristics and Risk Factors for Recurrence of Anal Fistula Patients," *Zhonghua Wei Chang Wai Ke Za Zhi = Chinese Journal of Gastrointestinal Surgery* 19, no. 12 (2016): 1370–74, https://pubmed.ncbi.nlm.nih.gov/28000193/.

[108] Li et al., "Clinical Characteristics and Risk Factors,"

summarise the potential risk factors for recurrent anal fistulas after surgery.[109] The authors found that males younger than 40 years of age were more likely to develop recurrent anal fistula than males older than 40 years; however, age and gender were not statistically significantly associated with anal fistula recurrence.[110] The findings from the Mei et al. (2019) study supported findings from the Li et al. (2016) study as they also identified age under 40 as a (nonsignificant) contributing risk factor for recurrent anal fistula. Similar results were found in a Pakistan study in which they assessed several facets linked to the recurrence of anal fistulas.[111] Approximately 80% of the 130 recurrent anal fistula patients were males and the average age was 38 years; age was found to be significantly associated with anal fistula recurrence but gender was not.[112] Another group of researchers also from Pakistan evaluated 100 patients at Jinnah Postgraduate Medical Centre in Karachi between 1998 and 2007 to determine the frequency of tubercular anal fistulas in recurrent anal fistulas.[113] Although the study reported that 92% of patients were males and the median age was 35 years olds, age and gender were not mentioned as significant contributors to recurrent tubercular anal fistulas in the study.[114]

In Europe, researchers from The Netherlands examined 179 patients from the Academic Medical Centre of University of Amsterdam to assess the potential risk factors for the development of recurrent anal fistulas in individuals who were specifically treated by fistulotomy or rectal advancements flap. Findings indicated that neither gender nor age were significantly associated with recurrent anal fistulas in both groups.[115] Researchers in Spain evaluated the risk factors of recurrence and incontinence (faecal) of anal fistulas among 279 patients who underwent anal fistula repair treatment at "the Hospitals of Sagunto and the Clınico Universitario de Valencia, between 1994 and 1998." They found that among the 279 patients, 214 were males and 65 were females; of the 279 patients, 61 were treated for a recurrent anal fistula.[116] On average, patients were 46.7 years of age, however, researchers did not adjust for age and gender in analysis, making it difficult to determine their potential association with recurrent anal fistula.[117]

Researchers examining recurrent anal fistulas reported similar findings as primary anal fistula as relates to gender, which males were the more prevalent gender for both primary and recurrent anal fistulas. However, different predominant age groups were found in recurrent and

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[109] Z. Mei et al., "Risk Factors for Recurrence after Anal Fistula Surgery: A Meta-Analysis," *International Journal of Surgery (London, England)* 69 (2019): 153–64, https://doi.org/10.1016/j.ijsu.2019.08.003.
[110] Mei et al., "Risk Factors for Recurrence,"
[111] M. Hashmi et al., "Factors Increasing the Risk of Recurrence in Fistula-in-Ano," *Journal of Population Therapeutics and Clinical Pharmacology* 31, no. 6 (2024): 1425–32, https://doi.org/10.53555/jptcp.v31i6.6689.
[112] Hashmi et al., "Factors Increasing the Risk,"
[113] I. Bokhari et al., "Tubercular Fistula-in-Ano," *Journal of the College of Physicians and Surgeons Pakistan* 18, no. 7 (2008): 401–3, https://pubmed.ncbi.nlm.nih.gov/18760061/.
[114] Bokhari et al., "Tubercular Fistula-in-Ano,"
[115] P. J. van Koperen et al., "Long-Term Functional Outcome and Risk Factors for Recurrence after Surgical Treatment for Low and High Perianal Fistulas of Cryptoglandular Origin," Diseases of the Colon & Rectum 51, no. 10 (2008): 1475–81, https://doi.org/10.1007/s10350-008-9354-9.
[116] J. Jordán et al., "Risk Factors for Recurrence and Incontinence after Anal Fistula Surgery," *Colorectal Disease* 12, no. 3 (2010): 254–60, https://doi.org/10.1111/j.1463-1318.2009.01806.x.
[117] Jordán et al., "Risk Factors for Recurrence and Incontinence,"

primary anal fistula studies. Findings show that individuals in a younger age group, particularly under the age of 40, were more prevalent in developing recurrent anal fistulas. Meanwhile, individuals in their 40s and 50s were more likely to develop a primary anal fistula.

Clinicopathological factors

Comorbidities

Similar to primary anal fistulas, comorbidities were identified as risk factors for the development of recurrent anal fistulas. Authors in Pakistan reported that diabetes and hypertension were both significantly associated with anal fistula recurrence.[118] Notably, hypertension was not mentioned as a risk factor for primary anal fistulas. A study from the USA that aimed to compare recurrence rates and long-term effects of anal fistula following surgeries found similar results as a study in Pakistan.[119] The authors found that diabetes mellitus and a history of anorectal abscess were significant predictors for anal fistula recurrence.[120] Similarly, chronic anorectal abscesses were found to be associated with recurrent anal fistulas by researchers in Spain; however, the association was not statistically significant.[121] In addition, scientists from Pakistan discovered that tuberculosis was a neglected cause of anal sepsis as perianal tuberculosis could occur in the absence of any other tuberculosis foci.[122] The anal sepsis was usually overlooked and not treated properly during primary anal surgery, which resulted in the reformation of an anal fistula. Additionally, diagnosing CD and intestinal tuberculosis based on their histological differences was challenging because CD was not a common disease in Pakistan and none of the individuals with recurrent anal fistulas were diagnosed with CD during the biopsy.[123] Tuberculosis was also a recognised risk factor for primary anal fistulas. Overall, a more diverse range of comorbidities were associated with primary anal fistulas as opposed to recurrent anal fistulas.

Postoperative care

Insufficient postoperative care could be a contributor to recurrence of anal fistulas. Findings from a study in Spain indicated that complications of the surgical wound during the postoperative period were correlated to recurrent anal fistulas; however, this association was not statistically significant.[124] Moreover, authors from a study in The Netherlands found that 42% of patients had post-surgery problems related to soiling, indicating that soiling was a considerable issue after anal fistula surgeries, but the authors did not report it as a risk factor for recurrent anal

[118] Hashmi et al., "Factors Increasing the Risk,"
[119] Khan et al., "Predictors of Recurrence and Long-Term Outcomes."
[120] Khan et al., "Predictors of Recurrence and Long-Term Outcomes."
[121] Jordán et al., "Risk Factors for Recurrence and Incontinence,"
[122] Bokhari et al., "Tubercular Fistula-in-Ano,"
[123] Bokhari et al., "Tubercular Fistula-in-Ano,"
[124] Jordán et al., "Risk Factors for Recurrence and Incontinence,"

fistula.[125] Postoperative complications, however, are not mentioned in literature as risk factors for primary anal fistulas.

Treatment history

Prior anal surgery was a widely studied predictor for the occurrence of recurrent anal fistulas. Authors from a study in China aimed to investigate the rate of recurrence of anal fistula in individuals who received surgery for primary anal fistulas and identify the pattern and risk factors of anal fistula recurrence.[126] They found a statistically significant increase in the risk of recurrent anal fistulas with sinus tract excision for perianal sinus.[127] Additionally, an internal opening was found in the re-operation for 44.4% of the individuals with recurrent anal fistulas, suggesting that an overlooked opening during the first operation may progress into a recurrent anal fistula tract.[128] Furthermore, another study in China reported that undetected internal opening and prior anal surgery both significantly increased the risk of developing recurrent anal fistulas.[129] In addition, a recent study from Pakistan found that the types of surgical procedure were statistically significantly associated with recurrence of anal fistulas.[130] Specifically, researchers pointed out that seton was the treatment with the highest recurrent rate, whereas fistulectomy and fistulotomy demonstrated much lower recurrence rates in comparison.[131] Another study in China also reported that seton treatment history had a significantly higher rate of recurrence than other treatment types.[132]

A study in the USA, which aimed to discover the risk factors associated with anal fistula recurrence, reported similar findings as the two studies in China, indicating that lack of identification of internal openings was statistically significantly associated with recurrent anal fistulas in the univariate analysis; however, it was not found to be a statistically significant risk factor in the multivariate analysis.[133] Additionally, researchers reported that the surgeon who performed the procedure was identified as an important risk factor for recurrent anal fistula in the multivariate analysis; however, it was not statistically significantly associated with recurrence in the univariate analysis.[134] Another group of researchers from the USA discovered sphincter sparing surgery, such as LIFT or plug/biologic procedures, were statistically significantly associated with high recurrent rates, whereas non-sphincter-sparing surgeries, such as

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[125] van Koperen et al., "Long-Term Functional Outcome and Risk Factors,"
[126] C. M. Poon, D. C. Ng, M. C. Ho-Yin, R. S. Li, and H. T. Leong, "Recurrence Pattern of Fistula-in-Ano in a Chinese Population," *Journal of Gastrointestinal and Liver Diseases: JGLD* 17, no. 1 (2008): 53–57.https://pubmed.ncbi.nlm.nih.gov/18392245/
[127] Poon et al., "Recurrence Pattern,"
[128] Poon et al., "Recurrence Pattern,"
[129] Mei et al., "Risk Factors for Recurrence,"
[130] Hashmi et al., "Factors Increasing the Risk,"
[131] Hashmi et al., "Factors Increasing the Risk,"
[132] Li et al., "Clinical Characteristics and Risk Factors,"
[133] J. Garcia-Aguilar, C. Belmonte, D. W. Wong, S. M. Goldberg, and R. D. Madoff, "Anal Fistula Surgery," Diseases of the Colon & Rectum 39, no. 7 (1996): 723–29, https://doi.org/10.1007/bf02054434.
[134] Garcia-Aguilar et al., "Anal Fistula Surgery,"

fistulotomy and seton treatment, had a lower rate of recurrence.[135] While the recurrent rate of fistulotomy aligned with findings from the China and Pakistan studies, the recurrent rate of seton treatments contradicted these findings.

Findings from The Netherlands were aligned with the findings from Pakistan in that individuals treated with fistulotomy had a lower rate of anal fistula recurrence.[136] Similar finding was also reported by a study in Spain that compared six different treatments, including fistulotomy, fistulectomy, seton, fistulectomy & sphincter repair, fistulectomy & advancement flap, and core out & closure of internal opening, with fistulotomy showing the lowest recurrent rate of al.[137] Core out & closure of the internal fistula opening had the highest recurrent rate.[138] This result aligned with the findings in the Pakistan study that fistulotomy had the lowest recurrent rate compared to other treatments, including seton treatment. However, researchers from the Pakistan study did not test for the core out & closure of internal opening to see whether it had a higher recurrent rate than seton treatment. Additionally, non-identification of the internal fistula opening by surgeons during primary anal fistulas was significantly correlated with recurrent anal fistula, which was in alignment with studies in the USA and China.[139] Another study in The Netherlands aimed to reveal whether preoperative three-dimensional endoanal ultrasound (3D-EAUS) was able to identify risk factors for recurrent anal fistula after surgeries.[140] They found that prior fistula surgery significantly increased the risk of recurrent anal fistulas, which aligned with the results from the study in China. Additionally, the presence of a secondary track formation was identified as a strong risk factor for recurrent anal fistulas. [141]

In summary, repeated surgical treatments for anal abscesses were identified as risk factors for primary anal fistulas. Similar patterns were observed in recurrent anal fistulas, where the recurrent rate could be increased by prior surgeries, particularly in certain types of procedures. Furthermore, if an undiagnosed fistula was overlooked during surgeries for anal abscess or primary anal fistula, it may appear as a primary or a recurrent anal fistula, respectively.

Types and position of primary anal fistulas

Certain types and positions of primary anal fistulas were found to increase the likelihood of developing recurrent anal fistulas. Researchers in China discovered that fistula height was statistically significantly associated with recurrent anal fistulas, with high anal fistulas having a significantly higher rate of recurrence than low anal fistulas.[142] Similarly, another group of researchers in China found that individuals who were previously treated for complex anal fistulas

[135] Khan et al., "Predictors of Recurrence and Long-Term Outcomes."
[136] van Koperen et al., "Long-Term Functional Outcome and Risk Factors,"
[137] Jordán et al., "Risk Factors for Recurrence and Incontinence,"
[138] Jordán et al., "Risk Factors for Recurrence and Incontinence,"
[139] Jordán et al., "Risk Factors for Recurrence and Incontinence,"
[140] A. P. Visscher et al., "Predictive Factors for Recurrence of Cryptoglandular Fistulae Characterized by Preoperative Three-Dimensional Endoanal Ultrasound," *Colorectal Disease* 18, no. 5 (2016): 503–09, https://doi.org/10.1111/codi.13211.
[141] Visscher et al., "Predictive Factors for Recurrence,"
[142] Li et al., "Clinical Characteristics and Risk Factors,"

had a higher risk of recurrence.[143] High anal fistulas and complex anal fistulas represent different classifications of anal fistula. A high anal fistula could often be a complex anal fistula due to the challenges in treatments posed by its position. Furthermore, a study in China revealed that high trans-sphincteric fistula, presence of horseshoe extensions, and multiple fistula tracts were statistically significantly associated with recurrence in anal fistulas.[144]

Researchers in the USA identified that complex types of primary anal fistulas and horseshoe extension were significant risk factors for recurrent anal fistulas, which was similar with the findings from the two studies in China.[145] Furthermore, a study in Spain reported that the presence of complex primary anal fistulas was significantly associated with recurrent anal fistulas, and suprasphincteric fistula was found to have the greatest risk of recurrence.[146]

Primary anal fistulas were influenced by the types of anal abscesses that developed before the formation of anal fistulas. Individuals with certain types of abscesses, such as ischiorectal abscess, were more likely to develop primary anal fistulas. Similarly, recurrent anal fistulas were influenced by the types and positions of the primary anal fistulas, with complex types of primary anal fistulas having an increased risk of developing recurrent anal fistulas.

Conclusion

Numerous studies were conducted across different countries to identify the risk factors for primary and recurrent anal fistulas. Overall, findings indicated that certain ages, genders and comorbidities increased the likelihood of developing either type of anal fistula. Recurrent anal fistulas, in particular, were associated with additional factors such as postoperative care. While these findings demonstrated consistency across Asia, Europe and the Americas, regional variations existed specifically regarding the influence of Crohn's disease and recurrent rates following particular surgeries. However, much of the existing literature is outdated and often based on small sample sizes. Furthermore, topics related to the incidence of both types of anal fistulas across some regions and the reasons behind specific risk factors, such as age and gender, remain underexplored; whereas some regions, such as the Middle East & North Africa and Sub-saharan Africa, are completely omitted from the literature, leaving much unknown. Future research should address these gaps by using larger and more representative sample sizes across all regions, and updated methodologies to gain a better understanding of primary and recurrent anal fistulas. Once we have a better global understanding of the risk factors associated with anal fistulas, this may lead to the establishment of preventative initiatives and accurate treatments for patients from diverse backgrounds, ultimately reducing the burden of anal fistula-related healthcare challenges across the world.

[143] Poon et al., "Recurrence Pattern,"
[144] Mei et al., "Risk Factors for Recurrence,"
[145] Garcia-Aguilar et al., "Anal Fistula Surgery,"
[146] Jordán et al., "Risk Factors for Recurrence and Incontinence,"

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This paper presents an ambitious and impressively detailed literature review on the sociodemographic and clinicopathological risk factors for both primary and recurrent anal fistulas, with an emphasis on regional differences. The scope, depth, and level of scientific engagement are commendable. The author has clearly invested a great deal of time and effort in compiling data from a wide range of peer-reviewed sources and synthesizing information from studies conducted across Asia, Europe, and the Americas. This effort alone speaks to a strong motivation to understand global trends in clinical epidemiology and to produce a piece of writing that contributes meaningfully to academic discussion.

One of the strengths of this paper lies in its broad literature base and the clear structure it follows when presenting findings across various categories—age, gender, lifestyle, comorbidities, microbiology, and treatment history. The inclusion of both sociodemographic and biological factors is thoughtful and appropriate for a comprehensive review. The author demonstrates an emerging ability to identify patterns and differences across regions, such as the varying impact of Crohn's disease on fistula prevalence or differences in recurrence rates after surgery. The effort to go beyond national boundaries and capture under-researched regional variation is admirable and certainly aligns with the stated aim of creating a global comparative review.

At the same time, several areas could be improved to bring the paper closer to academic standards expected even at undergraduate levels. The methodology section, while sufficient in a basic sense, lacks transparency in the literature selection process. It would be helpful to include more detail on how studies were screened, whether inclusion decisions were made by multiple readers, and what criteria were used to assess study quality. The choice to exclude prevalence-only studies and those focused on surgical innovations is questionable, particularly because some of these may contain valuable contextual or causal insights that pertain to risk factor analysis. Clarifying the rationale behind these exclusions would strengthen the review's credibility.

The writing is generally clear and grammatically strong, but the tone could be more formal and academically cautious. In several places, findings are presented at face value without sufficient critical engagement. For instance, some studies report associations without statistical significance or adjustment for confounders, but these caveats are not always acknowledged. At times, the narrative reads more like a summary of findings than a critical synthesis. For example, when discussing conflicting findings on gender as a risk factor, it would help to offer possible reasons for these discrepancies—sampling bias, cultural reporting differences, or differing diagnostic standards. Likewise, the discussion of lifestyle factors could be enhanced by engaging with broader public health literature on diet and physical activity across regions, rather than assuming direct causality from observed associations.

A more substantial concern is that the review does not clearly articulate a central thesis or organizing framework. While the accumulation of studies is impressive, the paper would benefit from stepping back and offering a more integrative perspective. For example, it could ask whether the observed cross-regional differences in risk factors are more likely to stem from biological diversity, healthcare system disparities, or sociocultural practices. Without such a unifying lens, the paper risks becoming an annotated bibliography rather than a coherent argument. The conclusion hints at these interpretive possibilities, especially in calling for future

research in underrepresented regions like sub-Saharan Africa and the Middle East, but it stops short of developing a clear analytical contribution.

Nonetheless, the paper shows genuine promise, and with further guidance, especially in developing critical thinking and synthesis skills, the author is well-positioned for future success in academic research. I would recommend the paper for publication in the *Convergence*, provided that minor revisions are made to sharpen the analytical voice, clarify the methodology, and streamline the writing in places where repetition occurs. This paper is a strong demonstration of potential and intellectual curiosity, and it deserves thoughtful encouragement.

Review of "Anal fistulas: a global review on sociodemographic and clinicopathological risk factors"

Thank you for submitting this comprehensive literature review to Convergence. This paper addresses an important yet often overlooked clinical condition that significantly impacts patient quality of life globally. The author has undertaken an ambitious project, synthesizing findings from 32 studies across multiple continents to identify risk factors for both primary and recurrent anal fistulas. This global perspective is particularly valuable and represents one of the paper's key strengths.

The manuscript demonstrates several commendable qualities that make it suitable for publication with minor revisions. The author has clearly invested considerable effort in reviewing the literature, and the paper is well-organized with logical sections covering sociodemographic and clinicopathological factors. The inclusion of both primary and recurrent fistulas provides a comprehensive view of the condition, and the attempt to identify regional variations adds an important dimension often missing from clinical reviews. The writing is generally clear and accessible, which is important given Convergence's diverse readership. However, several areas require attention before publication. The methodology section, while adequate for a literature review at this level, would benefit from additional detail about the search strategy and selection process. Including information about how conflicting findings were resolved and perhaps a PRISMA-style flow diagram showing the selection process would strengthen the paper's scientific rigor. Additionally, the databases searched (PubMed and Google Scholar) are appropriate, but the author might consider mentioning whether any regional databases were consulted, particularly for underrepresented areas like Africa and the Middle East.

The analysis of findings could be enhanced in several places. For instance, when discussing conflicting results about diabetes as a risk factor (with studies from China showing it as a risk factor while those from Thailand and the USA showing the opposite), the author could explore potential explanations for these differences. Are there variations in how diabetes is defined or managed in these countries? Could genetic factors or healthcare access play a role? Similarly, the interesting finding about gender differences deserves deeper exploration beyond the brief mention of hormonal factors. The author might also consider creating a summary table highlighting the main risk factors identified across different regions, which would help readers quickly grasp the key findings.

The discussion of regional gaps in research is one of the paper's strengths, but it could be developed further. The author correctly notes the absence of studies from the Middle East, North Africa, and Sub-Saharan Africa, but could expand on the implications of these gaps. What are the potential consequences for patients in these regions? How might social, cultural, or economic factors influence both research priorities and disease management in these areas? This discussion would add valuable context to the clinical findings.

Some statements throughout the paper would benefit from more nuanced presentation. For example, the characterization of European dietary and lifestyle habits, while potentially relevant, relies on generalizations that may not reflect the diversity within European populations. Similarly, when discussing bacterial findings, phrases like "the two predominant bacteria" could

be softened to "among the most commonly identified bacteria" to better reflect the complexity of microbiological findings across different studies.

The conclusion effectively summarizes the main findings but could be strengthened by offering more specific recommendations for future research. Rather than simply calling for "larger and more representative sample sizes," the author might suggest specific study designs, collaborative approaches, or priority areas for investigation. Additionally, discussing the clinical implications of the findings – how might healthcare providers use this information to better identify at-risk patients or improve treatment outcomes – would add practical value to the review.

Minor editorial improvements would enhance the paper's professional presentation. The reference formatting should be standardized throughout, and some citations appear incomplete. A few sentences are quite long and complex, which could be broken down for clarity. The abstract, while comprehensive, could be slightly condensed to meet typical journal length requirements. Finally, considering the medical nature of the topic, a brief glossary of technical terms might be helpful for readers less familiar with medical terminology.

Despite these areas for improvement, this paper represents a solid contribution to the student literature on anal fistulas. The author's attempt to synthesize global findings on this condition is commendable, and the identification of regional research gaps is particularly valuable. The paper demonstrates good understanding of the clinical literature and appropriate academic writing skills for an undergraduate publication. I recommend this paper for publication in Convergence following minor revisions. The suggested changes will strengthen the paper's scientific rigor and clarity without requiring fundamental restructuring. The author should be encouraged by this initial effort and should find the revision process straightforward. Once revised, this paper will provide a useful resource for other students and healthcare trainees interested in understanding the global epidemiology of anal fistulas and the importance of considering regional variations in disease risk factors.

Dear Reviewer,

Thank you very much for your thoughtful and constructive feedback on my manuscript, “Anal fistulas: a global review on sociodemographic and clinicopathological risk factors” I appreciate your time and valuable suggestions, which have helped strengthen the quality and clarity of the paper.

Below is a point-by-point response to your comments. Changes made in the manuscript are noted and referenced accordingly.

Comment 1: “The choice to exclude prevalenceonly studies and those focused on surgical innovations is questionable, particularly because some of these may contain valuable contextual or causal insights that pertain to risk factor analysis.”
Response: I have revised page 4, paragraph 5 of the Method section to clarify the exclusion of prevalence-only studies and surgical approaches more clearly.

Comment 2: “While sufficient in a basic sense, lacks transparency in the literature selection process. It would be helpful to include more detail on how studies were screened, whether inclusion decisions were made by multiple readers, and what criteria were used to assess study quality.”
Response: I have revised page 3, paragraph 2 of the method section to explain the process of screening and selecting studies. And add a paragraph (page 4) to explain the criteria of assessing study quality.

Comment 3: “While sufficient in a basic sense, lacks transparency in the literature selection process. It would be helpful to include more detail on how studies were screened, whether inclusion decisions were made by multiple readers, and what criteria were used to assess study quality.”
Response: I have revised page 3, paragraph 2 of the method section to explain the process of screening and selecting studies. And add a paragraph (page 4) to explain the criteria of assessing study quality.

Comment 4: “In several places, findings are presented at face value without sufficient critical engagement. For instance, some studies report associations without statistical significance or adjustment for confounders, but these caveats are not always acknowledged.”
Response: I have revised page 13, paragraph 1 of comorbidities under primary anal fistula section to explore deeper into the reasons (e.g. genetic differences, variations in diabetes managements) of the conflicting results across regions.

Comment 5: “At times, the narrative reads more like a summary of findings than a critical synthesis. For example, when discussing conflicting findings on gender as a risk factor, it would help to offer possible reasons for these discrepancies—sampling bias, cultural reporting differences, or differing diagnostic standards”
Response: I have revised page 7, paragraph 2 of age and gender under primary anal fistula

section to explore deeper into the reasons of the conflicting results between the USA and other countries. And add a new paragraph (page 7) to explore the potential factors causing the gender difference.

Comment 5: “Likewise, the discussion of lifestyle factors could be enhanced by engaging with broader public health literature on diet and physical activity across regions, rather than assuming direct causality from observed associations”
Response: I have revised page 9, paragraph 3 of socioeconomic status under primary anal fistula section to avoid making generalizations and assumptions on direct causality without sufficient amount of evidence.

Comment 6: “While the accumulation of studies is impressive, the paper would benefit from stepping back and offering a more integrative perspective. For example, it could ask whether the observed cross-regional differences in risk factors are more likely to stem from biological diversity, healthcare system disparities, or sociocultural practices.”
Response: I have revised page 13-14, paragraph 2 of comorbidities under primary anal fistula section to explore the reasons (e.g. genetics, environment) behind the cross-regional difference of Crohn’s disease.

Comment 7: “The discussion of regional gaps in research is one of the paper's strengths, but it could be developed further. The author correctly notes the absence of studies from the Middle East, North Africa, and Sub-Saharan Africa, but could expand on the implications of these gaps. ”
Response: I have revised page 20 conclusion section to explore the implications of lacking research data from these areas, and the factors that contribute to this situation.

Thank you again for your valuable feedback. I look forward to your response and am happy to make any further adjustments as needed.

Sincerely,
Qingpei

Dear Reviewer,

Thank you very much for your thoughtful and constructive feedback on my manuscript, “Anal fistulas: a global review on sociodemographic and clinicopathological risk factors” I appreciate your time and valuable suggestions, which have helped strengthen the quality and clarity of the paper.

Below is a point-by-point response to your comments. Changes made in the manuscript are noted and referenced accordingly.

Comment 1: “Additionally, the databases searched (PubMed and Google Scholar) are appropriate, but the author might consider mentioning whether any regional databases were consulted, particularly for underrepresented areas like Africa and the Middle East.”
Response: I have revised page 20 conclusion section to explain the lack of research from areas like Africa and the Middle East by recognizing my lack of systematic search on regional database is a limitation of my review.

Comment 2: “The methodology section, while adequate for a literature review at this level, would benefit from additional detail about the search strategy and selectio process. ”
Response: I have revised page 3, paragraph 2 of the method section to explain the process of screening and selecting studies.

Comment 3: “Including information about how conflicting findings were resolved and perhaps a PRISMA-style flow diagram showing the selection process would strengthen the paper's scientific rigor. ”
Response: I have page 4, paragraph 3 to explain how conflicting findings were resolved.

Comment 4: “The analysis of findings could be enhanced in several places. For instance, when discussing conflicting results about diabetes as a risk factor (with studies from China showing it as a risk factor while those from Thailand and the USA showing the opposite), the author could explorepotential explanations for these differences.”
Response: I have revised page 13, paragraph 1 of comorbidities under primary anal fistula section to explore deeper into the reasons (e.g. genetic differences, variations in diabetes managements) of the conflicting results across regions.

Comment 5: “Similarly, the interesting finding about gender differences deserves deeper exploration beyond the brief mention of hormonal factors.”
Response: I have added a new paragraph (page 7) to explore the potential factors causing the gender difference.

Comment 6: “Some statements throughout the paper would benefit from more nuanced presentation. For example, the characterization of European dietary and lifestyle habits, while potentially relevant,relies on generalizations that may not reflect the diversity within European populations.”

Response: I have revised page 9, paragraph 3 of socioeconomic status under primary anal fistula section to avoid making generalizations and assumptions on direct causality without sufficient amount of evidence.

Comment 7: “Similarly, when discussing bacterial findings, phrases like "the two predominant bacteria" could be softened to "among the most commonly identified bacteria" to better reflect the complexity of microbiological findings across different studies.”
Response: I have revised page 12, paragraph 4 of bacteriology and microbiology under primary anal fistula section to soften the tone of my writing.

Comment 8: “The conclusion effectively summarizes the main findings but could be strengthened by offering more specific recommendations for future research. Rather than simply calling for "larger and more representative sample sizes," the author might suggest specific study designs, collaborative approaches, or priority areas for investigation. Additionally, discussing the clinical implications of the findings – how might healthcare providers use this information to better identify at-risk patients or improve treatment outcomes – would add practical value to the review.”
Response: I have revised page 20 conclusion section to include specific details on recommendations for future research and explain how the findings could enhance clinical practices.

Comment 9: “A few sentences are quite long and complex, which could be broken down for clarity.”
Response: Two sentences each from page 8 lifestyles and behaviours section and page 3 introduction section are broken down for clarity.

Comment 10: “The reference formatting should be standardized throughout, and some citations appear incomplete. The abstract, while comprehensive, could be slightly condensed to meet typical journal length requirements. Finally, considering the medical nature of the topic, a brief glossary of technical terms might be helpful for readers less familiar with medical terminology”
Response: Incomplete references and duplicated entries are all resolved. Abstract is also shortened and a glossary is attached at the start of the review (after the abstract before the main body paragraphs)

Thank you again for your valuable feedback. I look forward to your response and am happy to make any further adjustments as needed.

Sincerely,
Qingpei

Anal fistulas: a global review on sociodemographic and clinicopathological risk factors

Abstract:

Anal fistulas affect individuals worldwide, yet existing literature primarily focuses on risk factors within specific areas, rather than providing comparisons of epidemiological trends between regions. This literature review aims to identify the sociodemographics and clinical pathological risk factors for both primary and recurrent anal fistula and how these factors differ across regions. While most risk factors, such as certain comorbidities and prior surgeries, are consistent across Asia, Europe, and the Americas, regional variations were found in the effect of Crohn's disease and recurrent rate following different surgical procedures. Notably, some regions were omitted from literature due to lack of research on anal fistula-related topics, suggesting the need for broader, more representative studies to address the gaps of healthcare challenges in anal fistulas among these regions.

Glossary

Epidemiology

The study of the distribution and determinants of health-related states or events in specified populations.

Incidence
The number of new cases of a disease or condition occurring in a specified population during a defined time period.
Prevalence
The total number of existing cases of a disease or condition in a population at a given time.
Comorbidity
The simultaneous presence of two or more diseases or medical conditions in a patient.
Anal Fistula
An abnormal, tunnel-like connection between the anal canal and the skin near the anus, often resulting from an infection or abscess.
Benign Anorectal Disease
Non-cancerous disorders affecting the anus and rectum, including hemorrhoids, fissures, abscesses, and fistulas.
Crohn's Disease
A chronic inflammatory bowel disease (IBD) causing inflammation of the digestive tract, which can lead to abdominal pain, severe diarrhea, fatigue, and malnutrition.
Inflammatory Bowel Disease (IBD)
A group of chronic inflammatory disorders of the gastrointestinal tract, primarily including Crohn's disease and ulcerative colitis.
Anal Abscess
A localized collection of pus near the anus caused by infection of the anal glands, which can be painful and may lead to fistula formation.
Sepsis
A life-threatening systemic response to infection, causing widespread inflammation and potential organ failure.
Postoperative Care
The management and monitoring of a patient's recovery following surgery, including wound care, infection prevention, pain management, and monitoring for complications such as sepsis.

Introduction

An anal fistula is a common colorectal condition that affects the anus and rectum. It is an abnormal inflammatory tunnel connecting the skin near the anus and the bowel. Anal fistulas can be both acute and chronic. The condition typically occurs when an anal abscess develops due to an infection of the anal gland.[1] This anal abscess is the acute phase that usually triggers the development of an anal fistula.[2] An anal fistula can be associated with other diseases as well, including inflammatory bowel disease (Crohn's Disease (CD)), tuberculosis infection, cancer,

[1] Jeremy Sugrue et al., "Pathogenesis and Persistence of Cryptoglandular Anal Fistula: A Systematic Review," *Techniques in Coloproctology* 21, no. 6 (2017): 425–30, https://doi.org/10.1007/s10151-017-1645-5.
[2] A. G. Parks et al., "A Classification of Fistula-in-Ano," *British Journal of Surgery* 63, no. 1 (1976): 1–12, https://doi.org/10.1002/bjs.1800630102.

etc.[3] It is difficult to eradicate an anal fistula because it can recur after having a history of anal abscess or fistula.[4][5]

The actual global prevalence of anal fistula is unknown. However, the mean prevalence of anal fistula is estimated to be 8-23 per 100,000 cases based on European studies.[6][7][8][9][10][11] Given these data, it is inferred that thousands of people are affected by anal fistula globally.

Different regions have shown various incidence rates of having both primary and recurrent anal fistula, indicating a difference in the level of risk patients are exposed to based on where they reside. In Asia, specifically in China, anal fistula is commonly seen in men in their second to fourth decade and the overall incidence is 1.67%-3.6% [12] In the United States, the number of new cases per year that underwent primary anal fistula treatment was 20,000 to 25,000 and 96,000 cases per year underwent recurrent treatment after a perianal abscess.[13] Whereas in Europe, a study analysed 16 studies from 1984 to 2019 among seven countries and suggested the overall prevalence rate of anal fistula is 16.9 per 100,000 people.[14]

Anal fistula often causes serious discomfort, highly interfering with patients' overall quality of life.[15] People can feel intense pain and fluids such as pus or blood may emerge around their anus. All levels of complexity of the fistulas would result in different inconveniences, impairing patients' routine activities. Additionally, patients would have to set restrictions on their daily entertainment to manage symptoms, which interfere with patients' relationships with their

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[3] Cleveland Clinic, "Anal Fistula: Causes, Symptoms, Diagnosis & Treatment," 2023, https://my.clevelandclinic.org/health/diseases/14466-anal-fistula.

[4] Sherif H. Emile, "Recurrent Anal Fistulas: When, Why, and How to Manage?" *World Journal of Clinical Cases* 8, no. 9 (2020): 1586–91, https://doi.org/10.12998/wjcc.v8.i9.1586.

[5] D. M. Skovgaards et al., "Fistula Development after Anal Abscess Drainage—A Multicentre Retrospective Cohort Study," *International Journal of Colorectal Disease* 39, no. 1 (2023), https://doi.org/10.1007/s00384-023-04576-6.

[6] K. Adamo et al., "Prevalence and Recurrence Rate of Perianal Abscess—A Population-Based Study, Sweden 1997–2009," *International Journal of Colorectal Disease* 31, no. 3 (2016): 669–73, https://doi.org/10.1007/s00384-015-2500-7.

[7] A. Bondurri, "Epidemiology of Anal Fistula and Abscess," *Coloproctology* (2021): 1–10, https://doi.org/10.1007/978-3-030-30902-2_1-1.

[8] D. García-Olmo et al., "Prevalence of Anal Fistulas in Europe: Systematic Literature Reviews and Population-Based Database Analysis," *Advances in Therapy* 36, no. 12 (2019): 3503–18, https://doi.org/10.1007/s12325-019-01117-y.

[9] S. R. Hokkanen et al., "Prevalence of Anal Fistula in the United Kingdom," *World Journal of Clinical Cases* 7, no. 14 (2019): 1795–1804, https://doi.org/10.12998/wjcc.v7.i14.1795.

[10] K. Sahnan et al., "Natural History of Anorectal Sepsis," *British Journal of Surgery* 104, no. 13 (2017): 1857–65, https://doi.org/10.1002/bjs.10614.

[11] C. Zanotti et al., "An Assessment of the Incidence of Fistula-in-Ano in Four Countries of the European Union," *International Journal of Colorectal Disease* 22, no. 12 (2007): 1459–62, https://doi.org/10.1007/s00384-007-0334-7.

[12] W. Yang, "My Views on the Diagnosis and Treatment of Anal Fistula," *Chinese Medical Journal* 47, no. 1 (2012): 18–20, https://doi.org/10.3969/j.issn.1008-1070.2012.01.007.

[13] R. L. Nelson, "Anorectal Abscess Fistula: What Do We Know?" *Surgical Clinics of North America* 82, no. 6 (2002): 1139–51, https://doi.org/10.1016/s0039-6109(02)00063-4.

[14] García-Olmo et al., "Prevalence of Anal Fistulas,"

[15] W. Chadbunchachai et al., "Long-Term Outcomes after Anal Fistula Surgery: Results from Two University Hospitals in Thailand," *Annals of Coloproctology* (2021), https://doi.org/10.3393/ac.2021.01.06.

partners and families and their perceptions of themselves, resulting in psychological distress and insecurity.[16]

In recent years, there have been many studies evaluating the efficiency and improving the procedures for anal fistula repair. Treatment such as endorectal advancement flap, novel approaches such as ligation of the intersphincteric fistula tract (LIFT), or using biological material as an alternative can provide a vast range of options for complex anal fistula cases. [17]

Even with these various treatment options, anal fistula recurrence remains high. These conditions are usually developed due to the failure of complete healing of the surgical wound which underlines the significance of post-operative care of the wound. Both recurrent and primary anal fistulas can be severe and require complex treatment. However, with recurrent anal fistulas health professionals face new challenges such as the possibility of re-recurrence and impairment of bowel continence, making treatments more complex.[18] Globally the anal fistula rate of recurrence ranges from 2.5% to 57.1%.[19] A study in Spain found the anal fistula recurrence rate to be 48.2% within an average follow-up time of 119.7 months, whereas, a study in China found a 13.3% recurrent rate of anal fistula with a median time of recurrence of 7.5 months. [20]

Scientists have focused their efforts on developing new procedures for treating complex anal fistulas, leaving much unknown regarding the epidemiological trends in anal fistulas. Although there are various treatment options available, it can be difficult for healthcare providers and patients to determine which approach is most suitable. This is because sociodemographic factors and medical histories can vary significantly based on the regions they live in and their cultural backgrounds.Previous reviews have stratified the risk factors for anal fistula by pathogenesis and demographic causes. To my knowledge, there has not been a study conducted globally that has identified the trends and risk factors that contribute to anal fistula development. Therefore, this literature review aims to identify the sociodemographics and clinical pathological risk factors for both primary and recurrent anal fistula and how these factors differ across regions.

Methods

A thorough search of the literature was conducted using PubMed and Google Scholar databases. Keyword combinations used in the search included “primary anal fistula,” “recurrent

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[16] N. Iqbal et al., “Living with Cryptoglandular Anal Fistula: A Qualitative Investigation of the Patient’s Experience through Semi-Structured Patient Interviews,” *Quality of Life Research* (2022), https://doi.org/10.1007/s11136-022-03098-y.

[17] E. Limura, “Modern Management of Anal Fistula,” *World Journal of Gastroenterology* 21, no. 1 (2015): 12, https://doi.org/10.3748/wjg.v21.i1.12.

[18] Emile, S. H, “Recurrent anal fistulas,” 1586.

[19] Z. Mei et al., “Risk Factors for Recurrence after Anal Fistula Surgery: A Meta-Analysis,” *International Journal of Surgery (London, England)* 69 (2019): 153–64, https://doi.org/10.1016/j.ijsu.2019.08.003.

[20] Chi-Ming Poon et al., “Recurrence Pattern of Fistula-in-Ano in a Chinese Population,” *Journal of Gastrointestinal and Liver Diseases* 17, no. 1 (2025): 53–57, https://www.jgld.ro/jgld/index.php/jgld/article/view/2008.1.9.

anal fistula," "risk factors," and "epidemiology." Studies from all regions related to primary and recurrent anal fistula were included during the initial search. After a general search of the databases, 216 articles were found.

Further selection was then determined based on eligibility criteria. All titles, key words and abstracts were initially screened based on the inclusion and exclusion criteria. Full text were then reviewed for further clarification and final selection. The same screening process were applied to the reference lists of excluded studies to identify additional eligible articles.

To assess the quality of included studies, attention was given to factors such as year of study, sample size, statistical analysis and clarity in reporting. Larger and more recent cohort studies that employed multivariate analyses were given greater weight during interpretation. In contrast, older studies with methodological limitations or smaller sample size received less focus in the analysis. In cases where studies reported conflicting results, potential explanations such as differences in demographic factors , biological variation and healthcare disparities were explored in the discussions.

Only empirical research on primary and recurrent anal fistula of adult populations after 1950 was included. These inclusion criteria were applied because research before 1950 may be outdated considering the rapid improvements in medical technologies and adult populations are more prevalent to anal fistula than child and adolescent populations. [21]

All review articles were excluded. Empirical research that solely reported the incidence or prevalence rate among regions were excluded, as they did not examine the epidemiological profile of their sample population or analyse the associations with risk factors that contributing to patients' conditions. Studies that focused on the anatomical and pathological aspects of anal fistula formation were excluded as they did not identify the risk factors that triggered the pathological changes. The assessment of different surgical approaches and their outcomes were excluded, as their primary focus was on comparing the improvement of patients' condition after different managements to evaluate treatment efficacy, rather than identifying potential risk factors contributing to the formation or recurrence of anal fistulas. Studies on innovations in treatment options such as novel surgical approaches or medications and improvements in perioperative management were excluded as they did not analyse the potential risk factors. Studies that analysed the surveys of patients' reflections on the changes in their quality of life were excluded as they focused on the effect of anal fistulas on patients' daily lives, not the associations between risk factors and anal fistulas. Lastly, articles focusing on improving surgical wound healing and postoperative patient care were excluded as they suggested new ways to enhance patients' recovery instead of identifying risk factors.

A total of 25 articles were identified once most of the eligibility criteria were applied. However, seven articles were review articles, thus, omitted from the inclusion, leaving 18 eligible articles. After reading through the seven ineligible review articles, 14 eligible empirical studies were found from the embedded references. Once all eligibility criteria were applied, there

[21] J. Deodhar, "Pediatric Fistula-in-Ano: Practice Essentials, Anatomy, Pathophysiology," Medscape (2023), https://emedicine.medscape.com/article/935312-overview#a7?form=fpf.

were a total of 32 articles included in the review with 22 studies investigating primary anal fistulas and ten studies examining recurrent anal fistulas (Figure 1).

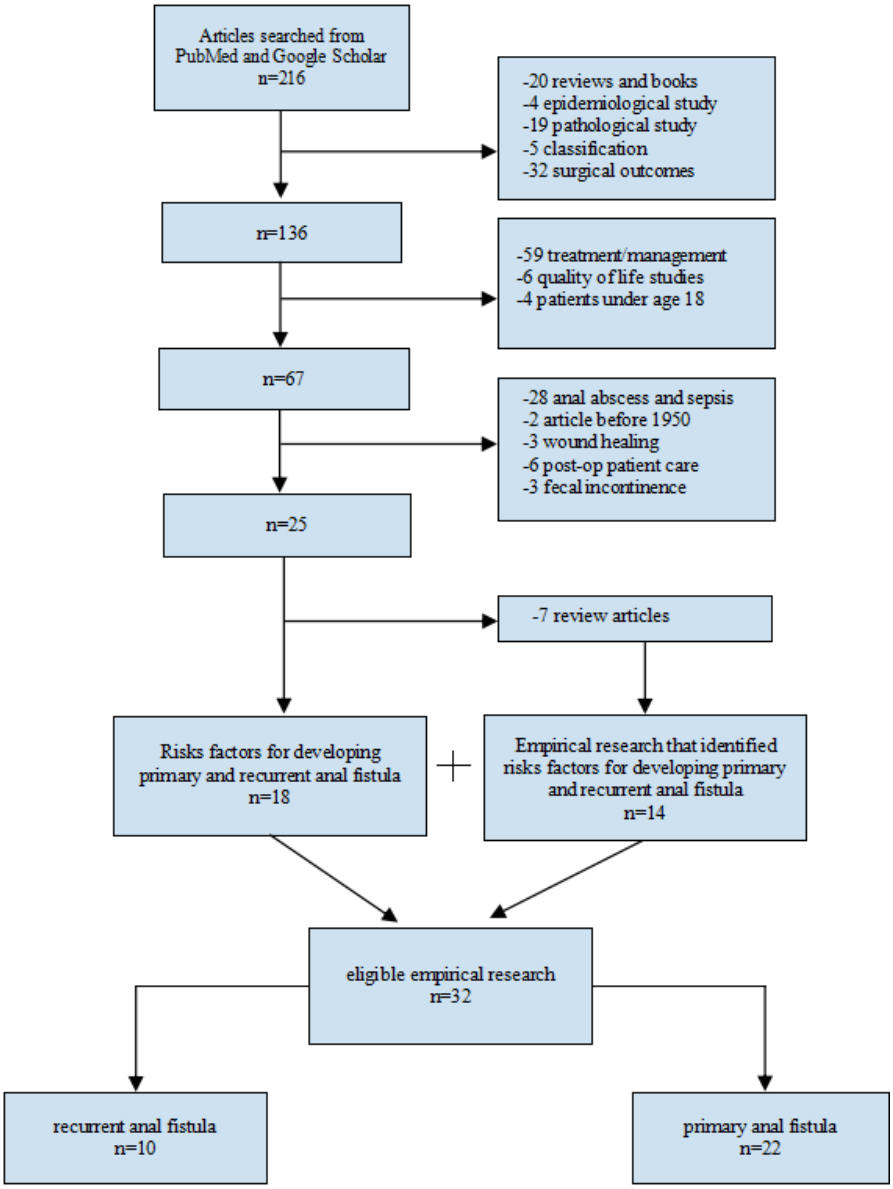

Figure 1. Flowchart of literature included in review

Primary anal fistula

Sociodemographic factors

Age and gender

Most studies in Asia have reported that primary anal fistulas are more prevalent in males than females. A study in Japan assessed 514 patients to evaluate the role of microbiological analysis in anorectal sepsis patients who developed anal fistula and approximately 90% were male.[22] Gender was found to be a significant risk factor.[23] In this same study, age was not found to be statistically significantly associated with primary anal fistula. However, age was measured as a continuous variable, but the results may have been different if it was measured categorically.[24] Another study in India analysed the modalities of anal fistulas in 150 patients with various demographic features and nearly 71% were males, which may indicate that in Asia anal fistula most commonly occurred in males or there was bias in the sample selection process.[25] The authors of this study found that both gender and age were not statistically significantly associated with primary anal fistulas.[26] Although the Japanese study contradicts the Indian study regarding gender, both studies present consistent evidence that age was not a statistically significant risk factor of anal fistula; however, both studies reported that people in their third to fifth decades were more prone to anal fistula. A study in China that assessed the clinical risk factors for patients with anal fistula found that age and gender were not significantly associated with anal fistula formation even though there was a clear trend of developing anal fistula in middle-aged males.[27] Researchers from a study in Thailand that aimed to determine factors influencing anal fistula formation after acute perianal abscess drainage also found that gender was not predictive of fistula formation.[28] However, results from the study indicated that individuals with age under 40 years had a higher risk of developing anal fistula compared to those over 40 years.[29] Another group of researchers from the USA aimed to investigate the potential risk factors that might contribute to the development of chronic anal fistula and recurrent perianal sepsis.[30] They found that individuals younger than 40 years had a higher risk of developing chronic anal fistulas compared to those over 40 years of age.[31]

Studies in the Americas also calculated the distribution of individuals with anal fistula in different gender and age groups. Results from a study in Brazil that aimed to draw the

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[22] T. Toyonaga et al., "Microbiological Analysis and Endoanal Ultrasonography for Diagnosis of Anal Fistula in Acute Anorectal Sepsis," *International Journal of Colorectal Disease* 22, no. 2 (2007): 209–13, https://doi.org/10.1007/s00384-006-0121-x.
[23] Toyonaga et al., "Microbiological Analysis,"
[24] Toyonaga et al., "Microbiological Analysis,"
[25] N. T. B., "An Observational Study on Clinico-Pathological Analysis of Fistula-in-Ano in a Tertiary Care Hospital," *Journal of Medical Science and Clinical Research* 8, no. 5 (2020), https://doi.org/10.18535/jmscr/v8i5.67.
[26] T. B., "Clinico-Pathological Analysis,"
[27] Ping Cai et al., "The Potential Roles of Gut Microbiome in Anal Fistula," *AMB Express* 13, no. 1 (2023): 1–12, https://doi.org/10.1186/s13568-023-01560-9.
[28] V. Lohsiriwat et al., "Incidence and Factors Influencing the Development of Fistula-in-Ano after Incision and Drainage of Perianal Abscesses," *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet* 93, no. 1 (2010): 61–65, https://pubmed.ncbi.nlm.nih.gov/20196412/.
[29] Lohsiriwat et al., "Incidence and Factors,"
[30] A. Hamadani et al., "Who Is at Risk for Developing Chronic Anal Fistula or Recurrent Anal Sepsis after Initial Perianal Abscess?" *Diseases of the Colon & Rectum* 52, no. 2 (2009): 217–21, https://doi.org/10.1007/DCR.0b013e31819a5c52.
[31] Hamadani et al., "Who Is at Risk,"

epidemiological profile of adult patients with anal fistulas revealed that two-thirds of the 117 patients were males and the predominant age group was 18 to 60 years old and both factors were found to be statistically significant risk factors for primary anal fistula.[32] However, not all findings in the Americas are consistent with those in Asian studies. For example, a study in the USA aimed to determine the prevalence of benign anorectal disease (BAD) in a large population. In this study, 102 adults between the ages 21 to 65 for both genders and all races who had a history of benign anorectal diseases including anal fistulas, haemorrhoids, etc. were interviewed. They found that 53% of the interviewers were female with an average age of 39 years.[33] The authors also found that the female gender was statistically significantly associated with BAD symptoms.[34] While the findings contradicted those from studies in Asia, a possible explanation is that the study in the USA focused on BAD in general rather than specifically on anal fistulas, which might lead to variations in results.

An European study found that males in their middle age (nearly 40 to 50 years old) were more prone to anal fistula just like other studies from other regions, but the reason behind this is unclear.[35] A study in the United Kingdom (U.K.) aimed to determine the factors that lead to a higher prevalence in males than females from an endocrinological perspective. In the study, although it was not statistically significant, they found that male individuals with anal fistula had an overall higher androgen level than male controls, which were individuals without anal fistula.[36] Whereas in females, those with anal fistula had higher levels of estrogen and lower progesterone compared to controls.[37] Based on those results, researchers further hypothesised that it was possible that local endocrinological factors also led to anal fistula formation.[38]

While hormonal factors might play a crucial role in gender differences in anal fistula, this pattern may also reflect anatomical and behavior variations. One study identified that males had a higher vascularity index in the inner anal canal than female, which could increase the likelihood of inflammation in anal glands and contribute to fistula formation.[39] Additionally, lifestyles differences between genders may influence prevalence rates. For instance, studies have shown that males were generally more likely to smoke than females, and smoking was associated

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[32] F. R. Fugita et al., "Epidemiological Profile of Patients with Fistula-in-Ano," *Journal of Coloproctology* 40, no. 1 (2020): 1–7, https://doi.org/10.1016/j.jcol.2019.09.009.
[33] R. L. Nelson et al., "Prevalence of Benign Anorectal Disease in a Randomly Selected Population," *Diseases of the Colon & Rectum* 38, no. 4 (1995): 341–44, https://doi.org/10.1007/bf02054218.
[34] Nelson, R. L. et al., "Prevalence of benign anorectal disease in a randomly selected population."
[35] P. Sainio, "Fistula-in-Ano in a Defined Population: Incidence and Epidemiological Aspects," *Annales Chirurgiae et Gynaecologiae* 73, no. 4 (1984): 219–24, https://pubmed.ncbi.nlm.nih.gov/6508203/.
[36] P. J. Lunniss et al., "Gender Differences in Incidence of Idiopathic Fistula-in-Ano Are Not Explained by Circulating Sex Hormones," *International Journal of Colorectal Disease* 10, no. 1 (1995): 25–28, https://doi.org/10.1007/bf00337582.
[37] Lunniss et al., "Gender Differences,"
[38] Lunniss et al., "Gender Differences,"
[39] S. M. Murad-Regadas et al., "Establishing the Normal Ranges of Female and Male Anal Canal and Rectal Wall Vascularity with Color Doppler Anorectal Ultrasonography," *Journal of Coloproctology* 38, no. 3 (2018): 207–213, https://doi.org/10.1016/j.jcol.2018.03.005.

with an increased risk of developing anal fistulas.[40][41] Cultural or healthcare-seeking behavior variations between genders may further influence the diagnosis rates contributing to the difference.

Generally, all three regions, Asia, the Americas, and Europe have shown similar trends in terms of the age and gender of individuals most at risk for anal fistula . Anal fistula is most likely to occur in males in their 40s and 50s. The reasons for a higher prevalence in males are still unclear, and further research is needed to understand mechanism behind the gender disparity in anal fistula prevalence.

Lifestyles and behaviours

Lifestyles and behaviours are also deemed as important factors that contribute to anal fistula development. Scientists in China examined 1342 patients and found that sedentary lifestyles with rare participation in sports, eating habits such as regular intake of high salt or spicy food and alcohol, plus prolonged sitting on the toilet for defecation could all increase the risk of developing an anal fistula.[42]

The USA study that evaluated the benign anorectal disease population found that fibre consumption and reading materials in the bathroom were positively correlated with BAD symptoms whereas time spent during defecation was negatively correlated; however, these findings were not statistically significant due to inadequate sample size.[43] These results are quite different from those of the Chinese study and these differences may be due to the fact that the USA study focused on a range of benign anorectal diseases, not just on anal fistula. A majority of this population tended to seek and adopt healthy lifestyles, including paying close attention to the choice of bread and fibre supplements. This suggests an awareness that certain unhealthy eating habits-particularly low fiber intake-would trigger the development of BAD.[44]

Smoking is another behavioural factor that researchers assessed to determine whether it was associated with anal fistula. Smoking was found to be significantly associated with the development of anal fistulas in a study in China.[45] Researchers in the USA found a similar relationship by asking 1,070 patients to complete a questionnaire about their smoking status and history during their visits to the General Surgery Clinic at the Department of Veterans Affairs

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[40] Centre for Health Protection, Department of Health (Hong Kong), *Men's Facts – Tobacco Use*, last modified 2015, https://www.chp.gov.hk/en/static/80021.html.

[41] Esteban Ortiz-Ospina, "Men Are More Likely to Smoke Than Women Almost Everywhere in the World," *Our World in Data*, January 25, 2024, https://ourworldindata.org/data-insights/men-are-more-likely-to-smoke-than-women-almost-everywhere-in-the-world.

[42] D. Wang et al., "Risk Factors for Anal Fistula: A Case-Control Study," *Techniques in Coloproctology* 18, no. 7 (2014): 635–39, https://doi.org/10.1007/s10151-013-1111-y.

[43] Nelson et al., "Prevalence of Benign Anorectal Disease,"

[44] Nelson et al., "Prevalence of Benign Anorectal Disease,"

[45] Wang et al., "Risk Factors,"

(VA) in San Diego.[46] The study aimed to test the hypothesis that recent smoking is a significant risk factor for developing anal fistula.[47] Results showed a significant relationship between the development of anal abscess and fistula with recent smoking behaviours.[48] Additionally, research revealed a trend that individuals' risk of developing anal fistulas decreased as their exposure to smoking shortened over time, which indicated that constant smoking would lead to an increased risk of developing anal fistulas.[49] However, another study from the USA found that smoking was not a risk factor for chronic anal fistulas.[50] Additionally, researchers from Thailand reported that smoking and alcohol consumption were not significant risk factors for developing anal fistula. [51]

Socioeconomic status

Socioeconomic status was evaluated to determine how and if they were associated with anal fistulas. For example, authors from a study in China found that people with higher education levels were more prone to the disease and these same individuals mostly belonged to the middle and upper class.[52] Researchers in India studied the socioeconomic status of patients and found that 70% of 150 anal fistula patients belonged to the middle class; however, this result was not statistically significantly associated with developing anal fistula. [53]

The study in the USA that interviewed 102 adults found that 73% of the interviewees were married and 93% of them were white.[54] Additionally, 91% had completed either high school or university and 72% of all interviewees had an annual income greater than $25,000, indicating that people in the middle class are more prevalent to develop anal fistula, which is similar to the findings from the China and India studies.[55]

Few studies in Europe have directly assessed behavioural factors such as lifestyles and habits or socioeconomic statuses of individuals with anal fistulas. One possible explanation is that some European regions exhibit relatively healthier public health patterns. For example, Southern European cultures are often associted with the Mediterranean diet, which has been linked to reduced risk of diabetes, certain cancers and cardiovascular diseases.[5657] Due to its anti-inflammatory and antioxidant properties, the diet may help reduce chronic inflammation,

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[46] B. Devaraj et al., "Recent Smoking Is a Risk Factor for Anal Abscess and Fistula," *Diseases of the Colon & Rectum* 54, no. 6 (2011): 681–85, https://doi.org/10.1007/DCR.0b013e31820e7c7a.
[47] Devaraj et al., "Recent Smoking,"
[48]Devaraj et al., "Recent Smoking,"
[49] Devaraj et al., "Recent Smoking,"
[50] Hamadani et al., "Who Is at Risk,"
[51] Lohsiriwat et al., "Incidence and Factors,"
[52] Wang et al., "Risk Factors,"
[53] T. B., "Clinico-Pathological Analysis,"
[54] Nelson et al., "Prevalence of Benign Anorectal Disease,"
[55] Nelson et al., "Prevalence of Benign Anorectal Disease,"
[56] Francesco Sofi et al., "Adherence to Mediterranean Diet and Health Status: Meta-analysis," *BMJ* 337 (September 11, 2008): a1344, https://doi.org/10.1136/bmj.a1344.
[57] T. Milenkovic et al., "Mediterranean Diet and Type 2 Diabetes Mellitus: A Perpetual Inspiration for the Scientific World. A Review," *Nutrients* 13, no. 4 (2021): 1307, https://doi.org/10.3390/nu13041307.

and improve the overall quality of life.[58] Additionally, some European cities were notable for pedestrian- and cyclist-friendly infrastructures that encouraged physical activity among citizens, which may further reduce the prevalence of sedentary lifestyles. However, diet and lifestyle habits can vary widely around different parts of Europe. More research is needed to cover a broader range of regions of Europe and to evaluate whether these public health habits influence the prevalence of anal fistulas.[5960]

Clinicopathological factors

Bacteriology and microbiology

Gut microbiomes have been shown to be associated with the formation of anal fistula. Researchers conducted a study in China that aimed to identify whether gut microbiome of patients with anal fistula contributed to anal fistula formation. They found that a much richer and more diverse gut microbiome culture was seen in individuals without anal fistulas compared to those with anal fistula.[61] More specifically, these researchers found that individuals with anal fistula were enriched in bacteria such as *Blautia, Faecalibacterium, Ruminococcus, Coprococcus, Bacteroides, Clostridium, Megamonas,* and *Anaerotruncus*, while individuals without anal fistula were higher in *Peptoniphilus* and *Corynebacterium.*[62] *Faecalibacterium* was found in both groups, those with and without anal fistula. However, *Faecalibacterium* might influence the progression of anal fistula when combined with *Butyricicoccus, Coprococcus* and *Gemmiger.*[63] Researchers evaluated 514 patients in Japan who were treated for a clinical diagnosis of acute anorectal sepsis and had undergone microbiological analysis to improve the diagnosis of anal fistulas following anorectal sepsis.[64] They found that aerobic organisms were much greater in individuals with anal fistulas than in individuals without.[65] Gut-derived organisms such as *E. coli, Bacteroides,* and *Klebsiella* species are more frequently seen in individuals with anal fistula, whereas skin-derived organisms such as coagulase-negative *Staphylococci* and *Peptostreptococcus* species tend to be seen more often in individuals without anal fistula.[66]

European researchers were also interested in the bacterium culture of anal fistula patients. Researchers found that gut bacteria are related to the formation of acute anal fistulas. A study in

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[58] M. Finicelli et al., "The Mediterranean Diet: An Update of the Clinical Trials," *Nutrients* 14, no. 14 (2022): 2956, https://doi.org/10.3390/nu14142956.
[59] World Health Organization, *Promoting Healthy Active Mobility*, 2021, accessed December 18, 2024, https://www.who.int/europe/activities/promoting-healthy-active-mobility.
[60] European Commission, *Active Mobility: Walking and Cycling*, 2021, https://transport.ec.europa.eu/transport-themes/urban-transport/active-mobility-walking-and-cycling_en.
[61] Cai et al., "Gut Microbiome in Anal Fistula,"
[62] Cai et al., "Gut Microbiome in Anal Fistula,"
[63] Cai et al., "Gut Microbiome in Anal Fistula,"
[64] Toyonaga et al., "Microbiological Analysis,"
[65] Toyonaga et al., "Microbiological Analysis,"
[66] Toyonaga et al., "Microbiological Analysis,"

the U.K. evaluated the bacteriology of anal fistula and confirmed that similar organisms were found in the pus of individuals with anal fistula and acute abscesses, indicating acute anal gland infection is associated with anal fistula formation.[67] *E. coli* was the predominant gram-negative aerobic organism and *B. fragilis* was the main gram-negative anaerobic organism, similar to those that grow from acute anal abscess.[68] Both bacteria were considered to be derived from the mucous membrane of the bowel, indicating they are gut- (bowel-) derived organisms.[69] Another study in the U.K. investigated the incidence of anal fistula and the original predominant microorganisms in acute anorectal sepsis reported similar results.[70] Among the 165 participants, most anal fistula patients started with a perianal abscess, others were triggered by Crohn's, anal carcinoma, etc.[71] Individuals with anal fistula were those who grew bowel-derived organisms from their pus, whereas, individuals without further developing anal fistula were those who grew skin-derived organisms from their pus.[72] These results are in alignment with the results of the Japanese study. Furthermore, a study in Denmark aimed to establish the true incidence of anal fistula in anal sepsis patients. Findings from this study aligned with the findings from other studies in which an anal fistula developed after an anorectal sepsis when intestinal microorganisms existed but an anal fistula did not develop after an anorectal sepsis when skin-derived organisms were present.[73] Another group of researchers in Denmark aimed to identify the clinical risk factors for developing anal fistulas following anal abscess treatments. They reported that *E. coli* pus cultures were statistically significantly associated with anal fistula formation.[74] Additionally, scientists from Finland aimed to assess the incidence of anal fistulas and related risk factors after acute anorectal abscess treatment. They reported findings similarly to the study in Denmark, indicating that abscesses with *E. coli* cultures were significantly more prone to fistula formation than those growing other bacteria.[75]

Although gut microbiomes were closely related to acute anal fistulas, studies suggested that the persistence of anal fistulas might be associated with factors other than bacteria. A study in the U.K. aimed to assess the role of microorganisms in chronic anal fistula, reported that there was little evidence to support the role of infection in fistula persistence.[76] Moreover, scientists from Spain who focused on whether the presence of permanent infections was related to chronic

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[67] F. Seow-Choen, A. J. Hay, S. Heard, and R. K. S. Phillips, "Bacteriology of Anal Fistulae," British Journal of Surgery 79, no. 1 (1992): 27–28, https://doi.org/10.1002/bjs.1800790107.
[68] Seow-Choen et al., "Bacteriology of Anal Fistulae,"
[69] Seow-Choen et al., "Bacteriology of Anal Fistulae,"
[70] R. H. Grace, I. A. Harper, and R. G. Thompson, "Anorectal Sepsis: Microbiology in Relation to Fistula-in-Ano," British Journal of Surgery 69, no. 7 (1982): 401–403, https://doi.org/10.1002/bjs.1800690715.
[71] Grace, Harper, and Thompson, "Anorectal Sepsis,"
[72] Grace, Harper, and Thompson, "Anorectal Sepsis,"
[73] S. Henrichsen and J. Christiansen, "Incidence of Fistula-in-Ano Complicating Anorectal Sepsis: A Prospective Study," *British Journal of Surgery* 73, no. 5 (1986): 371–372, https://doi.org/10.1002/bjs.1800730515.
[74] Skovgaards et al., "Fistula Development,"
[75] K.-P. J. Hämäläinen and P. A. Sainio, "Incidence of Fistulas after Drainage of Acute Anorectal Abscesses," Diseases of the Colon & Rectum 41, no. 11 (1998): 1357–1361, https://doi.org/10.1007/bf02237048.
[76] Lunniss et al., "Gender Differences,"

anal fistula from a bacteriological perspective also resulted in similar findings.[77] They analysed 27 patients with anal fistula and reported that nearly 80% of samples had a polymicrobial growth, with *E. coli, B. fragilis, S. aureus* and *Viridans streptococci* as the predominant species.[78] However, they found no significant relationship between the number and types of microbiomes and the chronicity of anal fistulas.[79] This result was confirmed by another study from the U.K. in which scientists aimed to identify mucosa-associated bacteria in Crohn's and idiopathic anal fistula tracts.[80] They found little to no bacteria on the luminal surfaces of fistula tracts from individuals with both idiopathic and Crohn's-related anal fistulas, which suggested that bacteria may not play a significant role in the persistence of anal fistula.[81] As both types of fistulas lacked significant bacterial colonisation, it suggested that the role of other factors such as genetic, immunological, or tissue repair could also play a role in fistula persistence.[82] This study suggested that researchers should further investigate the non-bacterial factors that could lead to the chronicity of anal fistulas.

Overall, studies from Asia and Europe reported similar results related to the role of bacteria and microbiomes in the formation of anal fistulas . Gut-derived organisms were widely found in individuals who developed anal fistula from anal abscesses, whereas skin-derived organisms are rarely found in these individuals. Specifically, *E. coli* and *B. fragilis* were reported to be the most commonly identified bacteria in anal fistula patients. Additionally, scientists implied that the persistence of anal fistula may be associated with non-bacterial factors based on findings that revealed bacteria was not significantly associated with the chronicity of anal fistulas.

Comorbidities

There are several comorbidities correlated with anal fistula formation. For example, researchers from China found that obesity (body mass index (BMI) exceeding 25 kg/m2 in a Chinese population), prior diabetes, hyperlipidemia, dermatosis, and a previous history of enteritis were independently associated with anal fistula development.[83] A study in India reported that some individuals with anal fistulas had a history of inflammatory bowel disease (IBD) or carcinoma, which indicated the link between anal fistula formation and other intestinal diseases.[84] Specific inflammation such as tuberculosis infection were two of the 150 cases, with the majority of remaining cases being non-specific inflammation.[85] Tuberculosis endemic countries in sub-Saharan Africa and Asia should be aware of this specific infection because it

[77] A. De San Ildefonso et al., "Bacteriology of Anal Fistulae," Revista Española de Enfermedades Digestivas 94, no. 9 (2002): 533–536, https://www.researchgate.net/publication/10900311_Bacteriology_of_anal_fistulae.
[78] De San Ildefonso et al., "Bacteriology of Anal Fistulae,"
[79] De San Ildefonso et al., "Bacteriology of Anal Fistulae,"
[80] P. J. Tozer et al., "What Role Do Bacteria Play in Persisting Fistula Formation in Idiopathic and Crohn's Anal Fistula?" Colorectal Disease 17, no. 3 (2015): 235–241, https://doi.org/10.1111/codi.12810.
[81] Tozer et al., "Role of Bacteria in Persisting Fistula Formation,"
[82] Tozer et al., "Role of Bacteria in Persisting Fistula Formation,"
[83] Wang et al., "Risk Factors,"
[84] T. B., "Clinico-Pathological Analysis,"
[85] T. B., "Clinico-Pathological Analysis,"

was a risk factor for an anal fistula.[86] Whereas, in Western countries, tubercular anal fistulas were rarely seen in individuals with anal fistulas.[87] Findings from the Thailand study showed that non-diabetic individuals had a higher risk of anal fistula formation, which was contradictory to the study in China.[88] Additionally, researchers from the USA reported that the non-diabetic individuals were more likely to develop chronic anal fistula; however it did not reach statistical significance on multivariate analysis.[89] These inconsistencies may reflect differences in how diabetes is defined, diagnosed, or managed across regions. Diagnostic criteria and management of diabetes may vary, potentially affecting whether diabetes appears as a significant risk factor. For example, traditional Chinese medicine interventions versus Western biomedical approaches may influence how diabetes are diagnosed or treated across regions. Genetic differences could also contribute to the differences in how closely diabetes is linked to obesity in each population. Thailand researchers also found that fever, leukocytosis, and location of abscess were not statistically significantly related to fistula formation.[90]

Crohn's disease is another risk factor associated with anal fistulas. Researchers conducted standardised calculations using data from The Health Improvement Network (THIN) to assess the point prevalence of anal fistulas and relevant comorbidities in individuals with and without Crohn's disease (CD) in the U.K. and European population.[91] Researchers estimated that the prevalence of anal fistula in the U.K. and European population were 1.80 and 1.83 per 10,000 individuals, implying that anal fistulas were infrequent in the general population. Additionally, they suggested that 25% of individuals with anal fistulas also had CD, whereas the associations with other comorbidities were relatively rare, highlighting the importance of CD as a complication associated with anal fistula.[92] Researchers found that, in the U.K., among those with anal fistula, those without CD were more prone to develop anal fistula-related comorbidities than those with CD, suggesting that CD might act as a protective factor in these cases. In the U.K. population, the majority of individuals without CD and over the age of 65 had at least one comorbidity.The most common comorbidity among individuals both with and without CD was diabetes mellitus.[93] Apart from diabetes mellitus, diverticulosis and hidradenitis suppurativa were the second most common comorbidities of anal fistula patients with and without CD respectively. Other comorbidities reported in the study were rectal infectious diseases, anal carcinoma and systemic diseases.[94] Moreover, a study from Denmark also revealed that CD and a C-reactive protein level of more than 100 mg/L were found to be statistically significantly associated with

[86] J. Jereb, "Tuberculosis," in CDC Yellow Book 2024, 2023, accessed December 18, 2024, https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/tuberculosis.
[87] Y.-W. Choi et al., "Clinical Features of Tuberculous Versus Crohn's Anal Fistulas in Korea," Journal of Crohn's and Colitis 9, no. 12 (2015): 1132–1137, https://doi.org/10.1093/ecco-jcc/jjv164.
[88] Lohsiriwat et al., "Incidence and Factors,"
[89] Hamadani et al., "Who Is at Risk,"
[90] Lohsiriwat et al., "Incidence and Factors,"
[91] Hokkanen et al., "Prevalence in the UK,"
[92] Hokkanen et al., "Prevalence in the UK,"
[93] Hokkanen et al., "Prevalence in the UK,"
[94] Hokkanen et al., "Prevalence in the UK,"

anal fistula.[95] Given CD was not a common disease among Asian countries, it was not a main risk factor among Asian individuals with anal fistula.[96] Although CD could affect individuals from any ethnicity, ut was most common in west Europe and North America, particularly among white population. This contibutes to regional differences in people with anal fistulas linked to CD. The reasons for these geographic patterns are complex and not fully understood, but CD was thought to result from a combination of genetic, environmental, and lifestyle factors such as diet and smoking.

Anal abscess and sepsis are usually the direct triggers of an anal fistula formation. Authors from a study in India found that approximately 65% of the 150 patients had perianal abscess before developing an anal fistula.[97] A study conducted in Turkey aimed to examine the prognostic factors for recurrence of anorectal abscess and anal fistula formations[98] Results indicated that the duration of time from disease onset to incision was the only statistically significant risk factor for anal fistula formation. Researchers hypothesised that over time, abscesses would lead to fistula formation and/or the establishment of infections in the surrounding tissue, which will facilitate fistula formation.[99] Another study, conducted in Canada, aimed to determine the number of patients who developed anal fistulas after having anal abscess treatments.[100] The authors found that 87% of patients who developed anal fistula had ischiorectal abscesses, whereas none of the patients with intersphincteric abscesses developed any further conditions. Generally, having a history of ischiorectal abscesses increased the likelihood of developing anal fistulas.[101] The study from Denmark found that low intersphincteric and ischioanal abscesses were risk factors for anal fistula formation, which are in alignment with the study from Canada.[102] Additionally, researchers from Finland identified that female individuals had a higher risk of developing fistulas originating from anterior abscesses.[103] They also reported that a history of repeat surgeries for treating anal abscesses was statistically significantly correlated with primary anal fistulas.[104] Furthermore, a study in Spain analysed the incidence of anal fistula after urgent drainage for anal abscess and found that the existence of an undiagnosed

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[95] Skovgaards et al., "Fistula Development,"
[96] S. C. Ng et al., "Worldwide Incidence and Prevalence of Inflammatory Bowel Disease in the 21st Century: A Systematic Review of Population-Based Studies," *The Lancet* 390, no. 10114 (2017): 2769–2778, https://doi.org/10.1016/s0140-6736(17)32448-0.
[97] T. B., "Clinico-Pathological Analysis,"
[98] T. Yano et al., "Prognostic Factors for Recurrence Following the Initial Drainage of an Anorectal Abscess," International Journal of Colorectal Disease 25, no. 12 (2010): 1495–1498, https://doi.org/10.1007/s00384-010-1011-9.
[99] Yano et al., "Prognostic Factors for Recurrence,"
[100] C.-A. Vasilevsky and P. H. Gordon, "The Incidence of Recurrent Abscesses or Fistula-in-Ano Following Anorectal Suppuration," *Diseases of the Colon & Rectum* 27, no. 2 (1984): 126–130, https://doi.org/10.1007/bf02553995.
[101] Vasilevsky and Gordon, "Incidence of Recurrent Abscesses or Fistula-in-Ano,"
[102] Skovgaards et al., "Fistula Development,"
[103] Hämäläinen and Sainio, "Incidence of Fistulas,"
[104] Skovgaards et al., "Fistula Development,"

fistula during the acute moment of anal abscess was statistically significantly associated with anal fistula formation.[105]

Recurrent anal fistula

There has been less literature investigating the risk factors for recurrent anal fistulas compared to primary anal fistulas . Researchers may not have prioritised examining risk factors for recurrent anal fistulas because recurrent anal fistulas are less prevalent typically than primary anal fistulas. The overall recurrence rates of anal fistulas varied across regions, ranging from 7% to 50%.[106] In Europe, a nationwide study in Spain reported a recurrence rate of 6.8% following surgical treatments for primary anal fistulas.[107] Whereas, a study in the USA showed a higher recurrent rate of approximately 12.5% after primary anal fistula treatments.[108] Findings in Asia appeared to have the highest recurrence rate of all, with a general study from Malaysia reporting a recurrence rate of 22.86% following laser ablation procedures.[109]

Sociodemographic factors

Age and gender

Certain ages and gender may be more prone to developing recurrent anal fistulas than others, but these differences may not all be statistically significant. For example, a study in China investigated the clinical characteristics and other risk factors for 1,783 patients with recurrent anal fistulas treated at Shuguang Hospital between 2013 and 2015. The sample consisted of 1,526 male patients with a median age of 36 years.[110] Thus, recurrent anal fistulas were mostly seen in male individuals under the age of 40; however, the study did not identify gender or age as significant risk factors.[111] Another group of researchers in China performed a meta-analysis to

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[105] C. Chaveli Díaz et al., "Recurrence and Incidence of Fistula after Urgent Drainage of an Anal Abscess. Long-term Results. Recidiva e Incidencia de Fístula tras el Drenaje Urgente de un Absceso Anal. Resultados a Largo Plazo," Cirugía Española, S0009-739X(20)30384-5 (2020), advance online publication, https://doi.org/10.1016/j.ciresp.2020.11.010.

[106] N. Bakhtawar and M. Usman, "Factors Increasing the Risk of Recurrence in Fistula-in-Ano," *Cureus* (2019), https://doi.org/10.7759/cureus.4200.

[107] Ó. Cano-Valderrama et al., "Surgical Treatment Trends and Outcomes for Anal Fistula: Fistulotomy Is Still Accurate and Safe. Results from a Nationwide Observational Study," *Techniques in Coloproctology* 27, no. 10 (2023): 909–919, https://doi.org/10.1007/s10151-023-02842-x.

[108] S. Khan et al., "Predictors of Recurrence and Long-Term Patient-Reported Outcomes Following Surgical Repair of Anal Fistula: A Retrospective Analysis," *International Journal of Colorectal Disease* 39, no. 1 (2024), https://doi.org/10.1007/s00384-024-04602-1.

[109] C.-Y. Tang and A. C. Roslani, "Laser Ablation of Anal Fistulae: A 6-Year Experience in a Tertiary Teaching Hospital in Malaysia," *Lasers in Medical Science* 37, no. 8 (2022): 3291–3296, https://doi.org/10.1007/s10103-022-03628-7.

[110] J. Li et al., "Clinical Characteristics and Risk Factors for Recurrence of Anal Fistula Patients," *Zhonghua Wei Chang Wai Ke Za Zhi = Chinese Journal of Gastrointestinal Surgery* 19, no. 12 (2016): 1370–74, https://pubmed.ncbi.nlm.nih.gov/28000193/.

[111] Li et al., "Clinical Characteristics and Risk Factors,"

summarise the potential risk factors for recurrent anal fistulas after surgery.[112] The authors found that males younger than 40 years of age were more likely to develop recurrent anal fistula than males older than 40 years; however, age and gender were not statistically significantly associated with anal fistula recurrence.[113] The findings from the Mei et al. (2019) study supported findings from the Li et al. (2016) study as they also identified age under 40 as a (nonsignificant) contributing risk factor for recurrent anal fistula. Similar results were found in a Pakistan study in which they assessed several facets linked to the recurrence of anal fistulas.[114] Approximately 80% of the 130 recurrent anal fistula patients were males and the average age was 38 years; age was found to be significantly associated with anal fistula recurrence but gender was not.[115] Another group of researchers also from Pakistan evaluated 100 patients at Jinnah Postgraduate Medical Centre in Karachi between 1998 and 2007 to determine the frequency of tubercular anal fistulas in recurrent anal fistulas.[116] Although the study reported that 92% of patients were males and the median age was 35 years olds, age and gender were not mentioned as significant contributors to recurrent tubercular anal fistulas in the study.[117]

In Europe, researchers from The Netherlands examined 179 patients from the Academic Medical Centre of University of Amsterdam to assess the potential risk factors for the development of recurrent anal fistulas in individuals who were specifically treated by fistulotomy or rectal advancements flap. Findings indicated that neither gender nor age were significantly associated with recurrent anal fistulas in both groups.[118] Researchers in Spain evaluated the risk factors of recurrence and incontinence (faecal) of anal fistulas among 279 patients who underwent anal fistula repair treatment at "the Hospitals of Sagunto and the Clınico Universitario de Valencia, between 1994 and 1998." They found that among the 279 patients, 214 were males and 65 were females; of the 279 patients, 61 were treated for a recurrent anal fistula.[119] On average, patients were 46.7 years of age, however, researchers did not adjust for age and gender in analysis, making it difficult to determine their potential association with recurrent anal fistula.[120]

Researchers examining recurrent anal fistulas reported similar findings as primary anal fistula as relates to gender, which males were the more prevalent gender for both primary and recurrent anal fistulas. However, different predominant age groups were found in recurrent and

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[112] Z. Mei et al., "Risk Factors for Recurrence after Anal Fistula Surgery: A Meta-Analysis," *International Journal of Surgery (London, England)* 69 (2019): 153–64, https://doi.org/10.1016/j.ijsu.2019.08.003.
[113] Mei et al., "Risk Factors for Recurrence,"
[114] M. Hashmi et al., "Factors Increasing the Risk of Recurrence in Fistula-in-Ano," *Journal of Population Therapeutics and Clinical Pharmacology* 31, no. 6 (2024): 1425–32, https://doi.org/10.53555/jptcp.v31i6.6689.
[115] Hashmi et al., "Factors Increasing the Risk,"
[116] I. Bokhari et al., "Tubercular Fistula-in-Ano," *Journal of the College of Physicians and Surgeons Pakistan* 18, no. 7 (2008): 401–3, https://pubmed.ncbi.nlm.nih.gov/18760061/.
[117] Bokhari et al., "Tubercular Fistula-in-Ano,"
[118] P. J. van Koperen et al., "Long-Term Functional Outcome and Risk Factors for Recurrence after Surgical Treatment for Low and High Perianal Fistulas of Cryptoglandular Origin," Diseases of the Colon & Rectum 51, no. 10 (2008): 1475–81, https://doi.org/10.1007/s10350-008-9354-9.
[119] J. Jordán et al., "Risk Factors for Recurrence and Incontinence after Anal Fistula Surgery," *Colorectal Disease* 12, no. 3 (2010): 254–60, https://doi.org/10.1111/j.1463-1318.2009.01806.x.
[120] Jordán et al., "Risk Factors for Recurrence and Incontinence,"

primary anal fistula studies. Findings show that individuals in a younger age group, particularly under the age of 40, were more prevalent in developing recurrent anal fistulas. Meanwhile, individuals in their 40s and 50s were more likely to develop a primary anal fistula.

Clinicopathological factors

Comorbidities

Similar to primary anal fistulas, comorbidities were identified as risk factors for the development of recurrent anal fistulas. Authors in Pakistan reported that diabetes and hypertension were both significantly associated with anal fistula recurrence.[121] Notably, hypertension was not mentioned as a risk factor for primary anal fistulas. A study from the USA that aimed to compare recurrence rates and long-term effects of anal fistula following surgeries found similar results as a study in Pakistan.[122] The authors found that diabetes mellitus and a history of anorectal abscess were significant predictors for anal fistula recurrence.[123] Similarly, chronic anorectal abscesses were found to be associated with recurrent anal fistulas by researchers in Spain; however, the association was not statistically significant.[124] In addition, scientists from Pakistan discovered that tuberculosis was a neglected cause of anal sepsis as perianal tuberculosis could occur in the absence of any other tuberculosis foci.[125] The anal sepsis was usually overlooked and not treated properly during primary anal surgery, which resulted in the reformation of an anal fistula. Additionally, diagnosing CD and intestinal tuberculosis based on their histological differences was challenging because CD was not a common disease in Pakistan and none of the individuals with recurrent anal fistulas were diagnosed with CD during the biopsy.[126] Tuberculosis was also a recognised risk factor for primary anal fistulas. Overall, a more diverse range of comorbidities were associated with primary anal fistulas as opposed to recurrent anal fistulas.

Postoperative care

Insufficient postoperative care could be a contributor to recurrence of anal fistulas. Findings from a study in Spain indicated that complications of the surgical wound during the postoperative period were correlated to recurrent anal fistulas; however, this association was not statistically significant.[127] Moreover, authors from a study in The Netherlands found that 42% of patients had post-surgery problems related to soiling, indicating that soiling was a considerable issue after anal fistula surgeries, but the authors did not report it as a risk factor for recurrent anal

[121] Hashmi et al., “Factors Increasing the Risk,”
[122] Khan et al., “Predictors of Recurrence and Long-Term Outcomes.”
[123] Khan et al., “Predictors of Recurrence and Long-Term Outcomes.”
[124] Jordán et al., “Risk Factors for Recurrence and Incontinence,”
[125] Bokhari et al., “Tubercular Fistula-in-Ano,”
[126] Bokhari et al., “Tubercular Fistula-in-Ano,”
[127] Jordán et al., “Risk Factors for Recurrence and Incontinence,”

fistula.[128] Postoperative complications, however, are not mentioned in literature as risk factors for primary anal fistulas.

Treatment history

Prior anal surgery was a widely studied predictor for the occurrence of recurrent anal fistulas. Authors from a study in China aimed to investigate the rate of recurrence of anal fistula in individuals who received surgery for primary anal fistulas and identify the pattern and risk factors of anal fistula recurrence.[129] They found a statistically significant increase in the risk of recurrent anal fistulas with sinus tract excision for perianal sinus.[130] Additionally, an internal opening was found in the re-operation for 44.4% of the individuals with recurrent anal fistulas, suggesting that an overlooked opening during the first operation may progress into a recurrent anal fistula tract.[131] Furthermore, another study in China reported that undetected internal opening and prior anal surgery both significantly increased the risk of developing recurrent anal fistulas.[132] In addition, a recent study from Pakistan found that the types of surgical procedure were statistically significantly associated with recurrence of anal fistulas.[133] Specifically, researchers pointed out that seton was the treatment with the highest recurrent rate, whereas fistulectomy and fistulotomy demonstrated much lower recurrence rates in comparison.[134] Another study in China also reported that seton treatment history had a significantly higher rate of recurrence than other treatment types.[135]

A study in the USA, which aimed to discover the risk factors associated with anal fistula recurrence, reported similar findings as the two studies in China, indicating that lack of identification of internal openings was statistically significantly associated with recurrent anal fistulas in the univariate analysis; however, it was not found to be a statistically significant risk factor in the multivariate analysis.[136] Additionally, researchers reported that the surgeon who performed the procedure was identified as an important risk factor for recurrent anal fistula in the multivariate analysis; however, it was not statistically significantly associated with recurrence in the univariate analysis.[137] Another group of researchers from the USA discovered sphincter sparing surgery, such as LIFT or plug/biologic procedures, were statistically significantly associated with high recurrent rates, whereas non-sphincter-sparing surgeries, such as

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[128] van Koperen et al., "Long-Term Functional Outcome and Risk Factors,"
[129] C. M. Poon, D. C. Ng, M. C. Ho-Yin, R. S. Li, and H. T. Leong, "Recurrence Pattern of Fistula-in-Ano in a Chinese Population," *Journal of Gastrointestinal and Liver Diseases: JGLD* 17, no. 1 (2008): 53–57.https://pubmed.ncbi.nlm.nih.gov/18392245/
[130] Poon et al., "Recurrence Pattern,"
[131] Poon et al., "Recurrence Pattern,"
[132] Mei et al., "Risk Factors for Recurrence,"
[133] Hashmi et al., "Factors Increasing the Risk,"
[134] Hashmi et al., "Factors Increasing the Risk,"
[135] Li et al., "Clinical Characteristics and Risk Factors,"
[136] J. Garcia-Aguilar, C. Belmonte, D. W. Wong, S. M. Goldberg, and R. D. Madoff, "Anal Fistula Surgery," Diseases of the Colon & Rectum 39, no. 7 (1996): 723–29, https://doi.org/10.1007/bf02054434.
[137] Garcia-Aguilar et al., "Anal Fistula Surgery,"

fistulotomy and seton treatment, had a lower rate of recurrence.[138] While the recurrent rate of fistulotomy aligned with findings from the China and Pakistan studies, the recurrent rate of seton treatments contradicted these findings.

Findings from The Netherlands were aligned with the findings from Pakistan in that individuals treated with fistulotomy had a lower rate of anal fistula recurrence.[139] Similar finding was also reported by a study in Spain that compared six different treatments, including fistulotomy, fistulectomy, seton, fistulectomy & sphincter repair, fistulectomy & advancement flap, and core out & closure of internal opening, with fistulotomy showing the lowest recurrent rate of al.[140] Core out & closure of the internal fistula opening had the highest recurrent rate.[141] This result aligned with the findings in the Pakistan study that fistulotomy had the lowest recurrent rate compared to other treatments, including seton treatment. However, researchers from the Pakistan study did not test for the core out & closure of internal opening to see whether it had a higher recurrent rate than seton treatment. Additionally, non-identification of the internal fistula opening by surgeons during primary anal fistulas was significantly correlated with recurrent anal fistula, which was in alignment with studies in the USA and China.[142] Another study in The Netherlands aimed to reveal whether preoperative three-dimensional endoanal ultrasound (3D-EAUS) was able to identify risk factors for recurrent anal fistula after surgeries.[143] They found that prior fistula surgery significantly increased the risk of recurrent anal fistulas, which aligned with the results from the study in China. Additionally, the presence of a secondary track formation was identified as a strong risk factor for recurrent anal fistulas. [144]

In summary, repeated surgical treatments for anal abscesses were identified as risk factors for primary anal fistulas. Similar patterns were observed in recurrent anal fistulas, where the recurrent rate could be increased by prior surgeries, particularly in certain types of procedures. Furthermore, if an undiagnosed fistula was overlooked during surgeries for anal abscess or primary anal fistula, it may appear as a primary or a recurrent anal fistula, respectively.

Types and position of primary anal fistulas

Certain types and positions of primary anal fistulas were found to increase the likelihood of developing recurrent anal fistulas. Researchers in China discovered that fistula height was statistically significantly associated with recurrent anal fistulas, with high anal fistulas having a significantly higher rate of recurrence than low anal fistulas.[145] Similarly, another group of researchers in China found that individuals who were previously treated for complex anal fistulas

[138] Khan et al., "Predictors of Recurrence and Long-Term Outcomes."
[139] van Koperen et al., "Long-Term Functional Outcome and Risk Factors,"
[140] Jordán et al., "Risk Factors for Recurrence and Incontinence,"
[141] Jordán et al., "Risk Factors for Recurrence and Incontinence,"
[142] Jordán et al., "Risk Factors for Recurrence and Incontinence,"
[143] A. P. Visscher et al., "Predictive Factors for Recurrence of Cryptoglandular Fistulae Characterized by Preoperative Three-Dimensional Endoanal Ultrasound," *Colorectal Disease* 18, no. 5 (2016): 503–09, https://doi.org/10.1111/codi.13211.
[144] Visscher et al., "Predictive Factors for Recurrence,"
[145] Li et al., "Clinical Characteristics and Risk Factors,"

had a higher risk of recurrence.[146] High anal fistulas and complex anal fistulas represent different classifications of anal fistula. A high anal fistula could often be a complex anal fistula due to the challenges in treatments posed by its position. Furthermore, a study in China revealed that high trans-sphincteric fistula, presence of horseshoe extensions, and multiple fistula tracts were statistically significantly associated with recurrence in anal fistulas.[147]

Researchers in the USA identified that complex types of primary anal fistulas and horseshoe extension were significant risk factors for recurrent anal fistulas, which was similar with the findings from the two studies in China.[148] Furthermore, a study in Spain reported that the presence of complex primary anal fistulas was significantly associated with recurrent anal fistulas, and suprasphincteric fistula was found to have the greatest risk of recurrence.[149]

Primary anal fistulas were influenced by the types of anal abscesses that developed before the formation of anal fistulas. Individuals with certain types of abscesses, such as ischiorectal abscess, were more likely to develop primary anal fistulas. Similarly, recurrent anal fistulas were influenced by the types and positions of the primary anal fistulas, with complex types of primary anal fistulas having an increased risk of developing recurrent anal fistulas.

Conclusion

Numerous studies were conducted across different countries to identify the risk factors for primary and recurrent anal fistulas. Overall, findings indicated that certain ages, genders and comorbidities increased the likelihood of developing either type of anal fistula. Recurrent anal fistulas, in particular, were associated with additional factors such as postoperative care.

While these findings demonstrated consistency across Asia, Europe and the Americas, regional variations existed specifically regarding the influence of Crohn's disease and recurrent rates following particular surgeries. This regional differences may not only reflect biological variations, such as genetics predispositions, but also disparities in health care infrastructure and diagnostic criteria. Sociocultural practices, such as stigma or gender norms, can further affect access to care and the likelihood of receiving professional medical care.

Much of the existing literature is outdated and often based on small sample sizes. Furthermore, topics related to the incidence of both types of anal fistulas across some regions and the reasons behind specific risk factors, such as age and gender, remain underexplored.

Some regions, such as the Middle East & North Africa and Sub-saharan Africa, are completely omitted from the literature, leaving much unknown. This lack of region-specifc date limits our understanding on how anal fistula affect specific populations and may result in under-diagnosis,

[146] Poon et al., "Recurrence Pattern,"
[147] Mei et al., "Risk Factors for Recurrence,"
[148] Garcia-Aguilar et al., "Anal Fistula Surgery,"
[149] Jordán et al., "Risk Factors for Recurrence and Incontinence,"

mismanagements, or chronic conditions due to inadequate medical support. In these ares, local healthcare may be focused on other, more prevalent and urgent conditions, while research efforts are constrained by cultural stigma, limited funding, and unstable political environment. However, it should be notes that regional databases in these areas were not systematically searched, which may be the reason of the limited number of studies from underrepresented ares such as Africa and the Middle East.

Future research should address these gaps through conducting multi-center cohort or case-control studies using larger and more representative sample sizes across all regions. Study designs should incorporate both biological and sociocultural variables and seek to identify universal risk patterns while also accounting for local contexts. The Middle East & North Africa and Sub-Saharan Africa should be considered high-priority areas for future research. Once we have a better global understanding of the risk factors associated with anal fistulas, this would support the establishment of preventative initiatives, improve diagnostic accuracy and treatments outcomes for patients from diverse backgrounds, ultimately reducing the burden of anal fistula-related healthcare challenges worldwide.

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