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Anal Fistulas: A Global Review on Sociodemographic and Clinicopathological Risk Factors

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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.

Keywords: primary anal fistula, recurrent anal fistula, risk factors, sociodemographic variables, clinicopathological factors, Crohn's disease, gut microbiome

Glossary

1. **Epidemiology**: The study of the distribution and determinants of health-related states or events in specified
2. populations.
3. **Incidence**: The number of new cases of a disease or condition occurring in a specified population during a
4. defined time period.
5. **Prevalence**: The total number of existing cases of a disease or condition in a population at a given time.
6. **Comorbidity**: The simultaneous presence of two or more diseases or medical conditions in a patient.
7. **Anal Fistula**: An abnormal, tunnel-like connection between the anal canal and the skin near the anus, often resulting from an infection or abscess.
8. **Benign Anorectal Disease**: Non-cancerous disorders affecting the anus and rectum, including hemorrhoids, fissures, abscesses, and fistulas.
9. **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.

10. **Inflammatory Bowel Disease (IBD)**: A group of chronic inflammatory disorders of the gastrointestinal tract, primarily including Crohn's disease and ulcerative colitis.
11. **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.
12. **Sepsis**: A life-threatening systemic response to infection, causing widespread inflammation and potential organ failure.
13. **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 (Sugrue et al., 2017). This anal abscess is the acute phase that usually triggers the development of an anal fistula (Parks et al., 1976). An anal fistula can be associated with other diseases as well, including inflammatory bowel disease (e.g., Crohn's Disease (CD)), tuberculosis infection, cancer, etc. (Cleveland Clinic, 2023). It is difficult to eradicate an anal fistula because it can recur after having a history of anal abscess or fistula (Emile, 2020; Skovgaards et al., 2023).

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 (Adamo et al., 2016; Bondurri, 2021; García-Olmo et al., 2019; Hokkanen et al., 2019; Sahnan et al., 2017; Zanotti et al., 2007). 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% (Yang, 2012). In the United States, the number of new cases per year that involved primary anal fistula treatment was 20,000 to 25,000, and 96,000 cases per year underwent recurrent treatment after a perianal abscess (Nelson, 2002). Whereas in Europe, a study analyzed 16 studies from 1984 to 2019 among seven countries and suggested that the overall prevalence rate of anal fistula is 16.9 per 100,000 people (Garcia-Olmo et al., 2019).

Anal fistula often causes serious discomfort, highly interfering with patients' overall quality of life (Chadbunchachai et al, 2021). Those with anal fistula may feel intense pain and fluids such as pus or blood may emerge around their anus. All levels of complexity of the fistulas could result in different inconveniences, impairing patients' routine activities. Additionally, patients may have to set restrictions on their daily entertainment to manage symptoms, thereby interfering with patients' relationships with their partners and families and their perceptions of themselves, resulting in psychological distress and insecurity (Iqbal et al., 2022).

In recent years, there have been many studies evaluating the efficiency and improvement of the procedures for anal fistula repair. Treatments such as endorectal advancement flap, novel approaches such as ligation of the intersphincteric fistula

tract (LIFT), or using biological material as a replacement can provide a vast range of options for complex anal fistula cases (Limura, 2015).

Even with these various treatment options, anal fistula recurrence remains high. These conditions usually result from the failure of complete healing of the surgical wound—this 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, thereby making treatments more complex (Emile, 2020). Globally, the anal fistula rate of recurrence ranges from 2.5% to 57.1% (Mei et al., 2019). A study in Spain found the anal fistula recurrence rate to be 48.2%, with 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 (Poon et al., 2008).

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 in which patients reside in and their cultural backgrounds. Previous reviews have stratified the risk factors for anal fistula by pathogenesis and demographic causes. To the author's 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 related to primary and recurrent anal fistula from all regions 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 texts were then reviewed for further clarification and final selection. The same screening process was 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 sizes 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 (Dendhar, 2023).

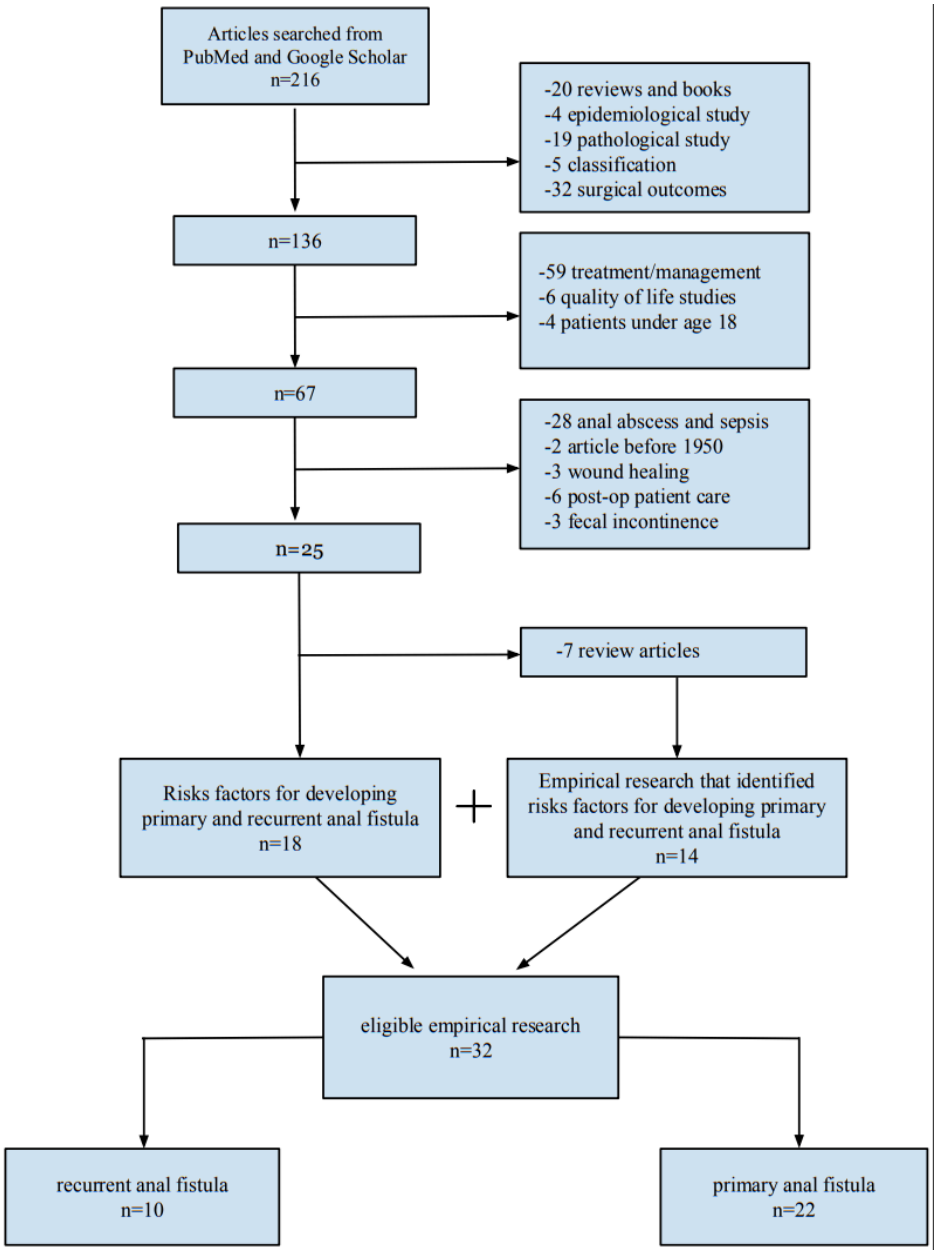

Figure 1. Flowchart of literature included in review

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 contribute 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 trigger 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 that contribute 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 analyzed surveys of patients' reflections on the changes in their quality of life were also 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.

Once most of the eligibility criteria were applied, a total of 25 articles were identified. However, seven articles were review articles and hence 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**).

Primary anal fistula

1. 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 found that approximately 90% were male (Toyonaga et al., 2007). Hence, gender was found to be a significant risk factor . 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, as the authors note. Another study in India analyzed 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 either most commonly occurs in males or there was bias in the sample selection process (TB et al., 2020). The authors of this latter study found that both gender and age were not statistically significantly associated with primary anal fistulas. 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, although 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 (Cai et al., 2023). 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 (Lohsiriwat et al., 2010). However, results from that study indicated that individuals with age under 40 years had a higher risk of developing anal fistula compared to those over 40 years.

Studies in the Americas also calculated the distribution of individuals with anal fistula in different gender and age groups. A 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 (Hamadani et al., 2009). As with the Thailand study, they also found that individuals younger than 40 years had a higher risk of developing chronic anal fistulas compared to those over 40 years of

age. 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 found to be statistically significant risk factors for primary anal fistula (Fugita et al., 2020). 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 (Nelson et al., 1995). 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. The authors also found that the female gender was statistically significantly associated with BAD symptoms. 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.

A 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 (Sainio, 1984). 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 (Lunniss et al., 1995). 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, whereas in females, those with anal fistula had higher levels of estrogen and lower progesterone compared to controls. Based on those results, the authors further hypothesised that local endocrinological factors also led to anal fistula formation.

While hormonal factors might play a crucial role in gender differences in anal fistula, gender differences may also reflect anatomical and behavior variations. One study identified that males had a higher vascularity index in the inner anal canal than females, which could increase the likelihood of inflammation in anal glands and contribute to fistula formation (Murad-Regadas et al., 2018). Additionally, lifestyle differences between genders may influence prevalence rates. For instance, some studies have shown that males were generally more likely to smoke than females, and smoking was associated with an increased risk of developing anal fistulas (Centre for Health Protection, 2015; Ortiz-Ospina, 2024). Cultural or healthcare-seeking behavior variations between genders may further influence the diagnosis rates contributing to the difference.

In summary, all three regions, Asia, the Americas, and Europe have generally 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 the 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, and prolonged sitting on the toilet for defecation could all increase the risk of developing an anal fistula (Wang et al., 2014).

The same USA study that evaluated the benign anorectal disease population also found that fiber consumption and reading materials in the bathroom were positively correlated with BAD symptoms, whereas time spent during defecation was negatively correlated—albeit,, these findings were not statistically significant due to inadequate sample size (Nelson et al.,

1995). 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 the population in the US study tended to seek and adopt healthy lifestyles, including paying close attention to the choice of bread and fiber supplements. This suggests an awareness that certain unhealthy eating habits—particularly low fiber intake—would trigger the development of BAD (Nelson et al., 1995).

Researchers have also assessed smoking as another behavioral factor that could be associated with anal fistula. In a study in China, smoking was found to be significantly associated with the development of anal fistulas (Wang et al., 2014). Researchers in the USA also 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 (Devaraj et al., 2011). The study aimed to test the hypothesis that recent smoking is a significant risk factor for developing anal fistula. Results showed a significant relationship between the development of anal abscess and fistula with recent smoking behaviours. Additionally, the same study 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. However, another study from the USA found that smoking was not a risk factor for chronic anal fistulas (Hamadani et al., 2009). Additionally, researchers from Thailand reported that smoking and alcohol consumption were not significant risk factors for developing anal fistula (Lohsiriwat et al., 2010).

Socioeconomic status

Several studies have evaluated socioeconomic status 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 (Wang et al., 2014). 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 (TB et al., 2020).

The study in the USA that interviewed 102 adults found that 73% of the interviewees were married and 93% of them were white (Nelson et al., 1995). 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.

Only a 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 associated with the Mediterranean diet, which has been linked to reduced risk of diabetes, certain cancers and cardiovascular diseases (Sofi et al., 2008; Milenkovic et al., 2021). Due to its anti-inflammatory and antioxidant properties, this diet may help reduce chronic inflammation and improve the overall quality of life (Finicelli et al., 2022). 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 (European Commission, 2021; WHO, 2024).

2. 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 (Cai et al., 2023). 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. More specifically, the authors 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*.

Cai et al. found *Faecalibacterium* in both groups: those with and without anal fistula. However, the presence of *Faecalibacterium* might influence the progression of anal fistula when combined with *Butyricicoccus*, *Coprococcus* and *Gemmiger*. 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 (Toyonaga et al., 2007). They found that aerobic organisms were much greater in individuals with anal fistulas than in individuals without. 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.

European researchers have also been 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 (Seow-Choen et al., 1992). *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. Both bacteria were considered to be derived from the mucous membrane of the bowel, indicating they are gut- (bowel-) derived organisms. Another study in the U.K. investigated the incidence of anal fistula, and the original predominant microorganisms in acute anorectal sepsis reported similar results (Grace et al., 1982). Among the 165 participants, most anal fistula patients started with a perianal abscess, while others were triggered by Crohn's, anal carcinoma, and other digestive tract-related diseases. 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. 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 (Henrichsen & Christiansen, 1986). 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. Another group of researchers in Denmark aimed to identify the clinical risk factors for developing anal fistulas following anal abscess treatments (Skovgaards et al., 2023). They reported that the association of *E. coli* pus cultures with anal fistula formation was statistically significant. Additionally, scientists from Finland aimed to assess the incidence of anal fistulas and related risk factors after acute anorectal abscess treatment (Hämäläinen & Sainio, 1998). They reported findings similar to the study in Denmark, indicating that abscesses with *E. coli* cultures were significantly more prone to fistula formation than those growing other bacteria.

Although gut microbiomes were closely related to acute anal fistulas, studies have 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 and reported that there was little evidence to support the role of infection in fistula persistence (Lunniss et al., 1995). Moreover, scientists from Spain, who focused on whether the presence of permanent infections was related to chronic anal fistula from a bacteriological perspective, also found similar results (de San Ildefonso et al., 2002). The latter study analyzed 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. However, they found no significant relationship between the number and types of microbiomes and the chronicity of anal fistulas. 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 (Tozer et al., 2015). 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. 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. 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 (Wang et al., 2014). A study in India reported that some individuals with anal fistulas had a history of inflammatory bowel disease (IBD) or carcinoma, which again indicates a link between anal fistula formation and other intestinal diseases (TB et al., 2020). Two of the 150 cases involved specific inflammation such as tuberculosis, while the majority of remaining cases involved non-specific inflammation. Countries in sub-Saharan Africa and Asia with a presence of tuberculosis should be especially aware of anal fistula, because tuberculosis is a risk factor for anal fistula (Jereb, 2023). Although, in Western countries, tubercular anal fistulas have rarely been seen in individuals with anal fistulas (Choi et al., 2015).

However, 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 (Lohsiriwat et al., 2010). Additionally, researchers from the USA reported that the non-diabetic individuals were more likely to develop chronic anal fistula, albeit without reaching statistical significance via multivariate analysis (Hamadani et al., 2009). 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 is 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 abscess location were not statistically significantly related to fistula formation (Lohsiriwat et al., 2010).

Crohn's disease is another risk factor associated with anal fistulas. Using data from The Health Improvement Network (THIN), researchers conducted standardized calculations 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 populations (Hokkanen et al., 2019). Researchers in this study estimated that the prevalence of anal fistula in the U.K. and European populations 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. Researchers found that., among those with anal fistula in the U.K., 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. 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. 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 (Skovgaards et al., 2023). Given CD was not a common disease among Asian countries, it was not a main risk factor among Asian individuals with anal fistula (Ng et al., 2017). Although CD could affect individuals from any ethnicity, it was most common in west Europe and North America, particularly amongst the white population. Hence, there are demonstrated regional differences in people with anal fistulas, as linked to CD. The reasons for these geographic patterns are complex and not fully understood, but CD has been thought to result from a combination of genetic, environmental, and lifestyle factors, such as diet and smoking (Mayo Clinic, 2024; Wu et al., 2025).

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 (TB et al., 2020). A study conducted in Turkey aimed to examine the prognostic factors for recurrence of anorectal abscess and anal fistula formations (Yano et al., 2010). Results from this study 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.

Generally, having a history of ischiorectal abscesses increased the likelihood of developing anal fistulas. Another study, conducted in Canada, aimed to determine the number of patients who developed anal fistulas after having anal abscess treatments (Vasilevsky & Gordon, 1984). 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. 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 (Skovgaards et al., 2023). Additionally, researchers from Finland identified that female individuals had a higher risk of developing fistulas originating from anterior abscesses (Hämäläinen and Sainio, 1998). They also reported that a history of repeat surgeries for treating anal abscesses was statistically significantly correlated with primary anal fistulas. Furthermore, a study in Spain analyzed the incidence of anal fistula after urgent drainage for anal abscess and found that the existence of an undiagnosed fistula during the acute moment of anal abscess was statistically significantly associated with anal fistula formation (Díaz et al., 2020).

Recurrent anal fistula

In comparison to primary anal fistulas, there has been less literature investigating the risk factors for recurrent anal fistulas. Researchers may not have prioritized examining risk factors for recurrent anal fistulas because recurrent anal fistulas are typically less prevalent than primary anal fistulas. The overall recurrence rates of anal fistulas varied across regions, ranging from 7% to 50% (Bakhtawar & Usman, 2019). In Europe, a nationwide study in Spain reported a recurrence rate of 6.8% following surgical treatments for primary anal fistulas (Cano-Valderrama et al., 2023). Whereas, a study in the USA showed a higher recurrent rate of approximately 12.5% after primary anal fistula treatments (Khan et al., 2024). 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 (Tang & Roslani, 2022).

1. Sociodemographic factors

Age and gender

Certain ages and genders 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 (Li et al., 2016). The sample consisted of 1,526 male patients with a median age of 36 years. Thus, recurrent anal fistulas were mostly seen in male individuals under the age of 40, although the study did not identify gender or age as significant risk factors. Another group of researchers in China performed a meta-analysis to summarise the potential risk factors for recurrent anal fistulas after surgery (Mei et al., 2019). 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. The findings from Mei et al. (2019) supported findings from the Li et al. (2016), 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 (Hashmi et al., 2024). 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. Another group of researchers 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 (Bokhari et al., 2008). Although the study reported that 92% of patients were males and the median age was 35 years old, age and gender were not mentioned as significant contributors to recurrent tubercular anal fistulas in the study.

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 (van Koperen et al., 2008). Findings indicated that neither gender nor age were significantly associated with recurrent anal fistulas in both groups. 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 (Jordán et al., 2010). 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. 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 the strength of potential association with recurrent anal fistula.

Researchers examining recurrent anal fistulas reported a similar relationship with gender as primary anal fistula, in which males were the more prevalent gender amongst those with both primary and recurrent anal fistulas. However, different predominant age groups were found in recurrent and 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 (Mei et al., 2019). Meanwhile, individuals in their 40s and 50s were more likely to develop a primary anal fistula.

2. 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 (Hashmi et al., 2024). 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 the aforementioned study in Pakistan (Khan et al., 2024). The authors found that diabetes mellitus and a history of anorectal abscess were significant predictors for anal fistula recurrence. Similarly, chronic anorectal abscesses were found to be associated with recurrent anal fistulas by researchers in Spain, although the association was not statistically significant (Jordán et al., 2010). 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 (Bokhari et al., 2008). In particular, 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 (Bokhari et al., 2008). 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 (Jordán et al., 2010). 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 fistula (van Koperen et al., 2008). 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 (Poon et al., 2008). The authors found a statistically significant increase in the risk of recurrent anal fistulas with sinus tract excision for perianal sinus. 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. Furthermore, another study in China reported that undetected internal opening and prior anal surgery both significantly increased the risk of developing recurrent anal fistulas (Mei et al., 2019). In addition, a recent study from Pakistan found that certain types of surgical procedures were associated with recurrence of anal fistulas to a statistically significant extent (Hashmi et al., 2024). 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. Another study in China also reported that seton treatment history had a significantly higher rate of recurrence than other treatment types (Li et al., 2016).

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 (Garcia-Aguilar et al., 1996). However, the study did not find this to be a statistically significant risk factor in the multivariate analysis. Additionally, the authors 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. 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 fistulotomy and seton treatment, had a lower rate of recurrence (Khan et al., 2024). 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 (van Koperen et al., 2008). Similar findings were 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 all (Jordán et al., 2010). Core out & closure of the internal fistula opening had the highest recurrent rate. These results aligned with the findings in the Pakistan study, which showed that fistulotomy had the lowest recurrent rate compared to other treatments, including seton treatment (Hashmi et al., 2024). 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 (Jordán et al., 2010). 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 (Visscher et al., 2016). 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.

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 (Li et al., 2016). Similarly, another group of researchers in China found that individuals who were previously treated for complex anal fistulas had a higher risk of recurrence (Poon et al., 2008). 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 associated with recurrence in anal fistulas to a statistically significant extent (Mei et al., 2019).

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 (Garcia-Aguilar et al., 1996). 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 (Jordán et al., 2010).

Primary anal fistulas were influenced by the types of anal abscesses that developed before the formation of anal fistulas (TB et al., 2020). Individuals with certain types of abscesses, such as ischiorectal abscess, were more likely to develop primary anal fistulas (Vasilevsky & Gordon, 1984). 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 pertaining to the influence of Crohn's disease and recurrent rates following particular surgeries. These regional differences may not only reflect biological variations, such as genetic 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-specific data limits our understanding on how anal fistula affects specific populations and may result in under-diagnoses, mismanagements, or chronic conditions due to inadequate medical support. In these areas, 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 noted that regional

databases in these areas were not systematically searched, which may be the reason for the limited number of studies from underrepresented areas, such as Africa and the Middle East.

Future research should address the aforementioned gaps through the conducting of 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 treatment outcomes for patients from diverse backgrounds, ultimately reducing the burden of anal fistula-related healthcare challenges worldwide.

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Mentor Contribution Statement

Bre Calhoun is a PhD Candidate in the Department of Population, Family and Reproductive Health at Johns Hopkins Bloomberg School of Public Health. She served as the Research Mentor for this project. Her support included guiding the student through the process of scientific research, providing advice on formulating research objectives, and assisting in the structuring of the paper. She also offered both detailed and general feedback with a focus on improving logical flow and content clarity.

Her involvement was entirely advisory, with the student maintaining full independence in identifying research objectives, reviewing relevant literature, interpreting data, and writing the manuscript. Bre Calhoun did not contribute directly to the manuscript's writing. Instead, she supported the student through regular weekly meetings, offering mentorship during the brainstorming stage and constructive suggestions during the revision process.

This contribution statement acknowledges her role as a mentor while affirming that all research and writing were conducted independently by the student.

Author Biography

Qingpei Liu is a student researcher from Beijing, China, studying at The High School Affiliated to Renmin University of China. She is passionate about the intersections of public health, medicine, and social equity. Her academic interests are grounded in a deep curiosity of how diseases are influenced by clinical and biological factors alongside socioeconomic and cultural factors.

Through her research on anal fistulas and their sociodemographic and clinicopathological risk factors, she aims to highlight regional differences in risk factors that contribute to certain health conditions, particularly anal fistula. She believes research should not only generate knowledge but also reflect real-world disparities in medical care in order to gain awareness and support improvements in access and quality of care.

Outside of her academic pursuits, she is interested in the philosophy of science and medicine, medical humanities, and the role of empathy in clinical practice. She hopes to pursue a career that bridges rigorous scientific research with compassionate, human-centered clinical practice.