CONSTRUCTION AND VALIDATION OF A FRAILTY INDEX FOR THE INFLAMMATORY BOWEL DISEASE POPULATION

By

Natalie Willett

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Dalhousie University is located in Mi'kma'ki, the ancestral and unceded territory of the Mi'kmaq. We are all Treaty people.

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3 Abstract

Frailty can be defined as a state of vulnerability to adverse health events. In this project, a standardized method for constructing a frailty index was followed using data from the SPOR IMAGINE IBD cohort. We constructed an IBD 77 item Frailty Index (FI) using a validated 10 step process using baseline data from 2714 participants. The histogram of FI scores showed a right skew, which is characteristic of an FI. In this distribution the upper limit (99^{th} percentile) of FI score is 0.529 displaying a submaximal limit, characteristic of other valid FIs. The mean FI score was higher in women. The mean age of our cohort was 45.8 years old (SD: 15), and the mean FI score was 0.17 (SD: 0.12), lower than that for other immune mediated diseases, and 30.6% of our sample was categorized as frail (FI score >0.21). FI scores were associated with IBD symptom severity (R=0.767).

4 List of Abbreviations Used

Frailty index (FI)

Inflammatory bowel disease (IBD)

Crohn's disease (CD)

Ulcerative colitis (UC)

Gut-associated lymphoid tissue (GALT)

Cardiovascular disease (CVD)

Comprehensive Geriatric Assessment (CGA)

Electronic medical records (EMRs

Systemic lupus erythematosus (SLE)

Human immunodeficiency virus (HIV)

Comprehensive Rheumatologic Assessment of Frailty (CRAF)

Rheumatoid arthritis (RA)

Canadian Scleroerma Research Group (CSRG)

Multiple sclerosis (MS)

Crohn's Disease Activity Index (CDAI)

Harvey Bradshaw Index (HBI)

Short Inflammatory Bowel Disease Symptoms Inventory (SIBDSI)

Classification of Disease (ICD) codes

Single nucleotide polymorphisms (SNPs)

Hospital Frailty Risk Score (HFRS)

Population Health Research Institute (PHRI)

Perceived stress scale (PSS10)

Revised Children's Anxiety and Depression Scale (rcads)

Patient health questionnaire (PHQ9)

General anxiety disorder 7 item scale (GAD7)

Body Mass Index (BMI)

Extra-intestinal manifestations (EIMs)

Claims based frailty index (CFI)

C-reactive protein (CRP)

International Classification of Disease (ICD) codes

5 Chapter 1: Introduction

Frailty is a concept that is commonly associated with biological aging, with most frailty studies conducted in older populations. Frailty can be defined as a state of vulnerability to adverse health events, resulting from a reduction in physiological processes that are protective for health (Fulop et al., 2010). A useful way to conceptualize frailty is through the Deficit Accumulation model which posits that frailty is a result of an accumulation of health deficits within an individual (Mitnitski et al., 2001). Throughout life, individuals acquire biological and physiological damage and the body's biological repair mechanisms are responsible for resolving this damage; if rates of repair cannot keep up with the rates of acquiring damage, the body sustains these insults at the cellular level which then present on a whole-organism level as a health deficit (Clegg et al., 2013; Taneja et al., 2016). Frailty arises when these health deficits accumulate, with an increasing susceptibility to adverse outcomes as the degree of deficit accumulation increases (Howlett et al., 2021).

Studying the concept of frailty is important because it is a means of studying variability in aging. Frailty is considered, statistically, as variability in risk of an adverse outcome for the same level of exposure (Vaupel et al., 1979). Frailty is a measurable phenomenon that is graded, which explain why individuals of the same age do not always have the same risk of death (Howlett et al., 2021). When frailty is measured in different populations, it shows common statistical properties: frailty has a positive association with age, women have higher frailty scores than men of the same age, there is a characteristic

rate of accumulation (regardless of number of items in the index), and there is a submaximal limit to frailty (Theou et al., 2014; Rockwood and Mitnitski, 2007).

Farrell et al (2016) used non-parametric network analysis models to show that when an individual is at age 80 FI score is most able to predict the age that person will die (death age). Individuals with lower FI scores die later and higher FI scores die earlier). Interestingly, they were unable to capture and explain the submaximal limit of frailty. Researchers created an information spectrum for their model which reflects the information added per deficit vs. the average degree of deficit, and discovered that normal deficits provide more information, but increasing the number of deficits does not linearly increase how informative the FI score is (increasing deficits makes the network distribution steeper, where there are less informative nodes). This modelling also shows longevity statistics aren't affected by deficit repair, because in this network model damage rates were found to be strongly affected by local frailty and when frailty is substantial, any repair is quickly re-damaged (Farrell et al., 2016).

An FI is a tool to measure frailty that operates within the Deficit Accumulation model (Mitnitski et al., 2001). Fitting with the explanation that frailty arises from deficits accumulate over time, an FI score given to a patient is the sum of the number of health deficits that patient has divided by the total deficits in the index. Health deficits in an FI come from a variety of health domains including mental health, physical health, and quality of life. This allows for frailty to be captured on a multidimensional scale. FIs exist for certain immune-mediated disease populations, such as patients with human immunodeficiency virus, systemic lupus erythematosus, rheumatoid arthritis, and

systemic sclerosis (Guaraldi et al., 2015; Legge et al., 2020a; Salaffi et al., 2020 Rockwood et al., 2014). Each index is made up of collection of health deficit variables that are chosen based on whether they meet specific criteria (Searle et al., 2008). An FI is useful for characterizing older clinical samples because older adults are more susceptible to accumulate health deficits due to aging, but an FI works for any age group because it captures the impact of small cumulative effects that can occur at any age and captures frailty that might not have manifested at the phenotypic level yet (Kulminski et al., 2011; Williams et al., 2023)

Measuring frailty in young people with chronic immune-mediated diseases is becoming increasingly important, and there is a need for research on how a disease's pathophysiology influences the process of becoming frail. Inflammatory bowel disease (IBD) is an immune mediated disease that results in physiological damage and insults to both the digestive tract, as well as extraintestinal organ systems, that has rising global prevalence rates (Ng et al., 2017). There is a current gap in knowledge surrounding how frailty can be measured in patients with IBD. Frailty research in IBD has mainly explored post-operative outcomes in frail IBD patients (Lightner et al., 2019a). Frailty is an independent predictor of anti-TNF therapy-associated infection risk, re-hospitalization, mortality, and post-operative outcomes (Kochar et al., 2020a; Qian et al., 2020; Kochar et al., 2020b; Telemi et al., 2018b).

Studies in IBD populations have used various methods to determine a patient's degree of frailty such as use of ICD codes and claims-based scoring. Some of these approaches do not fully embrace the complexity of frailty and are designed for use with

administrative data only. A measurement tool that incorporates variables from a variety of health domains, and only includes variables that satisfy Searle's criteria, can capture a wider picture of frailty by including a multitude of age-related health deficits into the measure (Searle et al., 2008). To address the shortcomings of using these other approaches to measure frailty, our project aims to address the research question of whether an FI can be successfully constructed for the IBD patient population. To achieve this aim, a standardized method for constructing an FI will be followed using data from the SPOR IMAGINE national IBD patient cohort. We will select a minimum of 30 variables to be incorporated into the index, and validity of the index will be evaluated. Finally, the index will be used to measure the proportion of patients who are frail at baseline in the IBD cohort, to test the index's usefulness and evaluate the potential utility of frailty as concept for the IBD population.

6 Chapter 2: Review of the Literature

6.1 Inflammatory bowel disease

IBD is an immune-mediated disease. Crohn's disease (CD) and ulcerative colitis (UC) are both classical subtypes of IBD. IBD affects the gastrointestinal tract and follows a relapsing-remitting disease course and is characterised by chronic intestinal inflammation (Yi-Zhen Zhang Yong-Yu Li, 2014). Epidemiological research has suggested that an abnormal reaction to intestinal microbiota may trigger IBD in genetically predisposed individuals (Kaplan 2015). Genetic susceptibility, the external environment, intestinal microbes and immune responses are each thought to play a role in the etiology of IBD (Yi-Zhen Zhang Yong-Yu Li, 2014).

Global prevalence rates of IBD in the 21st century are rising worldwide, and there is a notable a rise of incidence rates in new industrialized countries (Ng et al., 2017). The peak in incidence rates of both UC and CD occurs between the age of 20-40 (Molodecky et al., 2012). In Canada, the estimated increase in prevalence of IBD will be a jump from 0.7% in 2019 to 1.0% in 2030 which will be most evident in the elderly population (Coward et al., 2019). Aside from people with adult onset IBD growing older, It is estimated that 15% of all IBD cases are diagnosed in people age 65 or over (Gisbert and Chaparro, 2014). In the Western World the number of patients with IBD is expected to increase exponentially in the next 10 years, and in the next decade gastroenterologists will be responsible for caring for an aging IBD population (Kaplan, 2015).

Along with the rise in incidence and prevalence of IBD, there is also increasing economic burden on the healthcare system. The direct costs of caring for patients with

IBD in Canada that falls on public and private payers has been increasing in the last 15 years. In 2018 total direct costs were estimated to be $1.28 billion, which is attributable to increases in healthcare resource use and cost of prescription medications (Kuenzig et al., 2019). As well, issues of accessibility and disparities in healthcare resource availability are expected to rise in the near future and cause strain on the healthcare system (Kaplan, 2015). Most IBD patients receive their diagnosis at earlier stages of life (30 years of age) and face an increasingly long disease course (Nguyen et al., 2014). As the proportion of the Canadian population with this disease increases, the challenge of caring for a greater proportion of IBD patients of advanced age will become more apparent.

IBD is an impactful chronic disease involving the immune system, and while rising incidence of disease continues to burden Canadians and healthcare institutions, it is vital that researchers explore IBD disease etiology as well as patient needs. There is a current gap in literature regarding how frailty manifests in the younger IBD patient population and how frailty progresses in these patients as they approach elderhood (Sturm et al., 2017). Studying frailty in this patient population will help provide a holistic measure of health for IBD patients and help us understand the differences in patients' health and individual needs that are due to factors other than disease activity.

6.2 Frailty

Understanding frailty in specific disease populations requires that we understand how frailty is defined and operationalized. Frailty is defined as a state of being vulnerable to poor resolution of homeostasis, resulting from age-related decline in various physiological systems (Clegg et al., 2013). This state increases an individuals' likelihood of

experiencing a rapid change in health status after sometimes even a minor physiological stressor. In the frailty literature, this phenomenon is captured through two different models: the Frailty Phenotype model and the Deficit Accumulation model (Fried et al., 2001; Mitnitski et al., 2001).

The phenotype definition of frailty arose from the Cardiovascular Health Study in 2001 and regards frailty as a clinical syndrome distinct from comorbidity and disability, which involves phenotypical components (Fried et al., 2001). This model allows for individuals to be categorized as non-frail, pre-frail, and frail. The Fried phenotype model evaluates an individual's frailty level based on meeting three of the five criteria (slow gait speed, impaired grip strength, reduced physical activity, weight loss, and exhaustion).

The Deficit Accumulation model considers frailty to be a condition that results from an accumulation of health deficits over time, where "health deficits" may include any of the following: symptoms, signs, functional impairments, diseases, and abnormal laboratory measurements (Rockwood and Mitnitski, 2007; Mitnitski et al., 2001). Strong evidence from longitudinal studies supports the following model for aging: interactions between an individual's environment and their genetics elicit the biological mechanisms of aging; these mechanisms cause damage on a cellular level, and if unrepaired can lead to a pro-inflammatory state, and; this causes systemic changes at the organ level leading to an aging phenotype (Bektas et al., 2018). This aging phenotype involves individuals having a collection of health deficits. Different individuals accumulate deficits at different rates, and rate of aging can be approximated by the rate of accumulation of health deficits in a patient. The rate at which an individual will accumulate deficits is constant (estimated

at between 4-6% in longitudinal studies of community-dwelling people), exponential, and doubles every 15 years beginning at age 15 (Mitnitski and Rockwood, 2016). This finding reflects the increase of vulnerability to stressors that comes with older age. Further, the change in the number of deficits accumulated at the population level is proportional to changes in recovery time (Mitnitski and Rockwood, 2016). Interestingly, meaningful invariants are observed within the process of deficit accumulation. Two observations, consistent in frailty, that men and women will reach the same proportion of deficits (0.18 frailty score), and they will reach this at the same age (94 years old) (Mitnitski et al., 2002). It is important to note that biological changes that occur in frailty may not clinically present as disease status, so individuals who are frail may appear healthy (Rockwood and Mitnitski, 2007; Fulop et al., 2010). Also, frailty is a dynamic state that changes over time. Further, it can be managed through targeted interventions, and it is possible for individuals to transition health states and return to a state of a lower number of deficits (Hoogendijk et al., 2018; Theou et al., 2011; Mitnitski et al., 2006).

The interplay between biomarkers associated with frailty and physiological events that precede frailty is complex, and the causal chain of factors behind frailty has not been fully uncovered. The complexity of frailty and the fact that it is multiply determined has also made it difficult to understand its underlying genetics (Sathyan and Verghese, 2020). However there are clear hallmarks of aging at the cellular level that include: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (López-Otín et al., 2013). Damage accrual and

deficit accumulation that exists in frail patients are associated with these hallmarks of aging (Howlett et al., 2021).

Although there are many biological risk factors for frailty, psychological and social factors are also important determinants (Fulop et al., 2010). Social and environmental factors are thought to affect degree of frailty. Structural and social characteristics of neighbourhoods, including the occurrence of low social cohesion and socioeconomic status disparity, are associated with higher odds of frailty (Caldwell et al., 2019). Social vulnerability can determine an individual's degree of frailty, as social factors increase susceptibility to insults that have the potential to impact health status. When social vulnerability was operationalized through an index and compared to frailty, it was found that even after adjusting for frailty, each additional social vulnerability item (e.g.s. living situation, social supports, socioeconomic status) increased the odds of mortality (Andrew et al., 2008). Social deficits, such as dependence on others and burden on caregivers, are also thought to determine whether an individual can maintain independence in the community in a dynamic model of frailty (Rockwood et al., 1994). Frailty can also be sensitive to time period and can differ between generations. For example, in the U.S.A. rates of aging vary and at every year later in birth with Americans having 1% fewer health deficits at any given age (Abeliansky et al., 2020). This may be reflective of advancements in health care technologies and more widespread public knowledge of disease risks factors (ie risk of lung cancer due to smoking) in recent decades.

6.3 Aging and IBD development

There is a question of whether the aging process has the potential to influence the development of IBD; i.e. whether or not IBD could be considered a disease of aging. When considering this, it is useful to examine age-related epidemiological IBD trends. A widely accepted epidemiological concept is that there's a bimodal distribution of incidence of IBD where a second peak in incidence occurs at age 60-70 (Molodecky et al., 2012). Elderly or advanced age onset IBD refers to disease diagnosis at the age of 60 years or older (Sturm et al., 2017). Advanced age onset and non-elderly-onset are often grouped together in studies evaluating older IBD patients, but the difference between these two groups is important as the may have different phenotypes, and outcomes, and risk benefit profiles with pharmaceutical therapy (Sousa et al., 2023). In terms of phenotype, young onset UC and CD patients have a more extensive disease location and more aggressive penetrative disease compared to adult and advanced age onset; advanced age onset CD has more isolated colonic distribution and a predominantly inflammatory behaviour, and Advanced age onset UC involves a higher probability of left- side colitis (Ruel et al., 2014). Risk factors for IBD have been found to act differently depending on age: genetic influences are seen to act the strongest in those under <5 years old, and IBD-related environmental influences are strongest in teen years (Gower-Rousseau et al., 2013; Turner and Muise, 2017).

One plausible explanation for differences in phenotypes and natural history with age of onset is differences in host-gene-microbial interactions in older people. In the general population, considerable differences exist in the gut microbiota composition in

older adults compared to healthy youth, due to changes in gut motility and immune function with aging, but differences in gut microbiota profiles in pediatric onset vs. adult-onset IBD patients has not been well-studied (Ruel et al., 2014). Changes in the microbiome also occur in older age and older age is associated with decreased microbial diversity, thought to be due to age-related physiological changes such as decreased intestinal motility, fecal retention and increased use of laxatives and antibiotics (Hong and Katz, 2021). It is known that in the general population immune system functioning differs in older patients compared to younger patients. Gradual deterioration of the immune system, or immunosenescence, is known to occur with aging (Fulop et al., 2018). Immunosenescence is accompanied by increases in inflammatory markers, seen in older age is a result of frailty rather than healthy aging (Fulop et al., 2018). In the non-IBD population there are anatomical differences in the immune tissue in older adults compared to young people: the size of gut-associated lymphoid tissue (GALT) and Peyer's patches reduced (Charpentier et al., 2014). Interestingly, the age that this occurs coincides with the 'second peak' of IBD incidence (Ruel et al., 2014). Frailty is thought to coincide with the process of 'inflammaging', and in the instance of Alzheimer's disease and cardiovascular disease, this can eventually progress to the point of death by disease when the process of becoming frail becomes hyperinflammatory (Fulop et al., 2018). As mentioned, frail patients may have a pro-inflammatory state in the body where the immune system responses become deranged: this may coincide with onset of immune-mediated clinical diseases such as IBD. The aging process is thought to be a result of inflammatory mechanisms in human physiology that have been upregulated, and

researchers are still uncovering the role chronic systemic inflammation plays in biological aging and mortality (Furman et al., 2019). IBD and aging are thought to share pathophysiology of being related to inflammatory markers being upregulated, and like other autoimmune diseases, having IBD increases one's risk for cardiovascular disease (CVD), dementia, and type II diabetes (Faye and Colombel, 2022).

Ruel et al., (2014) comment that if timing of disease onset was only a random variable one would expect IBD phenotype to be similar across the age spectrum, so findings that the phenotypes differ could suggest there might be different biological pathways leading to different phenotypes according to age. Ultimately, this could support the idea that the degree of frailty may be a determinant in development of IBD. Quantifying and exploring frailty in IBD population may help us understand the role that aging plays in the development of IBD.

Patients with IBD often experience geriatric syndromes at earlier age, and older adults with IBD have poorer disease and treatment-related outcomes compared with younger adults with IBD (Kochar et al., 2021a). Hospitalizations are more frequent in advanced age onset UC (due to intestinal disease and comorbidities), mortality rates are higher in hospitalized advanced age UC patients, and immunomodulators and biologics are used less often in older UC patients compared to younger age groups as individuals above age 60 years on biologics have an increased risk of infection (Fries et al., 2022; Shaffer et al., 2023). Older IBD patients are more likely to receive corticosteroids compared to immunomodulators and biologics (Hong and Katz, 2021). There is a dearth of clinical trials that include participants over the age of 65 years for Anti-TNFs, so

clinicians rely on retrospective studies for guidance (Kochar et al., 2021b). In a systematic review of 222 phase 3 clinical trials in IBD from 1955-2021, age was used as an exclusion criterion in 58% of studies while very few have functional status as a criterion (Vieujean et al., 2022). Unfortunately, corticosteroid treatment is associated with higher risks of complications in advanced age patients as compared with younger patients so it is ideal to transition off of steroids and avoid reliance on this therapy for long term disease management in advanced age patients (Sturm et al., 2017). There is a higher risk for surgery in older onset IBD and older adults have a higher baseline risk for adverse events, and there is currently a gap in knowledge of how to optimally manage IBD individuals of advanced age because of different risk-benefit profiles and changes in functional status compared to those with IBD of younger ages (Bermudez et al., 2023). In older people with IBD, the main issues at play that need to be considered when making treatment plans include: polypharmacy, Immunosenescence (which may contribute to increased infection risk), comorbidities, and in-hospital mortality of hospitalized older adults (Sousa et al., 2023; Shaffer et al., 2023). For these reasons it is especially important for clinicians to have a measure that takes into account physiologic resilience rather than chronological age, to inform treatment and disease management for this specific population.

6.4 Perceptions of frailty

It is important that research done on clinical interventions and screening tools for frailty are informed by public and stakeholders' beliefs and understanding of the topic. Qualitative studies from various countries done by interview-based, focus group methods have revealed that community members (both non-frail and anywhere on the frailty

spectrum) and care providers hold the belief that frailty is an irreversible state that involves loss of a sense of independence, physical de-conditioning, and that it is associated with nearing the end of life (Archibald et al., 2017; Schreuders et al., 2020; Warmoth et al., 2016). Understanding care providers' views on frailty is of equal importance to understanding patient's perspectives, because a gap in understanding of frailty between care providers has the potential to lead to variability in care quality. It is important that healthcare teams understand how their definition of frailty may impact pre-frail and frail individuals, and be mindful of this when moving forward with prevention and treatment strategies (Schreuders et al., 2020). It has been suggested that it might be beneficial for care teams to move away from the medical deficits-based conceptualization of frailty, and towards an "adaptation and resilience based view", because clinical definitions focusing on deficits can make patients 'feel frailer' and these negative attitudes are major barriers to treating frailty and barriers for hospital admission (Nicholson et al., 2017). The drawback of changing our definition of frailty based on patients desire to feel empowered is that we lose the ability to accurately measure the construct, thus limiting our scientific advances in the field. Studies with a clear definition can help researchers understand adverse outcomes associated with frailty. With proper knowledge translation, it allows patients to understand the associated health risks. While it is important to consider patient views in frailty research, it is critical to maintain scientific rigour in how we define and measure frailty.

There may be a hesitancy in accepting and implementing new screening tools within care teams, and the reception of new frailty screening tools has been studied in

various disciplines (Moffatt et al., 2018; Rege et al., 2018). The experiential impact of screening the Frailty Assessment for Care Planning Tool used by nurses in Nova Scotia was studied and it was found that nurses had initial hesitancy to use the tool existed, due to time constraints feasibility concern (Moffatt et al., 2018). This, however, dissolved over time and the nursing staff grew confident in using the screening tool. It is important that frailty screening tools are designed with stakeholders' views and preferences in mind, in order for them to successfully be adopted and received positively. Qualitative research reveals the most important factors for acceptance and adoption of new technological frailty screening and management tools include: value (and perceived usefulness to the end user), affordability, usability, emotional and psychological benefits of the technology , independence and social visibility (how the technology would make them look to others after a frailty diagnosis) (Gwyther et al., 2019).

There is global inconsistency in the way that frailty is defined, and in the way that it is screened. A large study conducted by Gwyther et al.,(2018) investigated progress made in frailty research by global partners of the European Innovation Partnership on Active and Healthy Ageing (from 7 countries). The study aimed to compare the partners reported interventions for frailty, screening tools, scale to measure frailty and respective definitions of frailty. The study found that there was inconsistency across all countries in defining, measuring, and screening for frailty. They also found that most interventions touched on physical, cognitive and wellbeing elements of frailty, and there is a need for interventions that consistently utilize valid methods of measuring frailty (Gwyther et al., 2018). Although authors reflect there is a need for a universal, accurate protocol, it is

challenging to try and achieve this idealistic goal because there is variation in how frailty presents. Universal hallmarks of aging exist, and we know that complex biological systems fail in characteristic ways. It is possible to capture frailty when we have methods that are grounded in these principles; however, frailty presents differently between clinical disease populations and there is no perfect, standardized method that can capture frailty in every patient. Therefor the use of different methods should still be viewed as acceptable.

6.5 Measuring frailty

The broader goals behind measuring frailty are to identify cases of frail individuals for clinical care, and to be able to develop and implement interventions for people on all parts of the frailty spectrum to prevent frailty progression (Wu and Leff, 2018). Novel screening tools for frailty are needed to deliver better healthcare to an aging and chronically diseased Canadian population. In the context of IBD, frail patients incur higher hospital readmissions costs compared to non-frail IBD patients (Faye et al., 2020). This highlights the importance of early frailty screening assessments to allow for earlier interventions to stop frailty progression, to reduce costs to the healthcare system, and ultimately improve quality of life (Faye et al., 2020). This section will discuss tools that currently exist to measure health status in older adults.

A widely used tool that quantifies health in older adults is the Comprehensive Geriatric Assessment (CGA). The CGA explores four different domains (somatic, functional, mental, and social) and this assessment is a rating for the patient's overall health (Solomon et al., 2003). The CGA and other traditional assessments of health in older

adults are effective measurement tools but have been criticized for being on healthcare systems, time consuming, and difficult to conduct on a large scale (Wu and Leff, 2018). Research has shifted towards taking the CGA and using its components to create an FI. One study did this to introduce a new standardized construct, the CGA FI, to measure frailty while summarizing components of the CGA (Cooper et al.2021). The traditional CGA uses data collected at clinic visits to capture information on each geriatric domain. To use the CGA to measure frailty, data needs to be collected in a consistent manner. By creating a CGA based frailty assessment tool, authors reflected they could still deliver care and the best geriatric assessment, with certain geriatric domains measured slightly differently in the FI (Cooper et al.2021). In IBD, a systematic review breaking down the components of a CGA and how IBD patients experience these various components found that there was a significant association between impairment in all CGA components and a higher risk of adverse health outcomes in IBD patients (Asscher et al., 2019). As well, it has been shown that deficits in the geriatric assessment are highly prevalent in older patients with IBD (Asscher et al., 2021). Authors reflect that CGA components have rarely been used in IBD literature and specifically on older IBD patients, and a CGA which incorporates frailty could be a useful clinical tool (Asscher et al., 2019). Ultimately, issues with the CGA warrant the construction of a tool to assess frailty for IBD patients, so that the link between CGA components and health outcomes can be explored and understood.

An FI is a precise measurement tool used to capture and quantify frailty. FIs are constructed based on the health deficits accumulation model and can be constructed for any disease population using a set of health deficit variables. A reliable FI should include

a minimum of 30 candidate health deficits and increasing the number of deficits included in the index increases the precision of the estimate (Searle et al., 2008). Generally, if a sufficient number of variables are included in an FI, it has a stronger predictive ability for adverse outcomes (Farrell et al., 2016). The standard method for index construction published by Searle et al (2008) requires that all candidate deficits considered for inclusion in the index must satisfy certain requirements: 1) deficits must relate to health, 2) deficits must increase with increasing age, 3) deficits must not saturate too early, 4) deficits must cover a range of physiological systems. As well, it is recommended that during the process of construction, deficits in the index must be consistent from one iteration to the next. After FIs are constructed, they should be validated, which is done by assessing content, construct, and criterion validity (Searle et al., 2008).

FIs are useful for screening for frailty, in a way that captures a complete view of the patient from the perspective of multiple health domains, and it is a useful tool for predicting adverse health outcomes (Rockwood and Mitnitski, 2007). Meta-analysis results have shown that higher FI scores were associated with higher mortality risk (Kojima et al., 2019). A standardized method of constructing an FI was put forward by Searle et al (2008), and it is regarded as a reliable method that has been implemented in different clinical settings (Salaffi et al., 2020; Legge et al., 2020b; Franconi et al., 2018; Geessink et al., 2017).

A goal of the FI is also to take advantage of easily accessible, routinely collected health data. An electronic FI that was recently developed and validated in the UK identified cases of frailty in a primary care setting using information from electronic

medical records (EMRs) (Clegg et al., 2016). In Canada, a 36-item FI designed for use with EMRs in primary care was constructed and evaluated using data from an integrated primary care research program for older adults living with frailty in Alberta (Abbasi et al., 2019). the Canadian Institute for Health Information (CIHI) Hospital Frailty Risk Measure (HFRM) is a tool created from hospital administrative data that provides information on hospital-level prevalence of frailty (Amuah et al., 2023) The purpose for constructing these screening tools was to make use of the vast amount of information on physical and psychological health data contained in primary care databases, and ultimately serve as a quicker and easier way to measure frailty as compared to more expensive methods.

6.6 Frailty indexes in chronic disease populations

It is important to investigate and understand frailty in younger populations, as the overall pathology of frailty still is not clear. It is hypothesized that individuals can get to a frail state at younger ages as a result of accumulation of health deficits due to the process of chronic disease progression. While FIs have largely been used in research to measure frailty in older adults, increased vulnerability declining and physiological reserves in younger chronically diseased populations has also been a topic of interest in the frailty literature. The following section explores deficit accumulation across the life course, concept of an FI Lab, and summarizes current frailty research in different chronic immune mediated disease populations.

As mentioned in section 2.2, frailty is dynamic. Health deficits can accumulate across the entire life course, therefore frailty can manifest in individuals at any point over

the lifespan (Mitnitski et al., 2001). Health deficits accumulate with age, but individual deficit accumulation trajectories are dynamic and, in any fixed time interval, an individual's change in the number of health deficits can be approximated using a time dependent Poisson distribution (Mitnitski et al., 2012). Having a model that can approximate changes in frailty status over a fixed time interval is useful, as it allows for the calculation of probabilities of transitions from an initial health state (certain number of deficits) to another health state over a specific time period (Mitnitski et al., 2012). Other computational models of frailty have been constructed, such as complex connectivity network models (Rutenberg et al., 2018). More research is needed to understand characteristics of frailty and deficit accmulation in clinical samples because most previous studies of frailty are done with community samples, and there is the potential that active treatment within clinical samples can actually reverse some deficits (Rockwood and Mitnitski, 2006).

Frailty resulting from damage on a cellular level has led to the development of the FI Lab. The FI Lab is an innovative FI which contains biomarker items in the index, and data from laboratory tests and serology (Howlett et al., 2014). It is typically made by supplementing a traditional FI with data from laboratory tests, and in clinical populations can reflect disease activity. An FI Lab from the Canadian Study on Health and Aging was able to identify older adults at an increased risk of mortality (Howlett et al., 2014). An FI Lab study based on patients admitted to hospital in the UK found that increases in both the FI Lab and clinical frailty scale were associated with increases in mortality (Ellis et al., 2020). In the area of IBD, a recent genome wide genotype-protein association study

profiling serum protein levels in IBD patients and healthy controls showed that levels of albumin and APOE (which has a role in Alzheimer's and cardiovascular disease) both increased consistently with increasing age of patients, and MM7 (involved in would healing) was upregulated in older UC patients (Narzo et al., 2017). These upregulated 'aging' markers can be part of an FI Lab and could indicate frailty (as they are not a normal healthy part of the aging process). Authors commented that the blood proteome has a robust aging pattern, and this pattern is consistent across different disease groups. It should be noted that large FIs with a high number of health deficits are most informative for younger patients, and when choosing which biomarkers to include in an FI Lab, FIs should be constructed through an inclusive approach rather than a parsimonious approach (Farrell et al., 2016; Rutenberg et al., 2018).

Frailty research has been done in clinical samples of chronic disease populations. In the systemic lupus erythematosus (SLE) population, much work on developing and evaluating an SLE FI has been done by Legge et al. (Legge et al., 2019, 2020a). Using a standardized procedure, researchers systematically evaluated variables from an international systemic lupus clinics study cohort to serve as health deficits in the index. A 48- item index was created. This index was designed to identify SLE patients most vulnerable to adverse health outcomes (Legge et al., 2019). Authors comment that a strength of the accumulation of deficits approach that it is broad and measures the impact of multiple small effects allowing for robustness of the index's predictive capabilities. A subsequent study investigated the FI's ability to predict organ damage accrual in SLE patients, and results showed that higher baseline FI scores were associated with higher

rates of organ damage accrual during follow up (Legge et al., 2020b). This evidence supported that the index scores were valid health measures in SLE population. A follow-up study investigated scores from this FI and their association with hospitalization rates in SLE patients, and results showed that higher baseline scores were associated with more frequent hospitalizations during follow up (IRR 1.21; 95%CI 1.13-1.30), and higher baseline FI scores were able to predict a greater time spent in hospital during follow up (Legge et al., 2020c).

Frailty has been successfully captured and measured in the human immunodeficiency virus (HIV) population, through HIV-specific FIs. Franconi et al., (2018) successfully constructed a 72 item FI using data from a clinical database which including variables using biometric, psychiatric, blood testing, daily life activities, geriatric syndromes, and nutrition data. Authors showed that FI scores were higher among older HIV patients, verifying that frailty increased with age. Authors state that having a health tool that depicts health status and trajectory with routinely collected data would add important information to clinical evaluation (Franconi et al., 2018). Authors aimed to include information from the following domains in their index scoring: functional ability, cognition, physical and mental health, and SES status. A study done by Guaraldi et al., (2015) on HIV patients in Northern Italy found that a 37-item FI was able to predict survival and incident multimorbidity (a meaningful health outcome in those living with HIV). The candidate deficits in this FI came from routinely collected data and did not including variables representative of HIV viral replication or immune deficiency. Authors found that index score was a significant predictor of multimorbidity and mortality, and a

modified FI score including health deficits related to HIV was still a significant predictor of these outcomes. They also found this index performed similarly against another validated FI (VACS index) in their ability to estimate mortality risk (Guaraldi et al., 2015).

FI research has also expanded to the area of rheumatologic disease. The Comprehensive Rheumatologic Assessment of Frailty (CRAF) was a tool developed for the rheumatoid arthritis (RA) population to measure frailty (Salaffi et al., 2020). This tool aimed to capture frailty using the following domains: nutrition status, weakness, falls, comorbidity, polypharmacy, social activity, pain, fatigue, physical functioning, and depression. The FI was composed of 34 deficit variables. Ultimately this tool was found to have good convergent validity and discriminatory power. Authors reflected that this is the first known FI constructed in this population, and variables were chosen based on survey data from 39 specialists that were asked to rate importance of health domains responsible for fragility in RA patients. Comorbidity, polypharmacy, social activity, fatigue and depression were regarded as important factors present in RA patients' lives, and so these variables were included in the index (Salaffi et al., 2020).

FI work has also been done in the area of systemic sclerosis. A frailty index was constructed for a cohort of the Canadian Scleroerma Research Group (CSRG) Registry. Authors built a FI from data on a cohort of 1372 patients. This FI contained 44 items from the CSRG database, and successfully quantified health status in people with systemic sclerosis (Rockwood et al., 2014). The deficits in this FI came from 9 organ systems, and also included mood and fatigue as deficits. The study found that risk of death increased with higher FI scores, and that the FI was a better predictor of mortality than the Rodnan

Skin Score. Findings from this study include: the mean FI score (0.30) fell in the range of what is seen in the general population, and the maximum value (0.67) did not exceed the upper limit reported in other clinical settings (Rockwood et al., 2014). Authors justified studying frailty in this population by commenting that different scleroderma patients have different levels of need, and this difference is due to variability in health status, not just degree of damage. They also reflected that information from a FI could aid in decision making about which patients might benefit most from aggressive treatment options such as bone marrow transplantation (Rockwood et al., 2014).

There is also recent FI work done in the area of multiple sclerosis (MS). Zanotto et al. (2022) constructed a 30-item FI for MS patients who are wheelchair users, with the goal of exploring the relationship between frailty and the different MS clinical subtypes. Deficits in this index were from the domains of global health, physical function, cognition, sexual and psychosocial functioning. They found the mean FI score was 0.54 (SD 0.13). No statistically significant differences in FI score were found among participants with relapsing-remitting MS, primary progressive, and secondary progressive MS. As well, a univariable negative binomial regression found that FI score was associated with a greater number of falls reported in the previous six months (Zanotto et al., 2022). Authors acknowledge that if an FI is primarily composed of items measuring activities of daily living, as this means that the index fails to differentiate frailty from disability. In this study deficits came from a wide range of domains.

6.7 IBD clinical disease activity scales

Conceptually, quantifying disease activity is closely related to measuring frailty; each can capture damage caused by active disease. Biomarkers such as CRP and fecal calprotectin correlate well with endoscopic disease activity (Jones et al., 2008). Other disease Indices incorporate multiple attributes to offer a more thorough picture of disease activity. As noted, so can an FI Lab. Clinicians value disease activity scales, that in the adult IBD population include: the Crohn's Disease Activity Index (CDAI), the Harvey Bradshaw Index (HBI), The Short Inflammatory Bowel Disease Symptoms Inventory (SIBDSI), and the Mayo Clinic Index. Each differs subtly in which items have been incorporated. Still, they have fallen short, driving an FDA-mandated move toward more patient-defined measures of disease activity in clinical trials (Williet et al., 2014).

The CDAI captures symptoms in patients with Crohn's disease (CD) and is widely used in clinical trials to define if disease is active or in remission (Gajendran et al., 2018). CDAI items include number of liquid stools, severity of abdominal pain, general wellbeing, extraintestinal complications, use of antidiarrheal drugs, abdominal mass, hematocrit, and body weight (Best et al., 1976). Disease severity is defined by CDAI score. "Active" indicates a score >220, sub-categorized as mild (150-220), moderate (220-450), or severe (>450) (Van Assche et al., 2010).

The 5-item HBI index scores disease severity based on clinical criteria, It was designed to aid assessment of long-term disease progression and response to treatment in CD patient (Harvey and Bradshaw, 1980). The five variables are: general wellbeing (0= very well, 1= slightly below par, 2= poor, 3= very poor, 4 = terrible), abdominal pain (0=

none, 1 = mild, 2 = moderate, 3= severe), abdominal mass (0= none, 1= dubious, 2= definite, 3= definite and tender), number of liquid stools (any integer), and extraintestinal manifestations (1 point per manifestation). Scores are the sum of all components. A score of <4 is considered remission, whereas a score ≥7 is considered active disease (Harvey and Bradshaw, 1980). This index created by Harvey and Bradshaw is considered a simplified CDAI, that excludes laboratory data.

The SIBDSI, a shortened form of the IBD Symptoms inventory (IBDSI), was created in 2018 to serve as a patient reported outcome measure. The SIBDSI using symptoms from other IBD activity scales (HBI and Powell Tuckett Index) and contains 26 items (Sexton et al., 2019). The 26-item short form inventory excludes less commonly experienced IBD-related complications from the longer form, and the short form contains 3 subscales: bowel symptoms, abdominal discomfort, and fatigue. The SIBDSI is ultimately a valid and reliable measure of a patients experience of IBD symptoms, and collects the same important clinical information that the HBI captures (Sexton et al., 2019).

In adults, a common disease severity scale for UC is the Mayo Clinic Index. This index is widely used in placebo-controlled clinical trials, where disease severity is estimated from symptom and endoscopic data (Walsh et al., 2014). Scores range from 0-12 points. Partial Mayo scores are commonly used, which exclude the endoscopic component and is simply a combination of rectal bleeding, stool frequency physician global assessment sub-scores (Walsh et al., 2014). It has been found that the partial Mayo scores performs as well as the full Mayo Score in identifying patient perceived clinical response (Lewis et al., 2008)

The CDAI is widely used in clinical trials yet criticized for lacking subjective quality of life assessment and objective endoscopic factors. The HBI is a simple clinician administered measurement tool, and data is collected easily and quickly in an outpatient visit. The Mayo Index Score contains valuable endoscopic data. The SIBDSI is a patient reported outcome measure that has good internal consistency, convergent validity, and sensitivity and specificity to clinician rated active disease (Sexton et al., 2019). With the current shift towards patient reported outcome measures in clinical trials there is growing criticism of scales that contain an insufficient scope of symptoms and too few rating options. There is a trade-off between ease of use and validity of the scale, and indices containing a wider number of items and more options within each item are being recognized as valid, reliable, and useful.

6.8 Frailty in IBD

Faye and Colombel (2020) comment in a letter to the editor that the IBD population is a complex base to investigate frailty in because of patients' chronic disease course, relapsing-remitting disease nature, wide age range, and predisposition to malnutrition. Frailty studies in IBD have aimed to describe the decline in physiological reserves and resilience in IBD patients that comes with aging. Studies have identified unique needs of older IBD patients resulting from a long disease course, or combination of disease severity with underlying frailty (Asscher et al., 2019; Faye et al., 2020; Lightner et al., 2019b; Sturm et al., 2017). The European Crohn's and Colitis Organisation's current practice position 1 states that clinicians should assess an individual's frailty, rather than age alone, when making disease management decisions (Sturm et al., 2017). The group

also notes that frailty is steadily inclining in IBD patients, as incidence rates are increasing in older adults and the current IBD population is aging (Kaplan, 2015). This warrants the development of better frailty screening tools for IBD patients.

In a nationwide sample of hospitalized IBD patients in the USA, using the ICD-9-CM John Hopkins Adjusted Clinical Groups frailty-defining diagnoses from chart reviews to identify frailty, prevalence of frailty was found to increase over time (10.20% in 2010 to 11.45% in 2014) and frailty was associated with a higher risk of readmission and mortality independent of age and comorbidities (Faye et al., 2021). After removing malnutrition, weight loss, and fecal incontinence from the frailty-defining diagnoses, frailty still remained associated with an increased risk of hospital readmission.

Zhang et al. (2023) investigated whether frailty was a risk factor for advanced age onset IBD. Frailty was measured using the Fried phenotype, and Participants were followed from baseline until the first date of advanced age onset IBD diagnosis. Compared with non-frail, individuals who were frail (HR=1.40, 95 %CI: 1.13–1.73) and pre-frail (HR=1.15, 1.03–1.28) had a significantly higher risk of advanced age onset IBD after multivariable adjustment. A major limitation of this type of study design that the authors acknowledge is that frailty is a dynamic and reversible state where frailty status can change over time; frailty taken at baseline may not capture duration that the individual remained frail and if that changed prior to IBD onset.

Pre-treatment frailty in IBD patients receiving immunosuppression therapy can predict risk of post-treatment infections: frail patients have significantly higher odds of developing infection within the first year of treatment after adjusting for age,

comorbidities, corticosteroid use prior to treatment, and combination therapy (immunomodulators and Anti-TNFs together) (Singh et al., 2021). In this study, frailty was identified using ICD codes. In a cohort of biologic-treated IBD patients, nearly 50% were frail (according to validated claims-based hospital frailty risk scoring system (HFRS)) and frailty had no association with post-treatment infection (Singh et al., 2021). This measurement tool only has modest agreement with the frailty phenotype which the authors acknowledge this as a limitation to their study.

With increasing rates of diagnosis worldwide, and more therapies available, there is an important knowledge gap as to how frailty impacts response to IBD therapies and treatments. A recent study has suggested that baseline frailty in IBD may be improved with anti-TNFs (Kochar et al., 2022b). Researchers found that nearly 85% of patients who were frail prior to treatment demonstrated improvement in frailty following treatment, with frailty measured using a claims-based FI that uses a CD-9 diagnosis codes, CPT codes for procedures, and HCPCS codes. Authors acknowledge improvements in scores cannot be attributed to biologic use alone, and it could be as a result of heightened medical attention, management of comorbidities, and initiation of physical or nutritional therapy services (Kochar et al., 2022b). Other researchers comment that bias may be at play in this study, as it is not clear which items within the frailty measure were improved (ie. malnutrition, etc.) and although this is a novel index and differs from prior frailty measurement tool in the area there are still none currently validated for the IBD patient population (Faye, 2022).

Regarding frailty and mortality, a 2020 abstract in *Alimentary Pharmacology and Therapeutics* revealed that in a cohort of 11001 IBD patients, frailty was associated with mortality (OR: 2.90, 95% CI: 2.29-3.68) in a multivariable regression after adjusting for clinically relevant confounders (Kochar et al., 2020b). Frailty was a binary variable in this study and was identified using International Classification of Disease (ICD) codes: the presence of ≥1 frail-related ICD code identified patients as "frail". The most prevalent frailty diagnosis was malnutrition, and frailty in IBD patients increased with age. A major limitation of this study was that degree of frailty could not be captured; however, authors reflect that risk stratifying patients by frailty prior to treatment or surgery may help to prevent adverse health outcomes.

In IBD, frailty demonstrates significant associations with both post-operative complications and mortality. Frailty (measured by a modified 11-item FI) was an independent predictor of septic and cardiopulmonary complications, serious morbidity, and overall morbidity in UC patients who underwent colectomy surgery (Telemi et al., 2018b). Authors advocate for pre-operative frailty assessments as a means of risk stratifying patients before surgery. Wong et al. (2020) conducted a study on IBD patients undergoing major bowel surgery to investigate morbidity (defined by death, reoperation, or major complication within 30 days) in patients age 65 and older. The study found that being older was associated with major post-operative complications in UC, (OR: 1.3, 95% CI: 1.2-1.5), and that frailty was associated with greater morbidity in both UC and CD patients (Wong et al., 2020). In 2493 patients undergoing Ilial pouch anal anastomosis (IPAA) surgery, patients with one or more frailty related diagnosis code had more post-

operative complications and increased length of stay compared to those without a frailty related diagnosis (Cohan et al., 2015).

The association between frailty and postoperative recovery has also been studied in ostomy surgery. A retrospective review investigated the ability of a modified FI to predict failure of early discharge from ileostomy closure (Wen et al., 2017). In this study, 18% of the sample had a diagnosis of IBD, and the remainder of the sample was comprised of patients with cancer, fistula, polyps, diverticulitis, and polyposis. The study used a modified FI to measure frailty, and results from the univariate (crude) regression models showed that modified FI scores of 0 were associated with higher rates of discharge within 48 hours of ileostomy closure compared to those with index scores of ≤1 and ≤2 (Wen et al., 2017). This study's modified FI was constructed using 11 variables from the Canadian Study of Health and Aging FI, based on the methods of Farhat et al., 2011. Evaluating frailty in advanced age IBD patients prior to colorectal surgery, in addition to nutritional assessments, could be useful in reducing post-op complications because modifiable risk factors can be acted on, and frailty assessment could lead to more informed decision making regarding the pre-habilitation period (Lightner et al., 2019b).

Frailty may be a risk factor for IBD disease relapse, otherwise known as flares. A 2020 *American Journal of Gastroenterology* abstract investigated the ability of frailty (as measured by a 7-item index) to predict propensity for IBD flares and mortality. A higher proportion of frail IBD patients experience >5 IBD flares, and the frail group had the highest odds of mortality (Gondal et al., 2020).

Frailty can predict hospital readmission in IBD patients. Faye et al., (2020) reports that frailty in IBD patients, as defined by having at least one of the John Hopkins Adjusted Clinical Groups frailty defining diagnoses, was a significant predictor of hospital readmission (aRR 1.16, 95% CI: 1.14-1.17). Authors found frail IBD patients had a 6-day longer readmission stay compared to non-frail IBD patients. A sensitivity analysis that excluded patients with malnourishment as a frailty diagnosis revealed that frailty was still associated with readmission (Faye et al., 2020). Asscher et al., (2023) prospectively measured 'risk of frailty' in IBD patients using the G8 questionnaire, followed them for all cause hospital readmission and health related QoL scores. Patients at risk of frailty were more often hospitalized during follow-up for all-cause, acute, and IBD-related causes (Asscher et al., 2023)

A Mendelian randomization analysis of IBD data, sarcopenia data, frailty data (UK Biobank, using a 49 item FI) and genetic data (Swedish TwinGene) was performed by Wang et al. (2024). This type of analysis is used to infer whether phenotypic traits or exposures affect diseases or health-related outcomes. Researchers matched single nucleotide polymorphisms (SNPs) highly associated with exposure to the outcome database and constructed statistical models. Positive causal relationships were identified between UC and CD with the FI score. Authors conclude that UC and CD may possibly influence the development or prevalence of frailty (Wang et al., 2024)

In addition to measuring frailty in IBD, another closely related topic is risk of frailty within the IBD patient population. In Sweden, the Hospital Frailty Risk Score (HFRS) and cox modelling was used to compare frailty risk in IBD patients to matched healthy

counterparts and investigate associations between frailty risk and hospitalizations or mortality. Compared to non-frail older patients with IBD, patients at higher risk for frailty had increased mortality (HR:3.22, 95%confidence interval (CI): 2.86–3.61) and all-cause hospitalization (HR:2.42,95%CI: 2.24–2.61) after adjusting for comorbidities and confounders (Kochar et al., 2022a).

6.9 Summary

Frailty is an important health measure that provides a holistic picture of an individual's health, that can explain heterogeneity in health risks and predict adverse outcomes and hospitalizations. FI scores are useful for clinicians because they measure a construct that other clinical tests or disease activity scales do not capture. Our project will produce a novel, effective frailty measurement tool that includes laboratory and clinical data and is designed for use in the IBD patient population. Our project will benefit the current state of knowledge by allowing for frailty measures to be captured in the SPOR IMAGINE cohort and further studies to be conducted in the area of frailty in IBD. Researchers will be able to explore the predictive abilities of the index. As well, the index can be used to investigate characteristics of frailty within clinical samples of IBD patients (e.g. whether a submaximal limit exists). Assessing frailty status in patients with IBD offers great benefits in terms of adverse events risk assessment and may lead to more personalized care if frailty can be incorporated into clinical decision-making. Frailty is a dynamic state that can be reversed and understanding frailty in IBD patients may lead to interventions on modifiable risk factors to protect patients from becoming frailer. There is a possibility that interventions to reverse health deficits may alter disease prognosis,

and our index can allow for researchers to explore this possibility, and better understand the intersectionality between frailty and clinical disease.

7 Chapter 3: Objectives

The purpose of this research is to quantify frailty in the IBD population through building and evaluating an FI from a national cohort of IBD patients. I have three objectives for this thesis project:

1. To construct an IBD FI using data from the SPOR IMAGINE IBD patient cohort. To ensure the index is valid and reliable we will use at least 30 variables from the cohort. The index incorporates deficits from different health domains and includes both general health deficits and deficits that are specific to IBD.
2. To evaluate the construct validity of the index to ensure that the IBD FI is accurately measuring frailty.
3. To measure the prevalence of frailty in the IBD cohort using the IBD FI, and to compare the IBD FI to an existing IBD symptom severity index.

8 Chapter 4: Methods

8.1 Dataset

This project is a secondary data analysis from the SPOR IMAGINE IBD cohort. Data used for this thesis project was prospectively collected for the IMAGINE study containing data from 17 recruitment centres across Canada. SPOR IMAGINE is a pan-Canadian, observational prospective study investigating how genes, diet and mental health impact IBD and IBS patients. Data for this study was collected in REDCap at local sites and when questionnaires were completed on paper data was entered at each site into REDCap by a local researcher (sites had the option to maintain a confidential dataset locally). Data was then sent to a central database collection center at the Population Health Research Institute (PHRI) at McMaster University.

The IMAGINE dataset is patient-oriented in nature, collecting many patient-reported outcomes. Data collection for SPOR IMAGINE began in Oct 2017 and the planned end date was June 1, 2023 (Moayyedi, 2021). Enrollment is complete, but data collection is still ongoing, so the reported end date by Moayyedi was tentative. At our Nova Scotia site, 336 participants completed the study and 37 are currently participating (as of March 2024). This thesis project used baseline data only from the SPOR IMAGINE project and included data from centres within as well as outside of Nova Scotia. This thesis project was approved by the Nova Scotia Health Research Ethics Board (NSH REB file #1023284) in accordance with the Declaration of Helsinki's guidelines for research with human participants.

Inclusion criteria for the IBD cohort of interest for this project were the same as those for the IMAGINE study: adult and pediatric patients, age 4-99 with diagnosis of IBD (clinician diagnosed). The exclusion criteria for the IMAGINE study were as follows: having any major gastrointestinal surgery (including bowel resection), any major comorbid chronic condition (decompensated liver, or liver malignancy, end stage lung/cardiovascular disease, active HIV) where the expected survival is less than 5 years, conditions affecting informed consent, unable to communicate the language of the study (English/French), diagnosis of schizophrenia, and diagnosis of eating disorder (Moayyedi, 2021). We decided to exclude pediatric patients upon further investigation of the data, because pediatric patients completely different questionnaires than adult patients.

8.2 Variables

Baseline data from the SPOR IMAGINE cohort was comprised of survey data and biometric measures. The following baseline visit variables were available in the dataset: Demographic and background information (age, marital status, country of origin, education level, ethnicity , IBD medications, analgesic medications, psychotropic medications, tobacco smoking, sex, gender, sexual orientation), clinical information (height, weight, BMI, disease history, comorbidities, past surgeries, IBD diagnosis, extra intestinal manifestations, Montreal disease classification, current medications, current state of disease [active disease vs remission], past gastrointestinal resection surgeries, symptom severity [IBD symptom severity Inventory short form questionnaire, promis scale v10 questionnaires for belly pain, diarrhea, constipation, gas and bloating, Leeds short form dyspepsia questionnaire]), and psychological information (perceived stress

scale [PSS10], brief resilience scale, adverse childhood experiences scale, Revised Children's Anxiety and Depression Scale [rcads], pediatric quality of life inventory [pedsql], pain catastrophizing scale, work productivity and impairment questionnaires, patient health questionnaire [PHQ9], and general anxiety disorder 7 item scale [GAD7]).

The initial size of the adult IBD cohort for this study was 2714. Sample sizes in studies on FIs vary. A meta-analysis on FIs predicting mortality analyzed 19 studies, where study sample sizes ranged from 754 -36,306 (index sizes ranged from 23-70 deficits) (Kojima et al., 2018). A systematic review of FIs in perioperative and critical care included 13 studies, where sample size ranged from 61 to 415 patients (index sizes ranged from 31-70 deficits) (Darvall et al., 2018). Although this thesis project does not include power calculations, the number of SPOR IMAGINE patients included in index construction and who received FI scores (2607) adequately powers this study based on the sample sizes in other FI projects.

8.3 Establishing study sample

In this project, adult IBD patients in the IMAGINE study were included for construction of the index and data analysis. Pediatric patients (n=162) were not included A proportion of the IMAGINE sample did not answer any questionnaires following the initial baseline demographic questionnaires. To minimize missingness, this group (n=914) was screened out. Participants included in this project for data analysis were those who had responses to the initial question of the second study questionnaire (the IBDSI short form questionnaire).

8.4 Index construction

An FI can be constructed from any pre-existing dataset of a community, clinical, or convenience sample that has a wide variety of data that could serve as health deficits in the index (from surveys, interviews, medical charts, records or tests) (Theou et al., 2023). Searle et al.'s method of constructing an FI is a robust, flexible valid method grounded in the accumulation of deficits model of frailty with the index counting these deficits in a participant (a health deficit being a symptom, sign, disability, disease, or abnormal laboratory measurement) (Searle et al., 2008). Deficits must result from the chronological aging process, and be associated with adverse health outcomes (Rockwood and Mitnitski, 2007). According to Searle et al (2008), health deficits in the index must satisfy the following criteria:

1. variables must relate to health status
2. each deficit's prevalence increases with age
3. deficits do not saturate in the population too early
4. deficits that make up the index must belong to a range of physiological systems
5. variables included in the index will be consistent from one iteration to the next
6. The index must be composed of a minimum of 30 deficits in total to increase the precision of the frailty estimates (Searle et al., 2008).

Missingness in the data was investigated before constructing the index, to ascertain if there were patterns of missingness and if imputation could be performed.

The standard 10-step approach to constructing an FI from an existing dataset (Theou et al., 2023) was followed for this project:

1) identify variables in the dataset that measure a deficit in health

2) exclude variables with more than 5% missingness
3) re-code each variable response to a number on a 0-1 scale (where 0=no deficit, 1= deficit is present, multilevel ordinal variables assigned a numerical score on a cut-point equally spacing the levels apart between 0 and 1)
4) exclude variables where the deficit is either too rare (<1% of responses) or too common (>80% of responses)
5) screen variables for association with age
6) screen variables for correlation with each other
7) count the variables retained
8) calculate the FI scores (taking the number of health deficits an individual has and dividing by the total number of health deficits in the index)
9) test the characteristics of the FI (to assess construct validity)
10) Use the FI in your analyses

The first step to creating the index involved retaining all individual questions from each study questionnaires were to treat them as variables, rather than considering only the final questionnaire score as the variable (*e.g.*, all items in the PHQ9 that measured a health problem were included for consideration rather than the PHQ9 score itself). After retaining all variables measuring a health problem in adults with IBD, we then screened for duplicates (items that represented constructs that were already accounted for by other variables in the dataset) as part of step 2, while excluding variables that had >5% missingness. In cases of duplicate variables, the one with the least missingness was retained. At step 3, most variables were Likert-style or binary and could easily be recoded. BMI was the sole continuous variable transformed into a categorical BMI class variable based on the World Health Organization BMI classification scale. In this step we recoded 50 variables to a 0-1 scale, where interval size for equal spacing of the response between

0 and 1 was calculated by dividing 1.0 by the total number of categories minus 1 (*e.g.* for available with 5 possible responses, the interval size was ¼, so interval size was 0.25 and responses were recoded to 0, 0.25, 0.5, 0.75, 1). No variables showed a U-shaped relationship with adverse health outcomes *i.e.,* where both extreme low values or high values would indicate poor health. At step 4 we then removed deficits that were too rare (<1%) or too common (>80%) in the sample. At step 5, variable associations with age were assessed by plotting mean variable score over age and assessing the correlation coefficient between each variable and age. In clinical samples health deficit variables don't always have an association with age, so in this case the accepted method for choosing deficits is to retain variables that have been included in other validated FIs or that are established in the literature as positively associated with age (Theou et al., 2023). As part of step 5 we consulted the literature and compared items included in 25 different published FIs while also incorporating expert guidance from a gastroenterologist on the team (co-supervisor) on which gastrointestinal variables increase with age. Step 6 involved screening for autocorrelation between variables in the list of candidates, using Spearman correlation coefficients. Any pair with R> 0.90 were investigated. In each pair, the variable with the lowest missingness was retained. This led us to step 7 where we counted the total number of variables (77). After calculating FI scores, characteristics of the index were assessed as outlined below. Before assigning scores, all individuals who have a missing value for >20% of the deficits in the index were dropped as per the methods of Theou et al., (2023). We then assigned scores according to step 8. Content and construct validity are assessed in this master's project at step 9, but criterion validity

was not assessed because building a predictive model is outside of the scope of this project and there was no 'gold standard' or 'criterion referent' frailty measures in this dataset to use as a comparator.

8.5 Construct validity

Construct validity is ensuring that a given measure is correctly capturing the underlying construct; when there is construct validity, the operational definition is consistent with other measures of the phenomenon (Streiner et al., 2015). Characteristics of the FI were checked as part of the validated 10 step process to develop an FI, and investigating the characteristics of the index to determine whether they are in agreement with other FIs as a step to assess construct validity. In a true reliable and valid FI the correlation between age and rate of deficit accumulation should be similar to other validated FIs (Theou et al., 2014). In this project we assessed deficit accumulation rate by plotting a log plot and calculating the log-deficit accumulation rate and expressing it as a percent (which represents the percentage that baseline FI scores changed with each year of age). Typically, an acceptable measure is 0.03-0.06 per year in community samples, although this rate of deficit accumulation is not true for clinical samples (Searle et al., 2008; Mitnitski et al., 2016). Another characteristic of a successfully built FI is that the FI scores will follow a specific density distribution (right skewed) and exhibits different mean scores for the sexes where females typically have higher FI scores (this is true for both the general population and clinical samples) (Theou et al., 2014). Density distribution, upper limit (99^{th} percentile of frailty score) and gender differences in mean FI score were assessed in this project.

For this project we use the gender variable rather than sex, as there are social determinants to frailty status. Still, there was nearly 100% agreement between the sex and gender variable in adult IBD patients who answered the questionnaires (biological sex Male: 1,120 gender Male: 1,119, Biological sex female: 1,593, gender female: 1,595, 1 missing biological sex). Frequencies were identical for each variable (41% men, 59% women).

8.6 Content validity

Content validity assesses whether the approach being used is reasonable or sensible to experts in the field, or 'sensible on its face' (Guaraldi et al., 2015). Generally, If health deficits are derived from existing valid instruments, this form of validity is considered to be fulfilled (Legge et al., 2019). Data in the SPOR IMAGINE dataset were collected from well-validated IBD instruments and a panel of frailty and clinical experts (thesis supervisors and committee) reviewed the deficit variable list to assess whether items included were appropriate, so in this regard, our FI has content validity.

8.7 Estimating frailty prevalence and characterizing the cohort

Following construction of the index and scoring of participants, a validated frailty categorization scheme with score cut-points was used to identify participants who were relatively fit (score ≤ 0.03,) less fit (0.03 < score ≤ 0.10), least fit (0.10 < score ≤ 0.21), and frail (score > 0.21) (Rockwood et al., 2011). Descriptive statistics of demographics and clinical characteristics for the IBD cohort, and prevalence estimates for frail individuals (score > 0.21) with 95% confidence intervals were obtained. Descriptive statistics were calculated for the IBD-FI and distribution of FI scores were visualized on a histogram.

Differences in subgroups of FI score by gender and by medication use were tested using students t-tests. Hypothesis testing was only performed on gender because it was a variable that would likely show effect modification and was excluded from the index itself because of this effect modification. Demographics were investigated and changes in these (*e.g.* marital status, country of origin) by frailty category were explored. Data analysis was conducted using STATA -SE Version 17 (Statacorp).

9 Chapter 5: Results

9.1 Selection of health deficits for IBD FI

The process of selecting variables for inclusion in the FI can be seen in Figure 1. The initial list of potential deficits was comprised of all variables that measured a health problem (k=230 items). This initial list included biometric and patient reported outcomes questionnaire data. Next, 36 variables were removed in the screening and removing duplicates step (k=194). Additionally, 3 candidates (high cholesterol, IBS diagnosis, and colorectal cancer) were removed because these variables were not found in the dataset despite being listed in the data dictionary (k=191). At this step, 50 medication variables (IBD medication, analgesics, laxatives and psychotropic medications) were removed as these variables would not make up a polypharmacy variable capturing frailty (some essentially served as severity measures and signs of ways to limit impact of the disease IBD so they were not retained, k=141). Medications will be used in later steps of data analyses. This left a list of 141 items.

Candidate variables were screened for missingness and variables with over 5% missingness were dropped. During this step 41, variables were dropped (k=100). These can be seen in Table 1 (Appendix). There were no instances where patients answering “no” to previous questions were not asked the rest of the questionnaire items, so this type of missingness did not need to be handled though carry over of a ‘no’ answer as per methods of Theou et al., (2023). At this step 1 additional variable was dropped (Extra Intestinal Manifestations of IBD=none) because it was redundant and could be captured in the ‘no’ responses of other EIM variables (k=99). During this process no missing patterns were

considered problematic, and thus there was no need to perform imputation on the dataset.

The presence of deficit in each variable was then checked and variables were screened for being too rare or too common. In this step, dichotomous variables with less than 1% presence of a deficit should be excluded or combined with related variables, and presence of a deficit should not be greater than 80%. For non-dichotomous variables, the combined proportion of people with some level of the deficit (coded >0) should be at least 1%, and the proportion of people with a full deficit (coded as 1) should be no more than 80% (Theou et al., 2023). In this step, 4 variables were dropped due to presence being too rare and not able to be combined with related deficits (Cirrhosis [alcohol related, viral hepatitis related], Chronic kidney disease, and Interstitial cystitis, k=95).

Deficits were then screened for association with age. As this was a clinical sample, literature and expert guidance determined which variables were kept in the index. The IBD expert from the research (thesis co-supervisor) deemed the following gastrointestinal variables to be un-related to age: Abdominal pain intensity, abdominal tenderness, abdominal pain frequency, abdominal mass, rectum pain frequency, stool consistency, incomplete defecation, bloat, bloat frequency, passing gas, difficulty passing gas, gas intensity, vomiting, fistula, and nausea intensity. These 16 were dropped from the list (k=79).

Autocorrelations were investigated in the dataset where a correlation between two variables in the FI tentative deficit list was problematic if over 0.9 (as per guidance from Dr. Rockwood). At this step, 3 variables had Pearson correlation coefficients with

one another that were over 0.9 (see Table 3 Appendix). The variable with the lowest number of missing values was kept. At this step, 2 variables were dropped (Daily home activities [impaired because of pain] and Daily chores [impaired because of pain]). After this step, a final list of 77 deficits was retained as the IBD-FI.

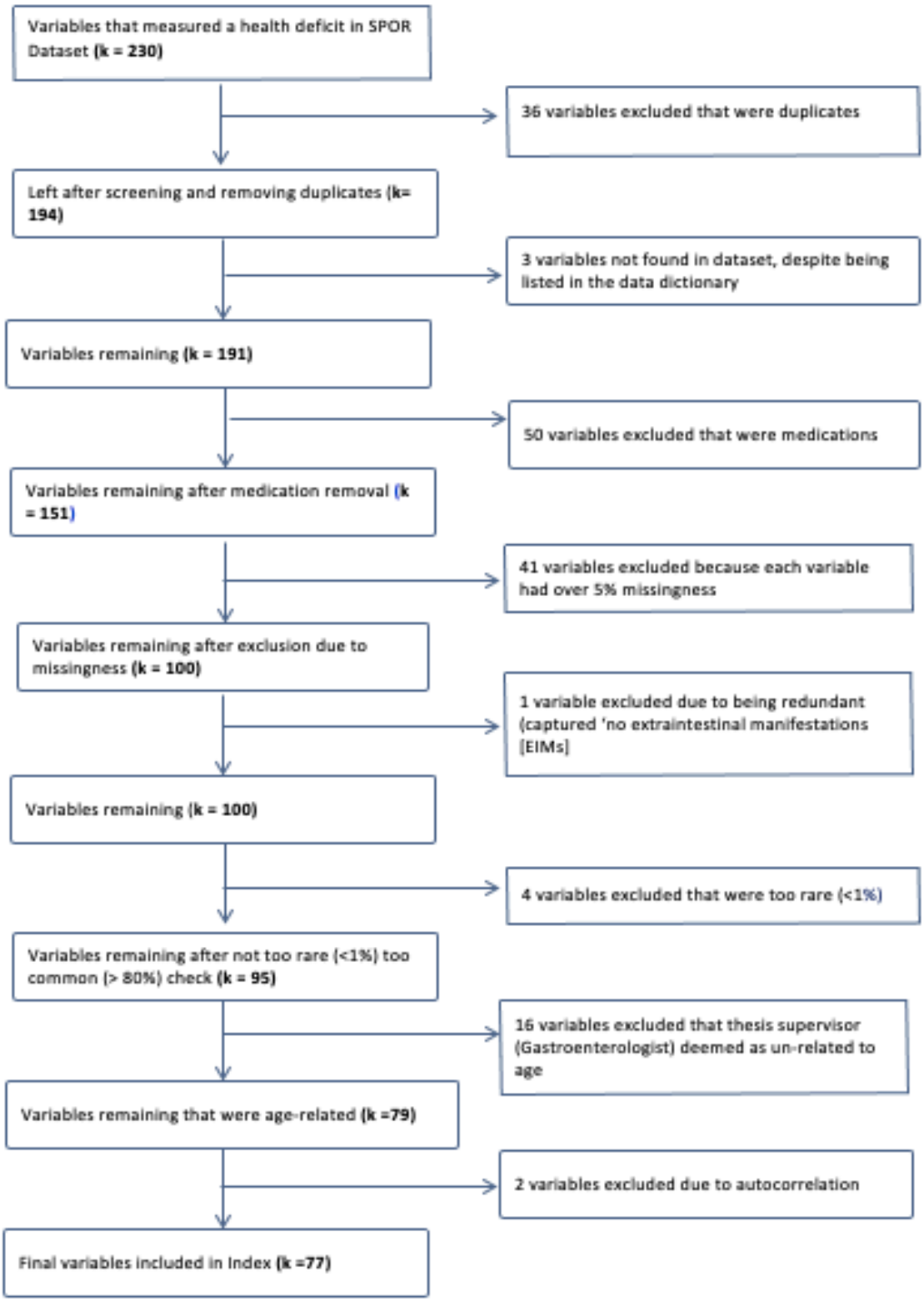

Figure 1. Flow chart illustrating the IBD FI candidate variable selection process.

9.2 The IBD FI

A total of 77 health deficits were included in the IBD-FI (Table 2, Appendix). The final list of health deficit variables was composed of 31% psychological (including sleep) (24/77), 25% gastrointestinal (including IBD flare/remission status) (19/77), 8% IBD extraintestinal manifestations (6/77), 16 % comorbidities (12/77), 16% daily tasks (12/77) and 5% fatigue (4/77). The remaining 2% of variables were overall health and general pain.

9.3 Validation of the FI

To ensure the FI displayed properties consistent to other FIs, we first explored the distribution of FI scores. The histogram of FI scores showed a right skew, which is characteristic of an FI (Figure 2). In this distribution the upper limit (99^{th} percentile) of FI score is 0.529 which is in agreement with the mathematical property of frailty where a submaximal limit must exist and is below 0.7 (Theou et al., 2014). Additionally, we found that mean FI score was higher in women (0.19) [95% CI: 0.13, 0.15] compared to men (0.14) [95% CI: 0.18, 0.19]) ($p< 0.001$)

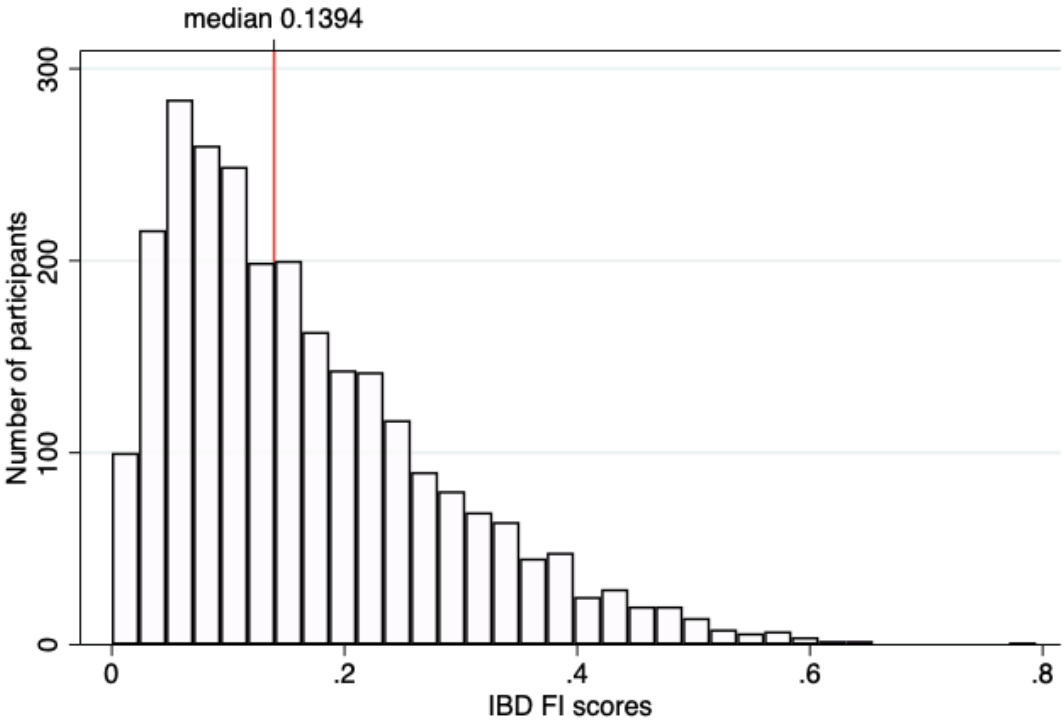

Figure 2 Distribution of FI scores for adult participants with IBD in the IMAGINE cohort.

A log plot was created for the FI (Figure 1, Appendix), with the log-transformation of the FI score plotted against age. This plot did not display a positive association between the age and log FI score variables. The Pearson correlation coefficient calculated for age and FI score was R= -0.049. The FI score does not appear to have a positive association with age, i.e.) a positive deficit accumulation rate over time.

9.4 Participant characteristics

There were 2714 participants with IBD in the SPOR IMAGINE cohort who satisfied inclusion criteria, had data available for baseline visits, and did not ignore study questionnaires after baseline demographics survey. In step 8 of FI construction, 107 participants were dropped because they were missing responses to over 20% of the

deficits in the final index (77 candidates, cut-off was >15 deficits missing). The final sample of participants in the analysis was 2607. Demographic and clinical characteristics of this sample can be seen in Table 1. Mean age of participants included in the final analysis was 45.8 (SD 15.0). Nearly 60% of the sample was female. The majority of participants were Caucasian (88%), married or common law (66%), and had a Masters, Professional, or Doctoral degree (42%). Just over half (58%) of the study sample smoked in the past, while only 7.3% currently smoke. Smoking is an epidemiological risk factor for IBD. Although Never-smokers in the newly diagnosed CD population in the West has increased over the last two decades, it's not uncommon for older IBD patients to have smoked in the past (Thomas et al., 2019). The majority of participants were born in Canada and did not identify as a member of the LGBTQ community. Few participants were currently on steroids to manage their IBD (16.3%) and most were on a biologic (50.4%) as opposed to an immunomodulator or 5ASA.

Table 1. Baseline demographics of the sample of adult IBD patients in the SPOR IMAGINE study. Mean FI scores are show for each level of the categorical variables.

Variable		**Estimate**	**Mean (SD) FI score**
Age at baseline, yrs mean (SD)		45.8 (15)	N/A
Gender n (%)	male	1,076 (41)	0.14 (0.11)
	female	1,531 (59)	0.19 (0.12)
Ethnicity n(%)			
	Indigenous (e.g.s. First Nations, Metis	52 (2.0)	0.23 (0.15)
	Caucasian	2,306 (88)	0.17 (0.12)
	Black	18 (0.69)	0.20 (0.15)

Variable		Estimate	Mean (SD) FI score
	Middle Eastern	32 (1.2)	0.16 (0.13)
	Latin American	20 (0.77)	0.17 (0.11)
	Chinese	15 (0.58)	0.12 (0.12)
	Japanese	3 (0.12)	0.14 (0.062)
	Vietnamese	1 (0.04)	0.08 (N/A*)
	Filipino	10 (0.38)	0.14 (0.15)
	Other East Asian	2 (0.08)	0.43 (0.31)
	South Asian	56 (2.15)	0.13 (0.11)
	Unknown (and prefer not to answer)	16 (0.62)	0.15 (0.096)
	Other	76 (2.9)	0.19 (0.13)
Marital status n (%)			
	Married/common law	1,711 (66)	0.16 (0.12)
	Widow	45 (1.7)	0.19 (0.12)
	Separated	71 (2.7)	0.19 (0.11)
	Divorced	168 (6.5)	0.20 (0.13)
	Single, never married	596 (23)	0.18 (0.12)
Highest education n(%)			
	Less than high school	81 (3.1)	0.20 (0.11)
	High school diploma or equivalent	370 (14)	0.18 (0.12)
	Some college	18 (0.69)	0.20 (0.18)
	Associate degree**	799 (31)	0.19 (0.13)
	Bachelor's degree	109 (4.2)	0.18 (0.12)
	Masters, Professional, or Doctoral degree	1,105 (42)	0.15 (0.11)
	Participant did not know, or preferred not to answer	75 (2.9)	0.13 (0.094)
Country of birth n (%)			
	Canada	2,311 (89)	0.17 (0.12)
	Outside of Canada	287 (11)	0.15 (0.11)

Variable		Estimate	Mean (SD) FI score
	Participant did not know	3 (0.12)	0.22 (0.14)
Have ever smoked (>100 cigarettes) n (%)			
	No	1,505 (58)	0.16 (0.11)
	Yes	1,068 (41)	0.18 (0.13)
	Participant did not know	26 (1)	0.17 (0.13)
Smoking status (of those who ever smoked) n (%)			
	Current	191 (7.3)	0.23 (0.14)
	Quit	858 (33)	0.17 (0.12)
	Participant did not know, or preferred not to answer	19 (0.7)	0.21 (0.15)
identify as LGBTQ** n(%)			
	No	2,446 (94)	0.16 (0.12)
	Yes	119 (4.6)	0.23 (0.14)
	Participant preferred not to answer	27 (1.0)	0.20 (0.10)
Biologic therapy n(%)	No	1,243 (49.6)	0.16 (0.12)
	Yes	1,264 (50.4)	0.17 (0.17)
Steroids n(%)	No	2,044 (83.7)	0.16 (0.16)
	Yes	398 (16.3)	0.20 (0.20)
Immunomodulator n(%)	No	1,768 (72.8)	0.16 (0.16)
	Yes	661 (27.2)	0.17 (0.17)
5ASA n(%)	No	1,583 (66.4)	0.17 (0.17)
	Yes	802 (33.6)	0.15 (0.15)

*Could not be calculated

**Occupational, technical or vocational program or academic associate degree)

**Gay, Lesbian, Bisexual, Transgender, Two-Spirited, Queer, or Questioning

9.5 Excluded participants

The original dataset contained 5611 total participants comprised of healthy controls and IBD patients (adult and pediatric). Healthy controls were only needed in case there were continuous variables to be included as deficits in the FI which a quantile scoring system would be used to re-code the continuous for a 0-1 scale using log ranking normalization with healthy controls. There were no continuous biomarker variables in the dataset so controls were not needed for this purpose. Through investigation of missingness patterns we discovered a proportion of patients had stopped answering surveys after the initial demographics questionnaire: missingness was investigated for all 16 forms and a form signature was created (16 digit number that has a 1/0 for each of the 16 forms completed or not completed per individual, where forms were considered 'completed' if any data was present). Based on the form signatures generated, there was a pattern of participants who stopped completing future forms after a certain point, with many of these participants not continuing after the first and second questionnaires. Based on this investigation, we dropped all participants that did not complete the first question of the second survey IBDSI short form questionnaire. This step involved dropping 914 participants. We also dropped 162 pediatric participants, which resulted in the final initial sample of 2714 used for index construction. This sample size was then reduced in the later stages of index construction and after step 8 of index construction the final sample size in the analysis was 2607.

9.6 Prevalence of frailty

Frailty scores were calculated for 2607 participants. FI scores ranged from 0.00 (minimum) to 0.79 (maximum) with a median (IQR) of 0.14 (0.062-0.22). The mean (SD) FI score of the cohort was 0.17 (0.12). Proportions of frailty and 95% confidence intervals are presented in Table 2 (both overall and stratified by age). The prevalence of frailty in this cohort was 30.6% [95%CI: 28.8-32.4]. Relatively fit individuals make up the lowest proportion in each respective age group (~5% in each age group). The proportions remain constant over every age group. Within each age group, the proportions of less fit, least fit and frail are all nearly 30%.

Table 2. Frailty category proportions by age group. All estimates are presented as proportion (95% Confidence interval). Frailty was categorized using the following scheme: relatively fit (score ≤ 0.03,) less fit (0.03 < score ≤ 0.10), least fit (0.10 < score ≤ 0.21), and frail (score > 0.21)

	Overall	**Under 30 years**	**30-45 years**	**45+ years**
Relatively fit	5.52% [4.71-6.47]	5.91% (4.10- 8.53)	5.70% (4.31-7.49)	5.29% (4.22-6.63)
Less fit	30.2% [28.4-31.9]	28.2% (24.2- 32.6)	29.7% (26.6- 32.9)	31.1% (28.7-33.6)
Least fit	33.8% [32.0-35.6]	31.8% (27.6-36.3)	33.3% (30.2-36.6)	34.7% (32.2- 37.3)
Frail	30.6% [28.8-32.4]	34.1% (29.8-38.7)	31.4% (28.3-34.6)	28.9% (26.6-.31.4)

We investigated frailty category by demographics (Table 3). We observed that for the least fit and frail categories there was a higher proportion of women than men. Two tailed hypothesis testing revealed a significant difference in FI score between men and women: 0.19 [95% CI: 0.18, 0.19] for women vs 0.14 [95% CI: 0.13, 0.15] for men, p<0.001). There were similar mean ages for each frailty category. The majority of participants

obtained a Masters, Professional or Doctoral degree (Table 1) and the proportions of these individuals were spread somewhat evenly across frailty categories with the exception of 'relatively fit'. Social factors that may influence the progression of frailty and accumulation of health deficits were explored. The lowest proportion of married participants belonged to the relatively fit category. Proportions of divorced individuals increased with increasing frailty category (data not included in table). The lowest proportion of participants not born in Canada were in the fit category, and there was no clear pattern of proportional increase over frailty categories. Regarding clinical factors influencing or relating to frailty, proportion of smokers and mean SIBDSI score both increased with increasing frailty category.

Table 3. Demographic variables by frailty category. For each frailty category, gender ratios, mean age, proportion with masters professional or doctoral degree, proportion of current smokers, proportion of married/common law, proportion born outside of Canada, and mean baseline SIBDSI score are shown. Standard errors and 95% confidence intervals are presented where appropriate.

	Relatively fit (score ≤ 0.03)	**Less fit (0.03 < score ≤ 0.10)**	**Least fit (0.10 < score ≤ 0.21)**	**Frail (score > 0.21)**
FI score (mean, SE)	0.0186 (.000599)	0.0655 (.000706)	0.149 (0.00106)	0.316 (0.00323)
Gender ratio (male/female)	(91/53)	(405/381)	(342/538)	(238/559)
Age at baseline [mean (SE)]	45.33 (1.26)	46.77 (0.546)	46.55 (0.514)	44.1 (0 .506)

	Relatively fit (score ≤ 0.03	**Less fit (0.03 < score ≤ 0.10)**	**Least fit (0.10 < score ≤ 0.21)**	**Frail (score > 0.21)**
Masters, Professional or Doctoral Degree [proportion (95% CI)]	7.78 (6.34-9.51)	33.7(30.9-36.5)	34.1(31.4-36.9)	24.4 (22.0-27.1)
Current smoker [proportion (95% CI)] (of those who ever smoked)	4.71 (2.47-8.81)	16.8 (12.1-22.7)	29.3 (23.3-36.2)	49.2 (42.2-56.3)
Married or common law [proportion (95% CI)]	6.14 (5.09-7.38)	31.9 (29.7-34.2)	34.0 (31.8-36.3)	27.9 (25.9-30.1)
Born outside of Canada [proportion (95% CI)]	5.23 (3.17 - 8.48)	37.97 (32.5-43.7)	32.1 (26.9 37.7)	24.7 (20.1-30.1)
Baseline SIBDSI* score [mean (SE)]	2.15 (0.1583)	6.63 (0.171)	13.6 (0.269)	26.3 (0.461)

* Inflammatory Bowel Disease Symptom Inventory

9.7 Investigation of FI score with clinical variables

As seen in Table 3, mean IBD Symptom severity scores increased over frailty categories. To further investigate the relationship between FI scores and symptoms we visualized the data using a scatterplot (Figure 3). We found that there is a positive association between FI score and IBDSI score, with a Pearson correlation coefficient of R= 0.767.

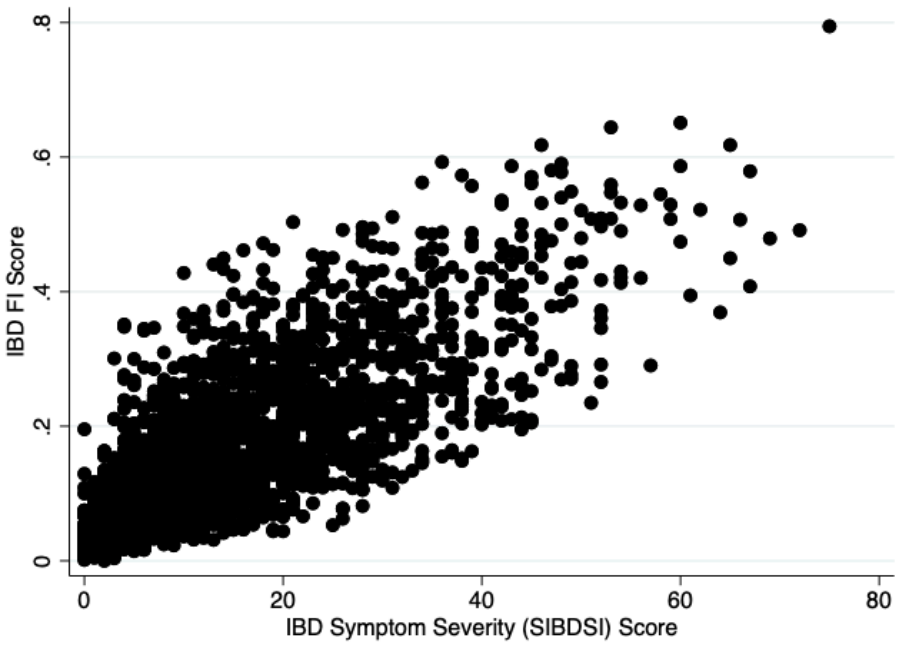

Figure 3. Scatterplot of SIBDSI score by FI score for adult participants with IBD in the IMAGINE cohort.

We then investigated the differences in FI score by IBD medication. Student t tests were conducted (Table 4). Results indicated that mean FI scores were significantly different if a participant was on a biologic, steroid, immunomodulator, and 5-ASA compared to if they were not on each of those drugs, respectively.

Table 4. Mean FI scores by medication status. Biologic drugs included: Humira (adalimumab), Remicade (infliximab), Inflectra (infliximab), Entyvio (vedolizumab), Simponi (golimumab), Stelara (ustekinumab), and Xeljanz (tofacitinib). Steroids included prednisone and budesonide. Immunomodulators included: Imuran, 6-mercaptopurine, and methotrexate. 5-ASAs included: 5-ASA (oral), 5-ASA enema, 5-ASA suppository, and Sulphasalazine.

		Fi score, mean SD)	**P value**
Biologic	no	0.16 (0.11)	
	yes	0.18 (0.12)	P< 0.001
Steroid	no	0.16 (0.11)	

		Fi score, mean SD)	**P value**
	yes	0.20 (0.13)	P< 0.001
Immunomodulator	no	0.16 (0.12)	
	yes	0.17 (0.12)	p= 0.0281
5- ASA	no	0.17 (0.12)	
	yes	0.16 (0.11)	p= 0.0027

10 Chapter 6: Discussion

10.1 Creating the IBD FI

With this project, an IBD FI was successfully constructed for the IBD patient population using data from the SPOR IMAGINE study. We followed a 10-step process to construct and use the IBD FI. Our FI was shown to have properties consistent with other validated FIs and includes a collection of deficits from a wide range of physiological systems. We were able to explore prevalence of frailty in the cohort, and frailty across age groups and demographic categories. Content and construct validity were assessed in this project but further studies are needed to evaluate criterion validity by using this tool to predict an outcome. Meta analyses of observational studies of frailty in IBD using non-FI tools show that frailty is a significant independent predictor of mortality in patients with IBD (Huang et al., 2022). Secondary analyses of this dataset should use the IBD FI to predict mortality risk (if data becomes available), or IBD disease complication risk.

This IBD FI is composed of 77 deficits. Searle argues that a valid FI must include a minimum of 30 deficits (Searle et al., 2008). Network modelling has now shown that increasing the number of deficits does not increase how informative the FI value is (Farrell et al., 2016). This index has satisfied the minimum requirement of items in order for it to generate a valid health measure, and adding more deficits such as biomarkers and clinical data may not linearly increase how informative the IBD FI score is. Searle's age-relation criterion for a variable to be a health deficit (increase in prevalence with increasing age) has been applied as part of standard FI construction in younger populations with immune mediated chronic disease (Guaraldi et al., 2015; Legge et al., 2020a; Salaffi et al., 2020).

This criterion has been applied when constructing an FI for the IBD population in the current project because the inflammatory processes occurring with disease activity share mechanisms with aging in accordance with the 'inflammaging' theory of aging (Fulop et al., 2018; Sallafi et al., 2023). Therefore, it is justified to apply this criterion in young populations because there is a possibility that they are theoretically undergoing cellular aging at a faster rate than non-chronically diseased young people.

Some candidate deficit variables, such as quality of life variables, did not increase with age. This is not unheard of. Although older IBD patients are more likely to have geriatric assessment deficits associated with lower health related quality of life scores, UK and Australian data shows that seniors with IBD adapted well to social isolation during the covid pandemic, having lower prevalence of depression and anxiety compared to younger patients with IBD (Asscher et al., 2022; Harris et al., 2020; Cheema et al., 2021). Inclusion of quality of life and psychiatric variables was part of the standard procedure for creating an FI, but the fact that these items had a negative correlation with age in our baseline SPOR IMAGINE dataset may be a contributing factor to why overall FI scores did not have a positive correlation with age after log transformation. Our index is largely made up of psychological and psychiatric deficits (31% of the index). In community samples of older people, correlation of frailty (as measured by an FI) and depression in late life is substantial and this association can't be fully explained by symptom overlap which suggests that psychological vulnerability may be an important component of frailty (Lohman et al., 2016). The mind-brain- gut connection has been well characterized (Kim, 2023; Aburto and Cryan, 2024); it is therefore important to capture manifestations of

frailty on the psychological domain because IBD patients are biologically more at risk of accumulating health deficits relating to psychological state and mood.

10.2 Patterns of frailty in the SPOR IMAGINE cohort

In the SPOR IMAGINE cohort, nearly one third (30.6%) of patients were classified as frail. According to a recent meta-analysis of nine observational studies of frailty in IBD patients, the final pooled frailty prevalence was 18% (95% CI: 12–24%) (Huang et al., 2022). Prevalence in our cohort is higher that this estimate, likely due to differences in measurement approach: the nine studies included used Frailty Risk Score, Claims based frailty index (CFI) using ICD9-codes, and the Hospital Frailty Risk Score (HFRS). Our FI score incorporates information from a variety of health domains and allows for a graded assessment of frailty, so we may have identified patients in the IMAGINE cohort as frail who would not have obvious manifestations of frailty if only using certain diagnostic codes. These patients would be missed using these other methods of identifying frailty and would be categorized as 'not frail' because they do not yet exhibit health deficits at the level of clinical disease states or functional deterioration.

The mean FI score in this cohort (0.17) was lower than other cohorts with immune mediated diseases (MS 0.54$\pm$ 0.13) (RA 0.26 $\pm$0.22)(systemic sclerosis (0.33 $\pm$0.14) but identical to the mean FI score for the SLE cohort (0.17 $\pm$0.08) (Zanotto et al., 2022; Salaffi et al., 2020; Legge et al., 2020a). This may be due to the fact that other cohorts used older clinical samples that had higher mean ages (MS: 60 $\pm$16, RA: 58 $\pm$ 13, SS: 58 $\pm$ 11.5)

compared to SPOR IMAGINE (45.8 ±15). Our sample is the most similar in age to SLE (35.7 ±13.4) which may explain the similarity in mean FI score.

In IBD cohorts, frailty prevalence increases with age: in a cohort of 11,001 patients with IBD, the prevalence of frailty increased from 4% (aged 20 to 29 years) to 25% (90 years of age and older) (Kochar et al., 2020b). Our findings showed a slight difference in frailty between age groups with our under 30 age group having a different prevalence of frailty (34.1% (95% CI: 29.8-38.7) to those over 45 years old (28.9% (95%CI 26.6-.31.4). If we had a larger sample for this project we may have been able to see a more significant different. As well, using longitudinal data would allow us to assess frailty in the same participant over time, and it's possible that FI scores may increase over time in the IMAGINE cohort using follow up visit data.

FI scores for participants in SPOR IMAGINE, from our IBD-FI, are not positively correlated with age. There is a higher prevalence of frailty in a immune modulated rheumatologic diseases such as psoriatic arthritis, ankylosing spondylitis, SLE, and systemic sclerosis which tend to be diseases affecting young people (Salaffi et al., 2023). In a review on IBD and frailty, Kochar et al (2021) comment that the fact that there is no linear increase of frailty in association with age in patients of all ages with chronic rheumatologic conditions "suggest that chronologic age underestimates biological age in patients with chronic systemic inflammatory conditions." Theou et al (2023) reports that in non-population-based sample, frailty and age are not consistently correlated because health is compromised for every individual and less likely to be a function of age.

It's notable that the FI scores correlate with IBD symptom severity. We did not have access to clinical disease activity measures and were restricted to the IBDSI score. Although 10 SIBDSI score items were components in the index itself, the correlation with symptom severity could hint at increased disease activity in frail individuals. In the future we will exclude these variables and do an analysis to check whether the association remains. Clinical and biochemical IBD disease activity measures (HBI, Partial Mayo score, Fecal calprotectin, CRP) are associated with presence of CGA deficits, and patients with geriatric deficits tend to also have a higher IBD symptom burden (Asscher et al., 2022). FI score is a distinct entity from disease activity. It is important to note that the expected relationship between FI score and disease activity may not be straightforward as frailty-related factors such as Immunosenescence may weaken autoimmune disease activity.

10.3 Use of this FI in clinical practice

Ideally, the scores generated from this index will be used as global health measures for clinicians that are diagnosing, managing and treating IBD. The FI score itself is comprised of psychological, clinical, and patient reported information. Adding biomarker data would enhance the FI as it would capture deficit accumulation at a biological level that has not yet accrued and resulted in a system or phenotype-level deficit. The index is balanced and not primarily composed of GI-related variables and for this reason, we have ensured that the index is not a proxy for disease activity. We have also not included medication variables in the index, as adding this information could simply capture disease-related damage treated with these pharmaceuticals.

The IBD FI in this study not only captures the physical and functional manifestations of frailty, but also the psychological/psychiatric components which are not captured in other tools such as the Fried phenotype or claims-based frailty scoring. Unfortunately, ICD code-based frailty assessments also fail to capture states of pre-frailty. Clinicians reviewing evidence from retrospective studies that have only used chronological age to stratify risks are lacking evidence that takes into account frailty and there is a pressing need for a new measure in IBD that takes into account function, reserve, and vulnerability (Kochar et al., 2021a).

There is also an emerging topic of interest in IBD research: understanding how controlling IBD inflammation through pharmacological treatments may impact frailty and modulate biological aging and senescence pathways. Salvatori et al (2023) investigated reversibility of frailty in IBD patients (age range 18-78), as measured by the Fried phenotype, and found that (19%) patients maintained a frail phenotype during a median follow-up of 8 months and (60%) and (21%) became pre-frail or fit. They found that the persistence of the frail phenotype was less frequent in patients who received therapy with steroids, or biologics, and hypothesize that reduction in frailty from treatments to control inflammation and reduction in frailty status could be as a result of attenuation of inflammation happening in the gut. Kochar et al (2022) found that frailty status was improved after Anti-TNF treatment for active disease where frailty was measured using a claims-based FI (primarily ICD-9 codes) but reflect this may be in part explained by heightened medical attention and initiation of physical and nutritional therapy services during Anti-TNF treatment. Our study found that mean FI scores were significantly higher

if a participant was taking a biologic, steroid, immunomodulator, and 5-ASA. It is likely that our results differ from these findings because our 77-item index FI score captures different manifestations of frailty from a variety of health domains (including psychiatric), without relying heavily on disease-related variables or conditions related to sarcopenia. This area of research is interesting and can only be expanded using validated frailty assessment tools.

10.4 Future directions

As mentioned previously, this FI should be used to predict outcomes of interest such as mortality and disease complications in the cohort it was initially created with (SPOR IMAGINE), if possible. FI scores generally are less predictive at younger ages, regardless of the number of health deficits included in the index (Farrell et al., 2016). It would be optimal to investigate the predictive abilities of this index with mortality in a cohort of advanced age IBD patients (mean age of approximately 80 years). Survival bias may make carrying out this type of study difficult and less feasible, considering that rates of disease related- complications and death are higher in hospitalized IBD advanced age patients compared to their younger counterparts.

It would be Informative to investigate the FI score with clinical disease severity indexes such as the HBI, CDAI and Partial Mayo Index Sore. In addition to this, we may adjust the index itself and add biomarker data to this FI if it becomes available from the SPOR IMAGINE main site. Follow up data may be used to monitor changes in frailty status over time in members of this cohort. We unfortunately did not have access to date of IBD

diagnosis (this variable was missing from our dataset following the data transfer). In the future we would like to stratify FI scores by disease duration because there are clinical differences in advanced age onset versus adult onset IBD patients. Future analysis should compare frailty in these different IBD groups.

Lastly, a future use of the IBD FI score in clinical research could be its use as an exclusion criteria for phase III clinical trials rather than chronological age. Problems using chronological age as an exclusion-criteria for IBD clinical trials has been previously described (Kochar et al., 2021b; Vieujean et al., 2022). Researchers exploring this have proposed the use of a measure that captures impairment in certain domains (functional, somatic and cognitive domains) as exclusion criteria for phase III trials instead of age is more optimal and if phase 4 trials could be conducted include people of older ages, researchers can investigate the effects of aging and frailty on the safety and efficacy of new compounds (Vieujean et al., 2022).

10.5 Strengths and limitations

This study has a number of strengths. The data source a prospective national cohort of IBD patients with a wide age range, which including objective health deficits variables that are collected from validated instruments. Sample size (2607) was relatively high compared to some other FI development studies. The dataset was patient-oriented in nature, as the SPOR IMAGINE project is patient-oriented, containing many patient-reported outcomes. Deficits came in a wide range of health domains (physical functioning, IBD symptom severity, quality of life, daily functioning, and mental health).

Operationalizing frailty from the accumulation of deficits model with an FI score allows for frailty to be captured on a continuous scale, which provides a more precise graded measure of the phenomenon in IBD patients compared to the use of other frailty measurement methods such as ICD codes or the frailty phenotype.

There are notable limitations to this study. We were restricted to mostly self-reported questionnaire data and did not access to objective disease markers traditionally found in clinical records (e.g. Fecal calprotectin, serum CRP). Inclusion of these types of items into the FI would allow for the creation of an FI that harmonizes clinical traits at the phenotypic level with biological data at the cellular level. Recall bias is also present, as most of our data was self-reported questionnaire data. Methods of validating the index were used on the same cohort as its construction which limits the generalizability of our study findings. Convergent validity is the demonstration of significant correlation between tools measuring a common construct and in FI research, this has been assessed using scatter plots and a Spearman's rank tests to estimate correlation coefficients between a FI of interest and other validated fIs (Duckworth and Kern, 2011). The dataset did not contain a gold standard frailty measure (*e.g.* items needed to generate FI score from another valid FI, and no score or measure capturing frailty) therefor this study could not assess convergent validity. This study did not contain IBD disease severity scores, disease complication data, hospitalization, or mortality data. We only had access to baseline data and did not have access to data from different points in time. For these reasons, we were unable to perform modelling to investigate predictive abilities of the FI scores or association of frailty with these outcomes.

11 Chapter 7: Conclusion

The aim of this project was to operationalize the accumulation of deficits approach to frailty and create a frailty measurement tool for the IBD population using variables from a wide variety of health domains. We successfully constructed an IBD Frailty Index (FI) using a validated 10 step process using baseline data from the SPOR IMAGINE cohort. The IBD FI is made up of 77 items, and is primarily composed of physical, functional and psychological/psychiatric health deficits. The mean age of our cohort was 45.8 years old (SD: 15), and the mean FI score was 0.17 (SD: 0.12), and 30.6% of our sample was categorized as frail (FI score >0.21). Although FI scores were not positively associated with age, FI scores were associated with IBD symptom severity (R=0.767). Future research projects using this FI should investigate FI scores predictive abilities for mortality and IBD disease complications and should explore the differences in frailty between patients diagnosed in middle of life (first epidemiological peak) versus later in life.

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13 Appendix

Table 1. Variables dropped from the dataset, with corresponding missingness percentage. Missingness percentage indicates the proportion of the variable that is missing. All 41 variables in this table have >5% missingness and therefore cannot be candidate deficits.

Variable name	Field label	Percentage (n missing/n total)
dbcan2	Have you had another diagnosis of cancer?	92.1 (2,500/2,714)
dbcan3	Have you had another diagnosis of cancer?	99.3 (2,696/2,714)
dbcan4	Have you had another diagnosis of cancer?	99.9 (2,711/2,714)
si24b	In the past week, my fistula was sore, swollen, or draining:	90.1 (2,446/2,714)
p6_2	In the past 7 days How much did having loose or watery stools interfere with your day-to-day activities?	34.5 (935 / 2,714)
p6_3	In the past 7 days How much did having loose or watery stools bother you?	34.5 (936 / 2,714)
p6_5	In the past 7 days How much did feeling you needed to empty your bowels right away interfere with your day-to-day activities?	42.4 (1,151 / 2,714)
p6_6	In the past 7 days How much did feeling you needed to empty your bowels right away bother you?	42.4 (1,150/2,714)
p9_2	In the past 7 days How much did hard or lumpy stools bother you?	67.8 (1,841/2,714)
p9_4	In the past 7 days How much did you usually strain while trying to have a bowel movement?	48.8 (1,324/2,714)
p9_5	In the past 7 days How much did straining during bowel movements bother you?	48.9 (1,326/ 2,714)

Variable name	Field label	Percentage (n missing/n total)
p9_7	In the past 7 days At its worst, how would you rate the pain in your rectum or anus during bowel movements?	60.1 (1,631/ 2,714)
p13_6	In the past 7 days In general, how severe was your bloating?	35.2 (954/ 2,714)
p13_7	In the past 7 days At its worst, how severe was your bloating?	35.1 (953/ 2,714)
p13_9	In the past 7 days How often did you know that you would feel bloated before it happened?	35.2 (956/ 2,714)
p13_10	In the past 7 days How much did feeling bloated interfere with your day-to-day activities?	35.1 (953/ 2,714)
p13_11	In the past 7 days How much did feeling bloated bother you?	35.1 (953/ 2,714)
p13_13	In the past 7 days How often did you have gurgling or rumbling in your belly when you were not hungry?	5.7 (155/2,714)
ph10	If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	16.5 (448/ 2,714)
ps1	1. In the last month, how often have you been upset because of something that happened unexpectedly?	5.1 (138 /2,714)
ps2	2. In the last month, how often have you felt that you were unable to control the important things in your life?	5.2 (141 /2,714)
ps4	4. In the last month, how often have you felt confident about your ability to handle your personal problems?	5.2 (141 /2,714)
ps5	5. In the last month, how often have you felt that things were going your way?	5.3 (143 /2,714)
ps6	6. In the last month, how often have you found that you could not cope with all the things that you had to do?	5.3 (144 /2,714)
ps7	7. In the last month, how often have you been able to control irritations in your life?	5.3 (141 /2,714)
ps8	8. In the last month, how often have you felt that you were on top of things?	5.2 (142 /2,714)

Variable name	Field label	Percentage (n missing/n total)
ps9	9. In the last month, how often have you been angered because of things that were outside of your control?	5.3 (143/2,714)
ps10	10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	5.4 (147 /2,714)
br3	It does not take me long to recover from a stressful event.	5.5 (150 /2,714)
br4	It is hard for me to snap back when something bad happens.	5.6 (151 /2,714)
br5	I usually come through difficult times with little trouble.	5.6 (153 /2,714)
p4_1	1. It's terrible and I think it's never going to get any better.	5.9 (160 /2,714)
p4_2	2. I become afraid that the pain will get worse.	5.9 (159 /2,714)
p4_3	3. I anxiously want the pain to go away.	5.9 (160 /2,714)
p4_4	4. I keep thinking about how badly I want the pain to stop.	5.9 (161 /2,714)
wp1	1. Are you currently employed (working for pay)?	5.9 (159/2,714)
wp2	2. During the past seven days, how many hours did you miss from work because of your health problems? Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.	36.6 (994/ 2,714)
wpai3	. During the past seven days, how many hours did you miss from work because of ?any other reason, such as vacation, holidays, time off to participate in this study?	36.8 (998/ 2,714)

Variable name	Field label	Percentage (n missing/n total)
wp4	4. During the past seven days, how many hours did you actually work?	36.6 (993/ 2,714)
wp5	During the past seven days, how much did your health problems affect your productivity while you were working?	43.0 (1,167/ 2,714)
wp6	During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?	65.2 (1,769/ 2,714)

Table 2. Inflammatory Bowel Disease Frailty Index (IBD FI) Health Deficits. The 77 deficits below were included in the FI.

Health Deficit	Field label	Scoring System
BMI	BMI (kg/m2)	0 underweight (0-18.5)| 0 normal (18.5-25)| 0.25 overweight (25-30)| 0.5 obese class 1 (30-35)| 0.75 obese class II (35-40)| 1 obese class III ((40+)
EIM arthritis	Check extraintestinal manifestations your patient has had: (Ever, up until current visit)	0 No, 1 yes
EIM Ankylosing spondylitis	Check extraintestinal manifestations your patient has had: (Ever, up until current visit)	0 No, 1 yes
EIM Erythema nodosum	Check extraintestinal manifestations your patient has had: (Ever, up until current visit)	0 No, 1 yes
EIM Pyoderma gangrenosum	Check extraintestinal manifestations your patient has had: (Ever, up until current visit)	0 No, 1 yes
EIM Iritis/uveitis	Check extraintestinal manifestations your patient has had: (Ever, up until current visit)	0 No, 1 yes
EIM Primary sclerosing cholangitis (PSC)	Check extraintestinal manifestations your patient has had: (Ever, up until current visit)	0 No, 1 yes
flare/remission	Current state of disease?	0 Remission, 1 active
Overall Health	My health was:	0 Very good | 0.2 Good | 0.4 Slightly below par |0.6 Poor |0.8 Very poor |1 Terrible
general pain	PAIN / DISCOMFORT	0 No Pain | 0.25 Slight Pain |0.5 Moderate Pain | 0.75 Severe Pain | 1 Extreme Pain
blood in stool	I noticed blood in my stool:	0 None | 0.5 Trace Amounts | 1 Obvious Bleeding
hard stool frequency	In the past 7 days How often did you pass very hard or lumpy stools?	0 Never | 0.25 One day | 0.5 2-6 days | 0.75 Once a day | 1 More than once a day

Health Deficit	Field label	Scoring System
bowel movements/day	On average, the number of bowel movements I had each day was:	0 Less than Once a day | 0.1 Two| 0.2 Three |0.3 Four| 0.4 Five| 0.5 Six | 0.6 Seven| 0.7 Eight |0.8 Nine |0.9 Ten|1 Ten or more
diarrhea frequency	The number of loose/liquid bowel movements or diarrhea I had most days was:	0 None | 0.0909 Some but <1 a day | 0.1818 One |0.2727 Two | 0.3636 Three | 0.4545 Four | 0.5455 Five | 0.6364 Six | 0.7273 Seven | 0.8182 Eight | 0.9091 Nine| 1 Ten or more
bowel movement urgency	Urgency of bowel movements	0 None | 0.25 A Little | 0.5 Moderate | 0.75 Quite a Lot | 1 Severe
lost control of bowels	Losing control of bowel movements	0 None | 0.25 A Little | 0.5 Moderate | 0.75 Quite a Lot | 1 Severe
constipation frequency	In the past 7 days How often did you strain while trying to have bowel movements?	0 None | 0.25 Rarely | 0.5 Sometimes | 0.75 Often| 1 Always
cancer	Have you ever had a diagnosis of cancer?	0 No | 1 Yes
Rheumatoid Arthritis	Rheumatoid Arthritis	0 No | 1 Yes
Diabetes	Diabetes	0 No | 1 Yes
Ischemic heart disease (angina, heart attack, myocardial infarction)	Ischemic heart disease (angina, heart attack, myocardial infarction)	0 No | 1 Yes
COPD (bronchitis, emphysema)	COPD (bronchitis, emphysema)	0 No | 1 Yes
Hypertension (high blood pressure)	Hypertension (high blood pressure)	0 No | 1 Yes
Depression	Depression	0 No | 1 Yes
Osteoporosis	Osteoporosis	0 No | 1 Yes
Blood clot in leg or lungs	Blood clot in leg or lungs	0 No | 1 Yes
Chronic fatigue	Chronic fatigue	0 No | 1 Yes
Fibromyalgia	Fibromyalgia	0 No | 1 Yes
Other disease	Other disease:	0 No | 1 Yes
walking	Are you able to go for a walk of at least 15 minutes?	0 Without any difficulty | 0.25 With a little difficulty | 0.5 With some difficulty | 0.75 With much difficulty | 1 Unable to do

Health Deficit	Field label	Scoring System
Loss appetite	I had loss of appetite:	0 None | 0.333 Mild | 0.666 Moderate| 1 Prolonged/severe
Waking due to BMs	Waking because of urge to have bowel movements	0 None | 0.25 A Little | 0.5 Moderate | 0.75 Quite a Lot | 1 Severe
Waking due to ABD pain	Waking because of abdominal pain	0 None | 0.25 A Little | 0.5 Moderate | 0.75 Quite a Lot | 1 Severe
dyspepsia (indigestion)	Indigestion (indigestion is a pain or discomfort in the upper abdomen).	0 Not at all | 0.25 Less than once a month | 0.5 Between once a month and once a week | 0.75 Between once a week and once a day | 1 Once a day or more
dyspepsia (heartburn)	Heartburn (heartburn is a burning feeling behind the breastbone).	0 Not at all | 0.25 Less than once a month | 0.5 Between once a month and once a week | 0.75 Between once a week and once a day | 1 Once a day or more
dyspepsia (regurgitation)	Regurgitation (regurgitation is an acid taste coming up into your mouth from your stomach).	0 Not at all | 0.25 Less than once a month | 0.5 Between once a month and once a week | 0.75 Between once a week and once a day | 1 Once a day or more
fatigue (frequency)	Feeling tired or having little energy	0 Not at all | 0.333 Several Days | 0.666 More than half the days| 1 Nearly Every day
fatigue (intensity)	Feeling fatigued or tired and worn out	0 None | 0.25 A Little | 0.5 Moderate | 0.75 Quite a Lot | 1 Severe
fatigue (activity avoidance)	I have trouble starting things because I am tired....	0 Not at all | 0.25 a little bit | 0.5 somewhat | 0.75 quite a bit | 1 very much
fatigue (physical and mental)	How run-down did you feel on average?	0 Not at all | 0.25 a little bit | 0.5 somewhat | 0.75 quite a bit | 1 very much
appetite	Poor appetite or overeating	0 Not at all | 0.333 Several days| 0.666 More than half the days| 1 Nearly every day
trouble focusing	Trouble concentrating on things, such as reading the newspaper or watching television	0 Not at all | 0.333 Several days| 0.666 More than half the days| 1 Nearly every day

Health Deficit	Field label	Scoring System
slow movements	Moving or speaking so slowly that other people could have noticed? Or the opposite -- being so fidgety or restless that you have been moving around a lot more than usual	0 Not at all | 0.333 Several days| 0.666 More than half the days| 1 Nearly every day
suicidality	Thoughts that you would be better off dead or of hurting yourself in some way	0 Not at all | 0.333 Several days| 0.666 More than half the days| 1 Nearly every day
insomnia frequency	Trouble falling or staying asleep, or sleeping too much	0 Not at all | 0.333 Several days| 0.666 More than half the days| 1 Nearly every day
insomnia intensity	I had a problem with my sleep...	0 Not at all | 0.25 A little bit | 0.5 Somewhat | 0.75 Quite a bit | 1 Very much
insomnia difficulty falling asleep	I had difficulty falling asleep...	0 Not at all | 0.25 A little bit | 0.5 Somewhat | 0.75 Quite a bit | 1 Very much
sleep quality	My sleep quality was....	0 Very good | 0.25 good| 0.5 Fair | 0.75 poor | 1 Very poor
fear	I felt fearful....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Often | 1 Always
helplessness	I felt helpless....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Often | 1 Always
apathy	Little interest or pleasure in doing things	0 Not at all | 0.333 Several Days| 0.666 More than half the days| 1 Nearly every day
feeling down	Feeling down, depressed, or hopeless	0 Not at all | 0.333 Several Days| 0.666 More than half the days| 1 Nearly every day
hopeless	I felt hopeless....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Often | 1 Always
Daily tasks (activities with others)	I have trouble doing all of my regular leisure activities with others....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Usually | 1 Always
Daily tasks (activities with family)	I have trouble doing all of the family activities that I want to do....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Usually | 1 Always
Daily tasks (usual work & chores)	I have trouble doing all of my usual work (include work at home)....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Usually | 1 Always

Health Deficit	Field label	Scoring System
Daily tasks (social with friends)	I have trouble doing all of the activities with friends that I want to do....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Usually | 1 Always
Daily activities (impaired because of pain)	How much did pain interfere with your day to day activities?	0 Not at all | 0.25 A little bit | 0.5 Somewhat | 0.75 Quite a bit | 1 Very much
Daily social activities (impaired because of pain)	How much did pain interfere with your ability to participate in social activities?	0 Not at all | 0.25 A little bit | 0.5 Somewhat | 0.75 Quite a bit | 1 Very much
Daily tasks (chores)	Are you able to do chores such as vacuuming or yard work?	0 Without any difficulty | 0.25 With a little difficulty | 0.5 With some difficulty | 0.75 With much difficulty | 1 Unable to do
Daily tasks (errands)	Are you able to run errands and shop?	0 Without any difficulty | 0.25 With a little difficulty | 0.5 With some difficulty | 0.75 With much difficulty | 1 Unable to do
Daily tasks (stairs)	Are you able to go up and down stairs at a normal pace?	0 Without any difficulty | 0.25 With a little difficulty | 0.5 With some difficulty | 0.75 With much difficulty | 1 Unable to do
Daily tasks (normal routine activities)	USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	0 I have no problems doing my usual activities | 0.25 I have slight problems doing my usual activities | 0.5 I have moderate problems doing my usual activities | 0.75 I have severe problems doing my usual activities | 1 I am unable to do my usual activities
Daily tasks (self care)	SELF-CARE	0 I have no problems washing or dressing myself | 0.25 I have slight problems washing or dressing myself | 0.5 I have moderate problems washing or dressing myself | 0.75 I have severe problems washing or dressing myself | 1 I am unable to wash or dress myself
Daily tasks (finishing tasks)	Finding it hard to get things done	0 None | 0.25 A Little | 0.5 Moderate | 0.75 Quite a Lot | 1 Severe
self-esteem (worthlessness)	I felt worthless....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Often | 1 Always

Health Deficit	Field label	Scoring System
self-esteem (letting others down)	Feeling bad about yourself -- or that you are a failure or have let yourself or your family down	0 Not at all | 0.333 Several days| 0.666 More than half the days| 1 Nearly every day
worry (can't stop worrying)	Not being able to stop or control worrying	0 Not at all | 0.333 Several days| 0.666 Over half the days| 1 Nearly every day
worry (multiple things)	Worrying too much about different things	0 Not at all | 0.333 Several days| 0.666 Over half the days| 1 Nearly every day
worry (hyper fixation)	I found it hard to focus on anything other than my anxiety....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Often | 1 Always
worry (overwhelmed)	My worries overwhelmed me....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Often | 1 Always
worry (uneasy)	I felt uneasy....	0 Never | 0.25 Rarely | 0.5 Sometimes | 0.75 Often | 1 Always
anxiety/depression	ANXIETY / DEPRESSION	0 I am not anxious or depressed | 0.25 I am slightly anxious or depressed | 0.5 I am moderately anxious or depressed | 0.75 I am severely anxious or depressed | 1 I am extremely anxious or depressed
nervousness	Feeling nervous, anxious, or on edge	0 Not at all | 0.333 Several days| 0.666 Over half the days| 1 Nearly every day
trouble relaxing	Trouble relaxing	0 Not at all | 0.333 Several days| 0.666 Over half the days| 1 Nearly every day
easily anxious	Becoming easily annoyed or irritable	0 Not at all | 0.333 Several days| 0.666 Over half the days| 1 Nearly every day
fearful of future	Feeling afraid as if something awful might happen	0 Not at all | 0.333 Several days| 0.666 Over half the days| 1 Nearly every day

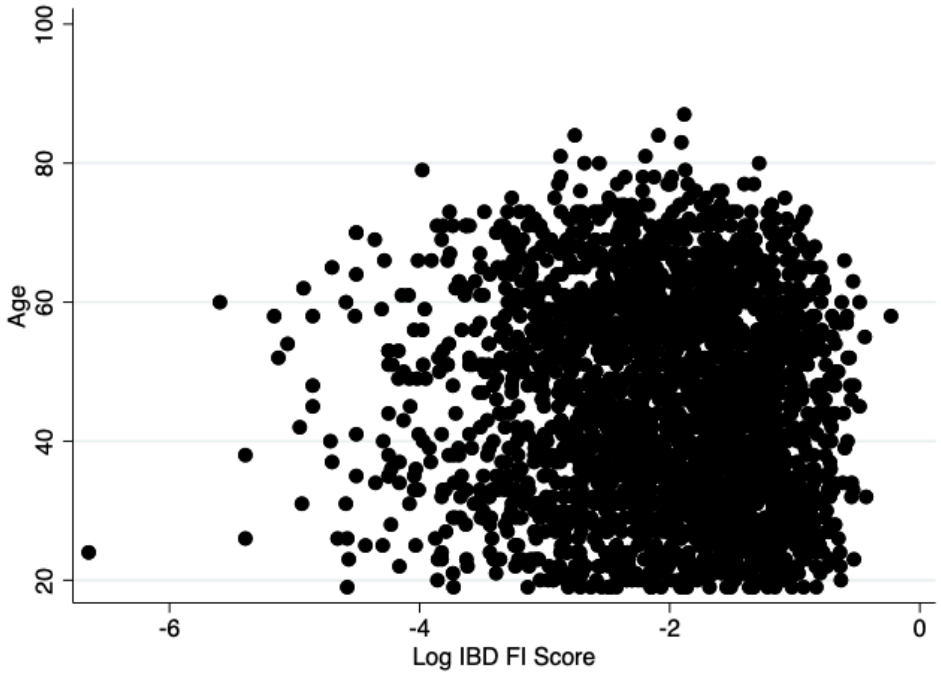

Figure 1. Scatterplot of Log frailty index (FI) score by age.

Table 3. Correlation matrix of FI candidates, where R> 0.9. The p29_26 variable represented Daily home activities (impaired because of pain)), the p29_25 represented Daily activities (impaired because of pain), and the P29_28 variable represented Daily chores (impaired because of pain). In p29_26/ p29_25 pair, p29_26 had more missing so removed this from my tentative list, In the p29_25/ p29_28 pair, p29_28 had more missing so removed this from my tentative list.

Variable	**p29_26**	**p29_25**	**P29_28**
p29_26	1	0.9204	0.9484
p29_25	0.9204	1	0.9112
P29_28	0.9484	0.9112	1