Age-related changes of the gastrointestinal tract

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Disorders of the gastrointestinal tract are common in those aged 65 years or older, impairing their quality of life and potentially increasing morbidity and mortality risk. Unlike many organ systems, the luminal gastrointestinal tract does not undergo much natural degeneration. However, age-related anatomical and functional changes of the gastrointestinal tract might promote pathophysiology and explain some atypical presentations of gastrointestinal disorders in older adults. This Review summarises current knowledge of major anatomical and functional changes that occur in the gastrointestinal tract during ageing. These changes are often more evident in older adults who are frail or multimorbid, and frailty in older age might also influence the presentation, prognosis, and management of older patients with gastrointestinal disorders.

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Introduction

Luminal gastrointestinal disorders are pervasive in the older population and can have a major impact on individuals' wellbeing, nutrition, and quality of life. Older people, commonly defined as being 65 years or older,[1] frequently experience gastrointestinal problems, which can range from minor, self-limiting episodes of acid reflux or constipation to potentially fatal episodes of infectious colitis or bowel ischaemia. A national gastrointestinal survey conducted in the USA in 2015 found that 55% of community-dwelling adults aged 65 years or older had at least one gastrointestinal issue in the past week.[2] Some of the most common gastrointestinal illnesses in older patients are gastro-oesophageal reflux disease, diverticular disease, and chronic constipation.[3] An Italian survey of 3100 people aged 60 years or older who were enrolled by their general practitioners while visiting for a medicial problem occuring during the previous 2 weeks, reported an overall prevalence of upper gastrointestinal symptoms of 43%, including abdominal pain (14%), acid reflux (22%), indigestion-dyspepsia syndrome (30%), gastrointestinal bleeding (1·2%), and non-specific symptoms (5%). Interestingly, upper gastrointestinal symptoms were more frequently reported by female participants, those who had a high number of comorbidities (especially psychiatric and respiratory diseases), those who were taking three or more drugs, and those who needed assistance in activities of daily living.[4]

Unlike many organ systems (eg, kidneys and cardiovascular system), the luminal gastrointestinal tract is thought to have a substantial functional reserve that means it does not experience a large amount of natural degeneration.[5] Ageing processes do not seem to be the primary cause of gastrointestinal functional impairments in older people; however, as people age, their digestive systems might become less efficient and more susceptible to stress and potential adverse injuries. Furthermore, age-related anatomical and functional changes of the gastrointestinal tract might lead to differences in the presentation of gastrointestinal disease. The presence of frailty (a multidimensional vulnerability status related to and associated with functional and cognitive impairments, malnutrition, comorbidities, and polypharmacy) might also influence the presentation, prognosis, and management of older patients with gastrointestinal disorders,[6,7] and might be useful to assess in this context.[8]

The aim of this Review is to summarise knowledge and novel insights regarding age-related changes in the luminal gastrointestinal tract and their clinical consequences in older patients.

Upper gastrointestinal tract in old age

Age-related anatomical and functional changes of the oesophagus

Since 1964, a clinical phenotype called presbyoesophagus has been used to explain age-related oesophageal changes.[9] It refers particularly to a reduction in peristaltic movements and the presence of frequent non-peristaltic contractions in older people.[9] This concept has been better elucidated through advances in manometry testing, which has shown age-related changes in oesophageal motility, such as in the amplitude and coordination of oesophageal contractions, that could impact the efficiency of bolus transit.[10] More specifically, age-related functional changes in the oesophagus include modifications in motility of the upper oesophageal sphincter, with a reduction in both pressure and relaxation; diminished oesophageal secondary peristalsis (ie, the peristalsis activated by oesophageal distention that follows primary contraction and propels any remaining bolus from the thoracic oesophagus); reduced lower oesophageal sphincter pressure and length; and decreased mucosal resistance to insult as a result of impaired epithelial cell regeneration.[11] These changes might result in reduced acid-clearing capacity and increased acid injury of the oesophagus in old age (figure 1).[11] Other age-related changes, such as reduced salivary secretion, delayed gastric emptying, and increased risk of duodeno-gastro-oesophageal reflux of bile salts, might also contribute (figure 1).[11] Moreover, some risk factors specific to or more common with ageing might predispose older people to oesophageal injury. These risk factors include an impaired ability to remain upright after eating because of changes in the anatomy of the thorax associated with dorsal kyphosis and collapse of the dorsal vertebrae; the high prevalence of hiatus hernia linked to the weakening of the diaphragm and increased abdominal pressure that may lead to

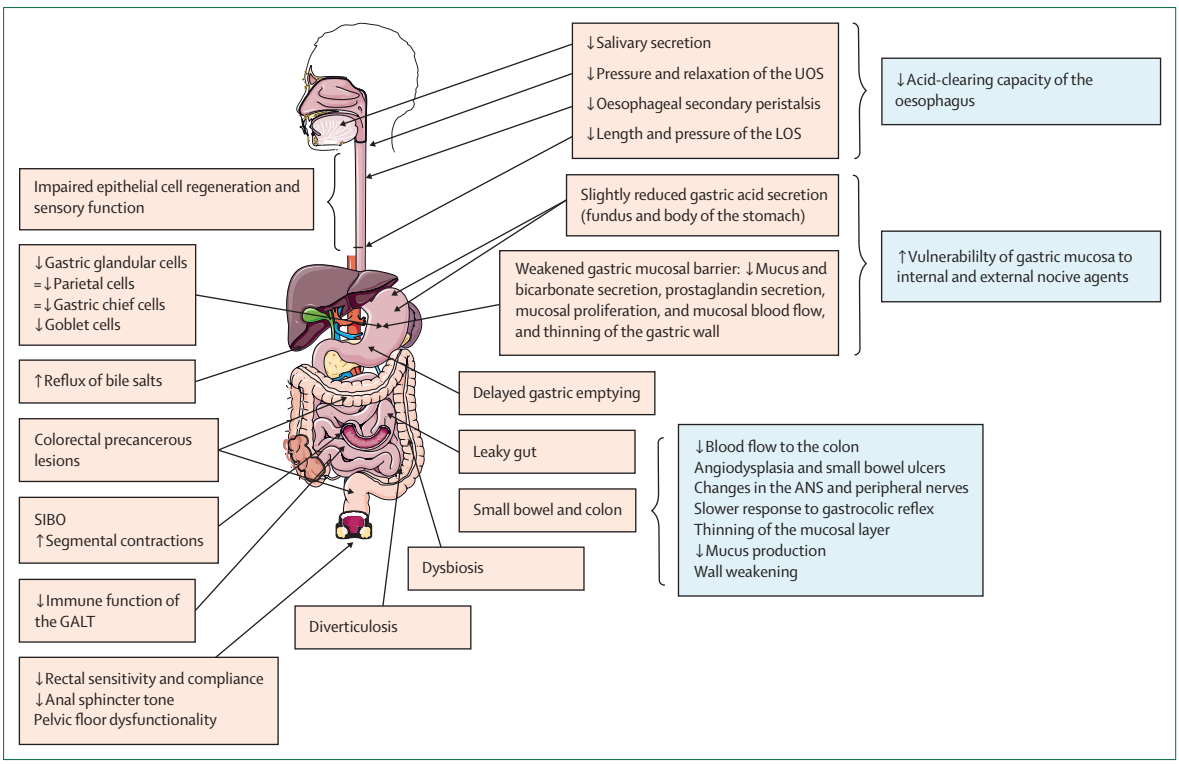

Figure 1: **Age-related changes of the gastrointestinal tract**
ANS=autonomic nervous system. GALT=gut-associated lymphoid tissue. LOS=lower oesophageal sphincter. SIBO=small intestinal bacterial overgrowth. UOS=upper oesophageal sphincter. =indicates relatively normal level of cells. Figure adapted from Servier Medical Art, licensed under CC BY 4.0.

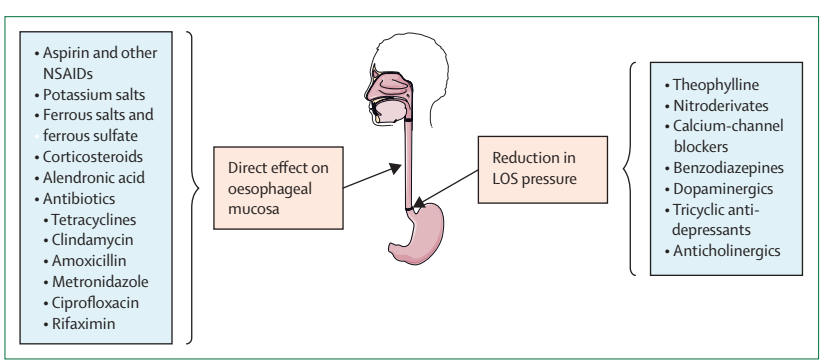

Figure 2: **Drugs that could contribute to oesophageal injury**
NSAIDs=non-steroidal anti-inflammatory drugs. LOS=lower oesophageal sphincter. Figure adapted from Servier Medical Art, licensed under CC BY 4·0.

recurrent episodes of acid reflux; radiation therapy to nearby or related structures; and infections more common in older age, such as candidiasis.[11] Furthermore, in some cases, older people might develop oesophageal injury due to medication effects, either directly through an effect on the mucosa or indirectly via reducing lower oesophageal sphincter pressure (figure 2).[12] The sensory function of the oesophagus might also deteriorate with age, increasing the likelihood of atypical, non-specific presentations, or long-term asymptomatic phases of oesophageal disorders.[13]

Clinical features of oesophageal disorders in older people

Oesophageal disorders can affect people of all ages; however, some clinical conditions are more common in older people than in younger adults (eg, Zenker's diverticulum and hiatus hernia). Moreover, clinical presentation of oesophageal disorders could include unique features in the older population due to age-related anatomical and functional changes.[11]

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease is a common oesophageal disorder. Although it is not well established whether the prevalence of symptomatic gastro-oesophageal reflux disease increases with advancing age, the rate of severe forms (oesophagitis) and complications is higher in older than in younger patients.[14] In a retrospective cross-sectional study conducted in the US among long-term nursing home residents older than 65 years, the prevalence of gasto-oesophageal reflux disease was 23%.[15] Older patients with gastro-oesophageal reflux disease also have more comorbidities than younger adults, with hypertension, dyslipidaemia, and diabetes among the most reported in one prospective study from Brazil.[16]

From a clinical point of view, older adults with endoscopically evident oesophagitis report fewer typical symptoms, such as heartburn, acid regurgitation, and

epigastric pain, than do younger adults.[17] They also report fewer pulmonary symptoms (ie, chronic cough, bronchial asthma, and chronic bronchitis) and laryngeal symptoms (ie, hoarseness and chronic laryngitis), and less non-cardiac chest pain, compared with younger adults. Conversely, although non-specific symptoms (ie, anorexia, weight loss, anaemia, and vomiting) are only occasionally observed in young and adult patients, they increase progressively with age, reaching almost 40% in patients with oesophagitis who are older than 65 years and over 65% in patients aged 85 years or older.[17] Dysphagia symptoms also increase with age in patients with gastro-oesophageal reflux disease. These findings suggest that the clinical diagnosis of gastro-oesophageal reflux disease might be more challenging in older than in younger patients. Diagnosis might be further complicated by the diminished sensitivity to visceral pain in older people.[18] The intensity of symptoms might be less severe in older patients and, therefore, symptoms might not receive the full attention of physicians or the patients themselves, allowing acid injury to accumulate before intervention.[18] Thus, the diagnosis of gastro-oesophageal reflux disease, even if present with long-term complications, such as strictures and Barrett's oesophagus, might be missed or delayed in older people. For these reasons, endoscopy should be the first diagnostic test done in older patients suspected of having upper gastrointestinal tract disorders, because this diagnostic tool can detect complications such as Barrett's oesophagus or oesophageal cancer.[19] In one US-based, retrospective study of patients undergoing their first endoscopy, the prevalence of Barrett's oesophagus in those with gastro-oesophageal reflux disease increased with age, particularly among White men (9·3% in the 6th decade of life *vs* 3·3% in the 4th decade of life).[20] Although there is a paucity of specific recommendations for evaluating and managing older patients with Barrett's oesophagus, endoscopic screening and surveillance requires a careful balance between benefits, risks, and costs associated with repeated invasive procedures, considering life expectancy and comorbidities rather than just chronological age.[21]

The management of gastro-oesophageal reflux disease in older people is usually pharmacological, with proton-pump inhibitors (PPIs) considered more effective than H2 receptor blockers.[11] Continuous PPI therapy in older patients is particularly useful to achieve a profound acid inhibition in cases of severe oesophagitis and Barrett's oesophagus, and to maintain complete symptom relief, minimising the occurrence of relapse at discontinuation of treatment, or relapse associated with intermittent use of antacids, alginic acid, and H2 receptor antagonists.[22] However, given the substantial risk of prescription inappropriateness in clinical practice,[23] the updated American Geriatrics Society Beers Criteria posed a strong recommendation against long-term PPI use (>8 weeks) among patients 65 years and older, with the exception of patients at high risk of gastro-oesophageal reflux disease (eg, due to oral cortiosteroid or chronic NSAID use), or patients with erosive oesophagitis, Barrett's oesophagus, pathological hypersecretory condition, or demonstrated need for continuous treatment. This recommendation is justified by the potentially increased risk of *Clostridioides difficile* infection, osteoporosis, and fractures (for which there is a high quality of evidence), as well as pneumonia and gastrointestinal malignancies (for which there is a moderate quality of evidence) for older patients treated with long-term PPI therapy.[11,24,25] There are scarce data on the long-term cost-effectiveness of PPI discontinuation in older patients with gastro-oesophageal reflux disease. However, a Cochrane review highlighted a reduction in drug burden with on-demand use compared with continuous treatment with PPIs, suggesting de-prescribing as a potential option, which could be useful for older patients, who tend to be at high risk of polypharmacy.[11,26] Although there is no single agreed definition of the term polypharmacy, it has been described as the use of four or more medications.[27] As stated by the American Gastroenterological Association, PPI discontinuation should be decided solely on the basis of a lack of indication for PPI use, and not because of concern for potential and not yet clearly proven PPI-associated adverse events (eg, dementia or chronic kidney disease).[28] A possible alternative could be the potassium-competitive acid-blocker medication vonoprazan, which has shown good efficacy, long-term safety, and low rates of drug–drug interactions;[29] however, further studies are needed specifically in frail, multimorbid, and polytreated older adults.

Oesophageal disorders of gut–brain interaction

In old age, several disorders, known as functional disorders or disorders of gut–brain interaction (DGBIs), might cause oesophageal symptoms without the direct involvement of evident pathophysiological changes in the oesophagus. The main oesophageal DGBIs are functional chest pain and heartburn, reflux hypersensitivity, oesophageal globus, and functional dysphagia.[30] It is hypothesised that visceral hypersensitivity and psycho-cognitive hypervigilance might contribute to the development of symptoms in individuals with normal upper gastrointestinal function.[30] DGBIs have been linked to alterations in the autonomic nervous system and psychological disorders being highly comorbid with anxiety, depression, and somatisation, highlighting the importance of interdisciplinary management.[31,32] Although it is uncertain whether oesophageal DGBIs affect older people more commonly than younger adults, the high prevalence of comorbid physical and psychological disorders in old age, and their related pharmacological treatments, can influence these disorders considerably.[33] For example, upper gastrointestinal diseases (including malignancies) increase in incidence with advancing age,[3] and these diseases could

present with symptoms overlapping with those of oesophageal DGBIs.[4,34] In this context, it is important to consider and exclude malignant or non-malignant organic disease, along with potential side-effects from medications, before diagnosing oesophageal DGBIs in older people.[33] Moreover, the current Rome IV criteria have not been validated with older patients,[35] therefore new onset or so-called alarm symptoms require further evaluation. If an oesophageal DGBI is diagnosed, recommending lifestyle improvements could be useful, including dietary modifications (eg, avoiding irritating foods, going to bed immediately after a meal, and weight reduction in older patients with high BMI or obesity).[11] If not properly treated, oesophageal DGBIs may increase the risk of maladaptive dietary restrictions also known avoidant/restrictive food intake disorders, and thus malnutrition. Therefore, dietitian support is recommended when executing diet-based therapies with older people.[36]

Age-related anatomical and functional changes of the stomach

Ageing leads to major anatomical changes in the stomach, which are primarily attributed to the process of cellular senescence; chronic inflammation; and the cumulative effects of environmental factors, such as diet, *Helicobacter pylori* infection, and medication use.[37] The most notable changes in the stomach affecting older people include gastric mucosal atrophy, characterised by the loss of gastric glandular cells and their replacement with intestinal-type epithelium (intestinal metaplasia) or fibrous tissue, often resulting from chronic *H pylori* infection or autoimmune gastritis; reduction in parietal cells, which are responsible for gastric acid production, diminishing the stomach's capacity to secrete hydrochloric acid (leading to hypochlorhydria) and intrinsic factor, essential for vitamin B12 absorption; and thinning of the gastric wall, impacting its contractility and motility and potentially impairing the stomach's ability to mix and propel food effectively. These anatomical changes lay the groundwork for subsequent pathophysiological changes that have profound implications for the presentation, diagnosis, and management of upper gastrointestinal disorders in older adults. These changes affect gastric motility, secretion, and mucosal defence.[37,38] Delayed gastric emptying (gastroparesis) is common in older adults[39] and might be caused by a reduction in the interstitial cells of Cajal, loss of neuronal nitric oxide synthase expression, and changes in the enteric nervous system. Age-related delay in gastric emptying is attributed to both impaired smooth muscle function and reduced vagal nerve activity.[40] Moreover, gastric mucosal blood flow can decline with age, reducing the stomach's ability to respond to injury, thus impairing healing. The secretion of gastric mucus and bicarbonate can also decline with age, compromising the mucosal protective barrier against gastric acid, which can lead to the so-called phenotype of ageing gastropathy.[41] Both the decreased effectiveness of the bicarbonate buffering system and the reduced mucus quantity (thickness of the mucus layer) and quality (poorer production of prostaglandins A and E due to age-related reduction of cyclo-oxygenase enzyme activity)[42] render the mucosa vulnerable to injuries, such as those caused by non-steroidal anti-inflammatory drugs (NSAIDs) and *H pylori* infection.[38]

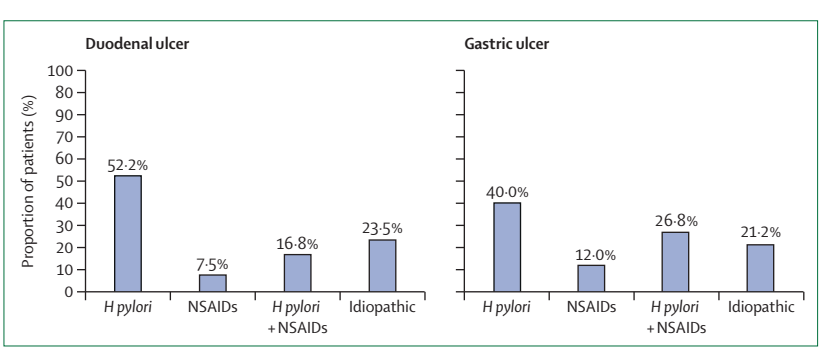

***Figure 3:* *H pylori* infection and NSAID use in patients with ulcers**
Data from a study of patients aged 65 years or older, living in the community.[46] *H pylori*=*Helicobacter pylori*. NSAIDs=non-steroidal anti-inflammatory drugs. *H pylori* + NSAIDs indicates patients positive for *H pylori* with a history of NSAID use. Figure adapted from Servier Medical Art, licensed under CC BY 4.0.

Clinical features of gastric disorders in older people

Age-related anatomical and functional changes in the stomach have profound clinical implications. The older stomach is less resilient to injury, slower to empty its contents, and less capable of defending itself from irritants like NSAIDs and *H pylori*. Delayed gastric emptying exacerbates symptoms of gastroparesis and increases the risk of small intestinal bacterial overgrowth.[40] The gastric mucosal blood flow decline is particularly relevant in the context of common conditions in older people, such as stomach ulcers from NSAID use, as mucosal blood flow is crucial for repair following NSAID-induced injuries, including peptic ulcer disease.[41,43] From a pathophysiological point of view, NSAIDs inhibit cyclo-oxygenase enzymes, thereby reducing the synthesis of prostaglandins that maintain gastric mucosal integrity. This effect is more pronounced in older adults due to diminished mucosal defence mechanisms (eg, reduced mucus, bicarbonate secretion, and blood flow).[42,44]

Peptic ulcer disease

In 2019, it was estimated that 346·89 per 100 000 people aged 70 years or older were affected by peptic ulcer disease, with increased prevalence with advancing age, and that complicated peptic ulcers had a high burden in terms of admission to hospital and mortality rate.[45] Factors that could explain the high rate of peptic ulcer disease in older patients include *H pylori* infection and the frequent use of mucosa-damaging drugs, such as aspirin and other NSAIDs. However, in one study of 520 community-dwelling patients in Italy aged 65 years or older with peptic ulcer disease, more than 20% of all

peptic ulcer disease cases were idiopathic and not related to NSAIDs or *H pylori*. (figure 3).[46]

The clinical presentation of peptic ulcer disease is often atypical in patients older than 60 years, with only around a third reporting typical epigastric pain and two-thirds reporting vague abdominal pain as a main symptom.[47] In older adults, peptic ulcer disease often presents as nausea, vomiting, weight loss, and anorexia, which can be initial or sole manifestations. Possibly partly due to the subtle clinical presentation in older patients, outcomes of peptic ulcer disease in these patients tend to be more severe compared with those in younger individuals.[48,49] It is not rare to observe upper gastrointestinal bleeding as a first clinical presentation of peptic ulcer disease in older patients. Upper gastrointestinal bleeding is a potentially life-threatening manifestation of haemorrhages arising proximally to the ligament of Treitz; advanced age is an important independent risk factor for upper gastrointestinal bleeding[50] and it is of particular concern for patients with additional risk factors, such as use of NSAIDs, antiplatelets, anticoagulants, or steroids; or who are multimorbid, polytreated, and frail (table). It is thus highly recommended in older patients to aim at reducing or stopping NSAIDs and other drugs associated with mucosal damage, to add co-treatment with PPIs, and to eradicate *H pylori* (if present).[37,52,53]

Atrophic gastritis

A common condition of the ageing stomach is atrophic gastritis. Its prevalence increases with age and reached roughly 48% among individuals older than 70 years in an autopsy study, compared with 7% in those aged 20–50 years and 21% in those aged 51–70 years.[54] Atrophic gastritis is caused either by autoimmune mechanisms or chronic *H pylori* infection, ultimately leading to the destruction of gastric glands and reduced production of gastric acid, pepsin, and intrinsic factor.[55,56] Although these effects could seem paradoxically beneficial, in terms of lowering the risk of acid-related conditions such as gastro-oesophageal reflux disease, they increase susceptibility to enteric infections and vitamin B12 deficiency.[47] The risk of pernicious anaemia and small intestinal bacterial overgrowth associated with atrophic gastritis is progressively higher with advancing age.[54,57] Atrophic gastritis is often asymptomatic, but can present with symptoms of malabsorption, such as diarrhoea, weight loss, and iron or vitamin B12 deficiency.[55] Testing for *H pylori* is essential, as its eradication can reverse some aspects of atrophic gastritis.[52] In this context, non-invasive tests, such as the determination of serum pepsinogen I and II concentrations (sPGI and sPGII, respectively), could be useful to detect whether gastric mucosa is atrophic or non-atrophic, and could have a role in screening for gastric precancerous lesions, but use for screening is debated.[52] sPGI and spGII are biomarkers of gastric mucosal inflammation and are known to increase in the presence of *H pylori* infection-related gastritis and both gastric and duodenal peptic ulcer disease. Moreover, sPGII concentrations correlate with the severity of mucosal inflammation.[58] A study of people aged 60–89 years reported that sPGII concentrations decreased significantly after successful

	Key considerations	Common findings	Comments
Initial presentation	Evaluate nature of bleeding	Haematemesis or melena suggests UGIB; haematochezia usually suggests LGIB, but can occur in massive UGIB	Presentation might be atypical due to altered pain perception and blunted autonomic response
Haemodynamic status	Assess for hypotension, orthostatic hypotension, and anaemia; remember reduced physiological reserve in older people	Delayed hypotension; higher risk of shock	Consider earlier fluid resuscitation and higher transfusion thresholds for patients with comorbidities at higher risk of tissue hypoxia (<8 g/dL) than for haemodynamically stable patients with no severe comorbidities (<7 g/dL)
Medication history	Polypharmacy increases risk of mucosal injury and bleeding	NSAIDs, SSRIs, anticoagulants, antiplatelets, and corticosteroids increase risk	Age-related decline in renal and hepatic function increases drug toxicity
Comorbidity assessment	Age-related comorbidities contribute to cause of bleeding	Comorbidities include liver cirrhosis, cardiovascular disease, respiratory and renal insufficiency, diabetes, and cancer	Comorbidities might modify management or increase recurrence risk
Suspected source	Based on presentation and comorbid profile	UGIB: peptic ulcer, erosive oesophagitis, varices, and Mallory–Weiss syndrome; LGIB: diverticulosis, angiodysplasia, neoplasm, haemorrhoids, and ischaemic colitis	Angiodysplasia and ischaemic colitis are more common in adults older than 60 years
Diagnostic tests	Tailored by presentation and patient stability	Oesophagogastroduodenoscopy for suspected UGIB; colonoscopy or CT angiography for LGIB	Consider capsule endoscopy if source remains obscure
Underlying ageing factors	Consider age-related pathophysiological changes	Changes include mucosal atrophy, decreased mucosal perfusion, altered coagulation, and reduced gastrointestinal motility	Changes increase vulnerability to both bleeding and poor healing

LGIB=lower gastrointestinal bleeding. NSAIDs=non-steroidal anti-inflammatory drugs. SSRIs=selective serotonin reuptake inhibitors. UGIB=upper gastrointestinal bleeding.

Table: **Stepwise diagnostic approach to gastrointestinal bleeding in older adults**[11,51]

H pylori eradication.[56] Furthermore, sPGI, or the sPGI to sPGII ratio, could be useful in identifying atrophic gastritis of the gastric corpus, and gastrin (particularly gastrin-17) could be an indicator of the morphological status of the gastric antral mucosa, even in centenarians.[59]

Lower gastrointestinal tract in old age

Age-related anatomical and functional changes of the gut

With ageing, the physiology of the bowel undergoes several changes that affect its function.[60] Age-related changes in the autonomic nervous system and peripheral nerves might cause a decrease in the strength and frequency of peristaltic contractions.[60,61] These changes could affect bowel motility and decrease the sensitivity of the rectum to stretch, leading to less frequent sensations of urgency, or the inability to sense fullness properly. Peristalsis might also be impaired by decreased mucus production due to a reduction in goblet cells, leading to friction, difficulty in stool passage, and discomfort.[61] Although an age-related decrease in propulsion forces of the colon has been described, delayed colonic transit could be secondary to other conditions commonly observed in older people. For example, changes in gastrointestinal function are also associated with psychological concerns, as well as immobility and malnutrition. Immobility and malnutrition are pervasive in the community-dwelling older population, with approximately 35% of people older than 70 years globally being mobility-limited[62] and 19% of people 60 years and older reportedly malnourished.[63]

In addition, specific anatomical abnormalities, such as rectoceles, sigmoidoceles, and rectoanal intussusception (although rare), can also affect the defecation process.[51] Finally, older individuals often have metabolic dysregulation, including insulin resistance, obesity, and dyslipidaemia. These conditions have been linked to altered microbiota composition[64] and are responsible for intestinal motility impairment.[51] With age comes increased intestinal vessel permeability (a so-called leaky gut), which might favour mucosal bleeding,[65,66] and villous atrophy and depletion of the microvessel network in the villi, which could reduce nutrient absorption.[5] Such modifications in gut function and structure (figure 1) make older people more prone to gastrointestinal disorders such as constipation, diverticulosis, and malabsorption, and expose patients to higher bleeding risk.[51] In turn, changes in gut microbiota composition have been associated with systemic ageing-related pathologies, including metabolic, immune, and neurodegenerative disorders.[67]

Gut microbiota, which consist of trillions of microorganisms residing in the human intestine, play a crucial role in maintaining overall health, influencing a range of physiological processes, including nutrient metabolism, immune system modulation, and protection against pathogens.[67] Specifically, a shift towards a less diverse microbiome, with a reduction in beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, is commonly observed in older adults[68] and has been proposed as a factor in the pathogenesis of mild cognitive impairment, Alzheimer's disease, and Parkinson's disease.[69] The reduction in microbiota composition diversity is accompanied by an increase in potentially harmful bacteria, including those from the Firmicutes (Bacillota) and Proteobacteria (Pseudomonadota) phyla.[70,71] These microbial changes are thought to contribute to a disruption in gut barrier function, leading to increased intestinal permeability, which facilitates the translocation of bacteria and endotoxins into the bloodstream.[72] Moreover, senescence-related impairment of gut-associated lymphoid tissues causing altered gut mucosal immune responses[73] might contribute to systemic chronic low-grade inflammation, known as inflammageing.[74,75] Systemic chronic low-grade inflammation is often observed in ageing and has been linked to numerous age-related chronic diseases, including diabetes, neurodegenerative disorders, and cardiovascular disease.[69,75,76]

Although most previous studies have used stool samples to assess large intestinal dysbiosis, the small intestinal microbiome also changes with age.[77] In one study of duodenal aspirates from 251 people, duodenal microbiome diversity was found to decrease with age, whereas the prevalence of Pseudomonadota and anaerobes was found to increase.[77] In analyses to disentangle confounding, the study found that *Bacteroides*, *Lactobacillus*, and *Escherichia* increased with chronological age alone, *Klebsiella* with medication use, and *Clostridioides* with the number of pathological conditions.[77]

The healthy small intestine uses various protective mechanisms to prevent colonisation and keep bacterial levels relatively low. Gastric acid, bile, and pancreatic secretions suppress the growth of both ingested and oropharyngeal bacteria that might move distally.[78] Antegrade motility patterns of the small intestine, including peristalsis and phase III of the interdigestive or migrating motor complex, help to reduce stasis and bacterial proliferation. Moreover, the intestinal mucosa has a mucus layer and intrinsic antimicrobial mechanisms, such as defensins and immunoglobulins. Lastly, the ileocaecal valve restricts the backward movement of anaerobic colonic bacteria.[79] As all these mechanisms can be impaired in older people,[51] advanced age and some common age-related conditions (such as Parkinson's disease, chronic renal failure, and diabetes) are associated with a higher likelihood of small intestinal bacterial overgrowth,[79] perhaps because of delays in gut transit, hypochlorhydria due to atrophic gastritis or anti-acid secretory medications, and small intestinal diverticular disease.[80,81]

Clinical features of gut disorders in older people

Differential diagnosis of gastrointestinal disorders in older people might be more challenging due to the increased prevalence of risk factors and medication use,

and identification and description of symptoms might be less accurate in those with cognitive impairment.[51] Furthermore, management of gastrointestinal disorders and prevention of associated complications frequently requires diet adaptations, new medications, and lifestyle changes that might not be achieved due to a potential for low compliance or a lack of caregiver collaboration.[47]

Constipation

Constipation is a frequent concern in older adults, with women often having more severe constipation than men.[82] As constipation has a major impact on quality of life and the use of health-care resources, it is important to identify its cause, and management should be based on the patient's overall clinical status and capabilities. Common causes of constipation in older adults are pelvic floor dysfunction and slow colonic transit, but psychosocial and behavioural issues should also be considered.[82] Age-related reduction of peristaltic contractions leads to slower transit times and constipation, whereas segmental contractions (local contractions within parts of the small bowel that help in mixing) might be enhanced, contributing to discomfort and bloating.[82] Faecal impaction is a common consequence of constipation, psychiatric and neurological conditions, and DGBIs, and is defined as a large mass of compacted faeces that cannot be evacuated spontaneously.[83] Faecaloma damage to the wall (ie, increased secretion, distensibility, and pressure), the intestinal lumen, or adjacent structures can lead to clinical implications, including obstruction, pseudo-obstruction, megacolon, colitis, ulcer, perforation, and fistula.[83] Faecal impaction in the rectum with liquid stool leaking around the hard, dry faecal mass is often associated also with faecal incontinence.[83] In older people, the most likely causes of incontinence are atypical rectal compliance because of ischaemia, pelvic floor dysfunction, sphincter problems, faecalomas, or proctitis due to anal fissures with rectal fibrosis. Causes can also include diabetic neuropathy, neurological diseases (eg, dementia or stroke), depressive symptoms, poor self-care, and polypharmacy.[84] Well documented negative outcomes associated with polypharmacy in older people are adverse drug events; non-adherence; drug interactions; and malnourishment associated with reduced fibre intake, fat soluble and B vitamins, and minerals, and increased intake of cholesterol, glucose and sodium.[85] Malnutrition due to polypharmacy specifically could be explained by different mechanisms including dysgeusia, xerostomia, and gastrointestinal symptoms (anorexia, diarrhoea, nausea, and vomiting), which are commonly provoked by several drugs.[86]

Diarrhoea

The clinical impact of diarrhoea can be more complex in older people due to specific age-related factors, such as structural and functional intestinal changes, concomitant illnesses, their consumption of preventive and therapeutic medications, an impaired sense of hunger and thirst, and compromised nutrition and hydration. Although the development of diarrhoea is common at all ages, in older people some specific risk factors are present, such as polypharmacy, malabsorption syndromes, chronic diseases, and small intestinal bacterial overgrowth—a syndrome involving an excessive number of mainly coliform bacteria within the small intestine (figure 4).[51]

Among the infections that cause diarrhoea is *C difficile* infection, which is very common in older people (people aged ≥65 years who are in hospital or living in institutions represent ~70–80% of all infections) and might be increased in the setting of dysbiosis.[87] Immunosenescence, increasing use of antibiotics and gastric acid-suppressive medications, and frequent exposure to health-care environments have been reported as factors associated with the disease.[87] Additionally, decreased functional status, cognitive impairment, and frailty are increasingly being recognised as important and independent risk factors for poor outcomes among older adults, further enhancing the risk and severity of *C difficile* infection.[88]

Diverticulosis, mesenteric ischaemia, and lower gastrointestinal bleeding

The prevalence of diverticulosis increases progressively with age. In one US study of 624 outpatients undergoing colonoscopies, the presence of diverticula was detected more often in patients older than 60 years than middle-aged and younger adults. Older adults were also more likely to have multiple (>10) large or deep diverticula.[89]

Risk factors for diverticulosis in older adults include impaired colonic motility and wall resistance, low-fibre diet, and postmenopausal sex hormone changes in women. A role of dysbiosis and chronic mucosal inflammation has been postulated to explain the diverticula formation but still needs to be verified.[90]

The prevalence of chronic mesenteric ischaemia also increases dramatically with age.[91] Atherosclerotic vascular stenosis of one or more mesenteric arteries, more common in older age, is the cause in more than 90% of cases of chronic mesenteric ischaemia.[92] In older adults, factors such as reduced collateral pathways and pain perception could lead to severe chronic mesenteric ischaemia complications including bleeding related to the rupture of the intestinal wall in cases of severe tissue infarction.

Other potential causes of overt or occult lower gastrointestinal bleeding in older adults are summarised in the table and can be of anatomic, vascular, inflammatory, neoplastic, or iatrogenic origin.[51] Cardiovascular, respiratory, and renal comorbidities, often reported in the older population, might worsen the severity and prognosis of lower gastrointestinal bleeding.[93] Furthermore, the widespread and chronic use of medications, such as NSAIDs, antiplatelet agents, and

anticoagulant agents, could increase the risk of lower gastrointestinal bleeding.[93]

Frailty and the multidimensional approach to the older patient

Chronological age alone cannot explain all the structural and functional changes of the luminal gastrointestinal tract that occur during ageing.[94] Frailty is a condition that might capture the complexity of older patients, providing a better estimate of real biological, rather than just chronological, age.[95] For example, older people with the same chronological age, but different levels of chronic low-grade inflammation (one of the putative drivers of accelerated ageing and thus of frailty) might have a different evolution of luminal gastrointestinal tract changes over time.[95] Frailty is defined as a clinical condition characterised by declines in functioning across multiple organ systems and an increased risk of negative health outcomes, including admission to hospital, admission to long-term care facilities, and mortality. It is more common in women and its prevalence and incidence increases with advancing age.[96] Notably, frailty is multidimensional in nature, encompassing physical, functional, and psychosocial factors that interact with acute and chronic diseases and drug treatments (frequently polytreatments in older people).[97] The presence of frailty could directly influence the prognosis and management of older patients with gastrointestinal tract disorders, and might be useful in informing clinical decisions. For example, independent of age, prefrail and frail middle-aged and older people have been shown to have a higher risk of gastro-oesophageal reflux disease compared with non-frail people.[6] Furthermore, gut dysbiosis has been associated with accelerated ageing and frailty in older adults.[98,99] Therefore, as suggested by the European Medicines Agency, it is important to assess frailty with a multidimensional approach, such as by using the Comprehensive Geriatric Assessment (CGA),[100] to better personalise the clinical management of patients with gastrointestinal diseases, including acute treatment, long-term follow-up, and the prevention of recurrences

	Diarrhoea		Constipation	
	Young adult	Older adult	Young adult	Older adult
1	Infections (viral, bacterial, or parasitic)	Polypharmacy and drugs: antibiotics, digoxin, metformin, diuretics, proton-pump inhibitors, anticholinergic agents, levodopa, alprazolam, antidepressants, drugs causing colitis (NSAIDs or chemotherapy), laxatives with osmotic activity (lactulose or sodium sulphate)	Low-fibre diet, dehydration	Reduced mobility
2	Poor food hygiene, contaminated water	*Clostridioides difficile* infection	Psychological factors (eg, stress, anxiety, or depression); social factors (eg, ignoring the urge to defecate or changes in routine)	Drugs: opiates, tramadol, NSAIDs, anticholinergic agents, calcium channel blockers, tricyclic antidepressants, dopaminergic agents, diuretics, phenothiazine derivatives, anticonvulsants
3	Dietary triggers (coffee, dairy, or artificial sweeteners); food intolerance (eg, lactose)	Changes in gastrointestinal physiology (eg, hypochlorhydria or achlorhydria due to gastric atrophy, small intestinal bacterial overgrowth)	Sedentary habits	Low-fibre diet, impaired sense of hunger and thirst
4	IBS, IBD, coeliac disease, hyperthyroidism	Malabsorption syndromes with pancreatic exocrine insufficiency	IBS, IBD	Reduction of peristaltic contractions leading to slower transit times
5	Stress and anxiety	Chronic diseases (eg, diabetes, hyperthyroidism, IBD, IBS, cancer, dementia, or stroke)	Drugs (opiates, NSAIDs, antacids, iron supplements, antihistamines, antidepressants, antiemetics, or calcium channel blockers)	Hypothyroidism, Parkinson's disease, dementia, diabetes, stroke
6	Drugs: antibiotics, metformin, proton-pump inhibitors, laxatives, chemotherapy, antidepressants	Initial clinical manifestation of faecal impaction	Hormonal factors during menstruation, pregnancy, or with oral contraceptives (in women)	Pelvic floor dysfunction, impairment in neural and motor control, impairment of the rectal perception of the presence of faeces
7	Traveller's diarrhoea	Surgical history (eg, bowel resection or cholecystectomy)	Neurological or structural abnormalities (eg, Hirschsprung's disease)	Social factors (eg, inadequate access to toileting, or suppression of urge); psychological factors (eg, depression or anxiety)

Figure 4: **Factors predisposing people to diarrhoea and constipation**[51]
Predisposing factors are listed from highest to lowest estimated prevalence and clinical impact, from red (highest prevalence) to white (lowest prevalence). IBD=inflammatory bowel disease. IBS=irritable bowel syndrome. NSAIDs=non-steroidal anti-inflammatory drugs.

and complications.[101] A previous study reported that the Multidimensional Prognostic Index (MPI)—a validated clinimetric prognostic tool derived from data collected from a standard CGA and based on the integrated assessment of individual functional (ie, basal and instrumental activities of daily living), cognitive, nutritional, and psychosocial characteristics, along with comorbidity and polypharmacy—had high accuracy in predicting short-term and long-term mortality in older patients with acute upper gastrointestinal bleeding. The MPI also showed a greater discriminatory power for predicting 1-month mortality than the organ-specific, prognostic Rockall and Glasgow–Blatchford scores.[102] In a 2023 population-based cohort study of 457 older patients (aged ≥60 years) with *C difficile* infection, MPI-assessed frailty was significantly more accurate in predicting 3-month mortality than chronological age and the severity of *C difficile* infection.[103] MPI score was also strongly associated with postoperative major complications in older patients (≥75 years) undergoing elective colorectal cancer surgery in one cohort study.[104] Furthermore, a randomised clinical trial of 217 older patients (≥70 years) with *C difficile* infection showed that early CGA and frailty evaluation, through the MPI, was significantly associated with fewer deaths directly attributable to the infection after 3 months' follow-up than standard of care (44% *vs* 82%, p=0·020).[105]

These findings further support the concept that a multidimensional and interdisciplinary approach is warranted in the management of older people with gastrointestinal disorders, particularly in patients with comorbidities, polypharmacy, and frailty. A CGA-based method could promote a personalised clinical approach to help to both avoid ageist undertreatment for patients deemed too complex to treat, and to limit the use of unnecessary interventions.[95] A multidisciplinary process, incorporating health-care professionals' expertise, patients' preferences, and caregiver options and preferences, is crucial to reach shared clinical decisions. Such an approach favours diagnostic, prognostic, and therapeutic management that is tailored individually, as recommended by experts in frailty,[8] supported by evidence from umbrella reviews and meta-analyses,[106] and recommended in guidelines for the clinical management of older people.[107]

Conclusion

Age-related anatomical and functional changes in the luminal gastrointestinal tract have clinical implications in older people. The ageing luminal gastrointestinal tract has slower and impaired kinetics, is less resilient to injury, and less capable of defending itself from irritants such as NSAIDs and *H pylori*. Older adults often present with atypical, non-specific symptoms, making timely diagnosis a challenge. Understanding anatomical and functional changes will allow physicians to better diagnose, manage, and prevent gastrointestinal diseases in the older population. Luminal gastrointestinal changes might arise in older people who are already frail, multimorbid, and polytreated. In this context, the use of a CGA for the assessment of multidimensional frailty might be useful, although further evidence is needed to verify utility in different luminal gastrointestinal disorders.

Search strategy and selection criteria

We searched MEDLINE (PubMed) using MeSH and free terms in the English language (both UK and US spellings) for the concepts of "frailty", "ageing", "aging", "senescence", "elderly", "older", and "geriatric assessment" matched with "esophagus", "oesophagus", "stomach", "gut", "small bowel", "colon", "upper gastrointestinal tract", "lower gastrointestinal tract", "microbiome", and "microbiota", among articles published from database inception in 1996 to Dec 18, 2024. Highly relevant studies from outside of these publication dates were also considered. We restricted the search to only English-language papers. More than a thousand papers were found with this search strategy, the majority of which were unrelated to the subject of this Review and were not considered. We selected only studies exploring the possible link between age-related changes of the luminal gastrointestinal tract and their clinical consequences on the most frequent upper gastrointestinal and lower gastrointestinal disorders in older people.

Contributors

AP: conceptualisation and writing (review and editing). CC, LC, and WM: writing (original draft) and visualisation. NV: methodology and writing (original draft). MF: writing (review and editing).

Declaration of interests

AP received speaker honoraria from GSK and Thermo Fisher Scientific, and is General Secretary of the European Interdisciplinary Council on Ageing (unpaid). All other authors declare no competing interests.

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