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Exploring the Link between Constipation and Cardiovascular Risk: Evidence and Mechanisms

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Abstract

Background & Objectives: Constipation, characterized by infrequent bowel movements and related symptoms, is increasingly recognized as a potential predictor for cardiovascular diseases (CVD), including myocardial infarction, atrial fibrillation, peripheral artery disease, stroke, heart failure, and major adverse cardiac events (MACE). This literature review aims to evaluate the current evidence linking constipation with cardiovascular outcomes, understand potential underlying mechanisms, and identify gaps requiring further research. **Methodology:** A comprehensive review was conducted, analyzing observational cohort studies, population-based studies, Mendelian randomization studies, systematic reviews, and meta-analyses. These studies were evaluated for their findings, methodological strengths, limitations, and adjustments for confounding factors. **Results:** Several studies revealed significant associations between constipation and cardiovascular outcomes. A Danish cohort study (n = 83,239) demonstrated increased risks for myocardial infarction (1.24-fold), atrial fibrillation (aHR 1.27), peripheral artery disease (aHR 1.34), and heart failure (aHR 1.52) in patients with constipation. A systematic review

and meta-analysis reported a 41% increased stroke risk, particularly ischemic stroke (50% higher). Additionally, analysis of the UK Biobank data indicated a significant association between constipation and increased risk of MACE. Proposed mechanisms include gut dysbiosis, systemic inflammation, vagal nerve stimulation, increased intra-abdominal pressure, and medication-related electrolyte disturbances. **Conclusion:** Constipation is associated with increased cardiovascular risk, implicating potential mechanisms such as gut microbiota alterations, inflammation, and physiological stress during bowel movements. Despite robust observational associations, establishing causality remains essential, necessitating future Mendelian randomization and clinical intervention studies. Enhanced understanding and targeted management strategies may significantly impact cardiovascular outcomes, particularly in high-risk populations such as elderly individuals, diabetics, and patients with existing heart failure.

Keywords

Constipation, Cardiovascular Disease, Myocardial Infarction, Stroke, Atrial Fibrillation, Heart Failure, Peripheral Heart Disease, Bowel Dysfunction, Major Adverse Cardiac Events, Mace, Gut Microbiota, Intra-Abdominal Pressure, Electrolyte Imbalance, Short Chain Fatty Acids

1. Introduction

Constipation is defined clinically as the passage of three or fewer stools per week, with patients frequently complaining of difficulty and straining [1]. Stools are often described as hard, lumpy, and incompletely evacuated with corresponding diffuse abdominal pain and bloating [2]. Traditionally, constipation is viewed as a benign condition that poses significant quality-of-life issues that can lead to more serious complications, such as fecal impaction [3]. There is growing recognition of constipation's systemic relevance, as studies have associated it with increased incidence of cardiovascular and inflammatory complications [4]. Rates of venous, especially splanchnic, venous thrombosis, myocardial infarction, stroke, and peripheral artery disease have been significantly linked to patients with constipation [4]. The mortality risks, even among laxative users, are shown to increase with constipation significantly [5]. This recent link between constipation and cardiovascular disease is clinically meaningful as both share significant risk factors and contribute to systemic inflammation. Hypertension, western dietary patterns, and diabetes mellitus are some of the many risk factors that ultimately contribute to the risk of major adverse cardiac events [6]. Increased C-reactive protein (CRP) levels in constipation further highlight the inflammatory manifestations that affect major chronic diseases and mortality risks [7]. The aim of the review is to evaluate the existing evidence linking constipation to cardiovascular disease, explore proposed biological mechanisms and discuss clinical relevance and research gaps.

2. Definition, Prevalence, and Diagnostic Challenges

Constipation is a complex and multifactorial condition with a significant healthcare burden in the U.S. and the world. Differences in how constipation is defined globally have led to a wide range of reported prevalence; however, estimates suggest that constipation affects 15% - 20% of the global population [8]. The elderly are at a 20% increased risk of chronic constipation compared to younger populations, and elderly women, in particular, have a 2 - 3 times higher risk of constipation than elderly men [9]. Similar discrepancies are also seen in pregnant and premenopausal women when compared to their male counterparts. Besides age and sex, other risk factors include low fiber and water intake, sedentary lifestyle, socioeconomic status, and concurrent usage of pharmaceuticals like antipyretic, antidepressant, and antiepileptic drugs [10] [11].

The term 'constipation' is non-specific, which makes direct comparison and meta-analysis across studies difficult, as its diagnosis can be based on subjective symptoms. Nevertheless, the Rome IV criteria, which were updated from the Rome III in 2016, outline the most accepted current definitions for chronic constipation and its subtypes [12]. Patient reports are still a key aspect of these definitions, but the use of the Bristol Stool Form Scale (BSFS) to characterize stool appearance and consistency increases reliability. The first subtype, Irritable Bowel Syndrome with Constipation (IBS-C), is defined under Rome IV as recurrent abdominal pain greater than 1 day per week for the last three months and associated with two or more of the following criteria: pain related to defecation, pain associated with a change in frequency of stool, pain associated with a change in form/appearance of stool. Abnormal bowel movements in IBS-C must also be consistent with BSFS types 1 or 2, greater than 25% of the time, and BSFS types 6 or 7, less than 25% of the time. Functional Constipation, the next subtype, is defined as the presence of two or more of the following: straining for >25% of defecations, lymph or hard stools (BSFS 1 - 2) for >25% of defecations, sensation of incomplete evacuation for >25% of defecations, sensation of anorectal blockage for >25% of defecations, manual manoeuvers to facilitate >25% of defecations, and fewer than 3 spontaneous bowel movements per week [8]. The Rome IV criteria acknowledge the apparent overlap between IBS-C and functional constipation, stating that functional defecation disorder diagnoses may be made on the symptom criteria of either condition. Rome IV also includes opioid induced constipation (OIC) as another subtype due to the increasing relevance of opioids in clinical practice, defining OIC as new or worsening symptoms of constipation following the initiation or change in opioid therapy, using the same symptom and frequency cut-off as other subtypes (>25% BSFS type 1 - 2) [12]. Despite frameworks like the Rome IV criteria, there remains ambiguity between constipation subtypes and variability across the literature in how constipation is defined.

3. Methodology

Objective

The aim of this systematic review is to present current evidence regarding the association between constipation and cardiovascular risks. We chose this study population because of the prevalence of constipation and cardiovascular issues seen in the elderly population. These cardiovascular risks include myocardial infarctions (MIs), strokes, atrial fibrillation, heart failure, peripheral artery disease, and major adverse cardiac events (MACE). This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. PRISMA provided this review as a guideline that would describe the methodology and reproducibility.

Search Strategies

The systematic literature review search used PubMed, Google Scholar, Embase, Scopus, and Cochrane Library. The search was performed between March 1, 2025 and April 10, 2025. We gathered studies from 2002 to 2025. The following keywords were used in the search: constipation, cardiovascular disease, myocardial infarction, stroke, atrial fibrillation, heart failure, peripheral heart disease, bowel dysfunction, major adverse cardiac events (MACE). Additional keywords also included gut microbiota, intra-abdominal pressure, electrolyte imbalance, dietary fiber and short-chain fatty acids. Boolean operators were also used to refine the search. Terms such as constipation and cardiovascular disease were used in the search query.

Inclusion Criteria

Studies that were included were based on study design, population, outcomes, and reporting. The inclusion criteria for this paper were: (a) Peer reviewed studies, mendelian randomization studies, systematic reviews and meta-analysis using adults aged 18 years or older; (b) Having constipation as a risk factor; (c) Studies that reported on cardiovascular outcomes such as myocardial infarction, stroke, atrial fibrillation, heart failure, peripheral artery disease, and MACE; (d) Studies that gave their effect estimates with confidence intervals and adjustments for confounding variables. Studies addressing potential mechanistic links including alterations in gut microbiota, inflammatory markers, electrolyte imbalance, Valsalva maneuver, and dietary fiber intake were included if it either directly or indirectly had a link to constipation cardiovascular outcomes in humans.

Exclusion Criteria

The studies that were not included in our paper included non-human studies, non-peer-reviewed publications, populations less than 18 years old, studies that did not measure cardiovascular complications with constipation, and studies that did not adjust for confounding variables.

Study Selection and Discrepancy Resolution

Study selection was conducted independently by multiple reviewers, each of whom was assigned to specific sections of the review. Titles and abstracts were screened by individual reviewers based on the pre-set inclusion and exclusion criteria. Full-text articles were assessed for eligibility within each assigned section. Duplicate publications were screened to avoid repetition. Inclusion decisions were

taken based on each reviewer's own judgment within the scope of their section.

Data Extraction and Synthesis

Data extraction was conducted using key information that was captured for each study, which included the following: study characteristics such as design and sample size, demographics of the population, including age and sex, and definitions of constipation (self-reported and clinical) and cardiovascular outcomes tested. Demographics such as age and sex were recorded, as well as cardiovascular outcomes measured in each study.

PRISMA

Using the guidelines mentioned above, Figure 1 contains the study selection flow chart.

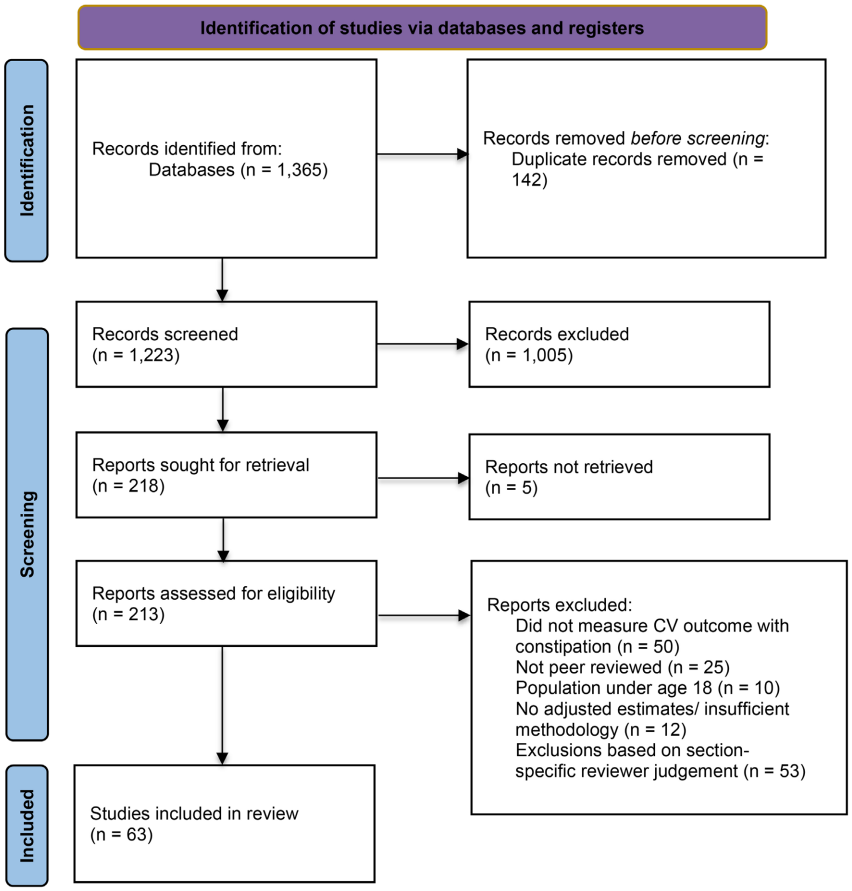

Figure 1. PRISMA 2020 Flow Diagram: Process in selecting study for systematic review of the association between CV risks and constipation.

4. Epidemiological Evidence Linking Constipation to Cardiovascular Disease

Epidemiologic evidence has suggested that constipation may be a possible risk factor for cardiovascular disease and its subtypes. Investigators have begun exploring this link via observational studies, but outcomes have varied and causation has yet to be confidently established. Prospective cohort, retrospective cohort, and

cross-sectional studies have been employed across different populations to work towards establishing an association between CVD and constipation. A Danish cohort study demonstrated an increased risk of several cardiovascular diseases, especially VTE, in patients experiencing constipation [4]. Cohort studies like these serve as a foundation in forming positive associations that guide subsequent research, such as Mendelian randomization studies and meta-analyses. MR studies and meta-analyses are key in strengthening evidence for a causal relationship and increasing statistical power, respectively. For example, a two-sample MR analysis revealed causal associations between atrial fibrillation and constipation [13]. MR studies such as these have great potential to enhance results of other observational studies, as they utilize genetic variables that are not influenced by confounders. The following paragraphs will explore the major findings of multiple epidemiologic design types, including cohort, cross-sectional, Mendelian randomization, and meta-analysis.

Cohort studies serve as excellent starting points in exploring the link between cardiovascular disease and constipation. As mentioned above, the Danish population-matched cohort study used comorbidity- and medication-adjusted hazard ratios (aHRs) to retrospectively measure CVD outcomes in patients with constipation [4]. Sundbøll *et al*. (2020) matched 83,239 constipated individuals 1:10 with 832,384 non-constipated individuals for age, sex, and calendar year. CVD outcomes were then assessed using cases of myocardial infarction (MI), stroke, peripheral artery disease (PAD), venous thromboembolism (VTE), atrial fibrillation (AF), and heart failure (HF). Based on the aHR values, it was determined that constipation is significantly associated with each of these CVDs, especially VTE (aHR = 2.04) [4]. Furthermore, since definitions of constipation may vary, it's important to note that Sundbøll *et al*. define constipation in two ways: 1) A primary or secondary inpatient diagnosis using ICD-10 code K59.00, or 2) Outpatients with a laxative prescription. The addition of laxatives in the definition of constipation left the association outcomes unchanged. Overall, the approaches to minimize confounders and the large sample size of this study provide reliable evidence of a likely association, offering a solid basis for further comparison and analysis.

To begin identifying patterns in this data, it may be beneficial to introduce another retrospective cohort study. Zheng *et al*. (2024) examined 408,354 participants from the UK Biobank to determine the role of constipation on CVD. CVD outcomes here are defined as MACEs, or major adverse cardiac events, which capture episodes of acute coronary syndrome (ACS), ischemic stroke, and HF. Additionally, an official diagnosis (ICD-10 K59.00) was used to select constipation cases. After controlling for CVD risk factors and medications, the study concluded that those diagnosed with constipation are up to 2.5x more likely to experience MACEs compared to their non-constipated counterparts [6]. HF specifically had the most statistically significant association with constipation (OR = 2.72, $P < 1.00 \times 10 - 300$), followed by ischemic stroke (OR = 2.36, $P = 2.02 \times 10 - 230$). Moreover, findings from this UK Biobank study were analyzed alongside seven addi-

tional observational studies in a systematic review and meta-analysis from Suenghataiphorn *et al*. (2024), which displayed a 50% increase in ischemic stroke risk in constipated patients [14]. This study provided a summary of results from 5,360,573 participants that compared stroke incidence (ischemic, hemorrhagic, and mixed-type) between constipated and non-constipated individuals. ICD-10 codes, self-reports, and the Rome IV Diagnostic Criteria were used to define constipation across the studies reviewed. Despite the lack of uniformity across constipation definitions, a statistically significant association between constipation and stroke risk was thoughtfully demonstrated.

The evidence presented above has indicated strong associations between constipation and CVD risk, however, a positive association does not imply causation. Mendelian randomization studies can use genetic variants associated with constipation to explore this prospective causal relationship. Results from these studies are important in furthering research, as the nature of MR analysis can bypass more confounders than a traditional cohort study. Dong *et al*. (2023) used three MR methods to evaluate SNPs linked to constipation and their relationship to CVD, specifically CAD, MI, HF, AF, stroke, and stroke subtypes (LAS, SVS, and CES) [13]. Ultimately, only AF showed a significant association with constipation. This implicates constipation as a risk factor for AF, which reinforces the link found in the Danish cohort study. Similarly, Du *et al*. (2023) also employ MR analysis to genetically examine constipation and CVD, but with a focus on ischemic stroke, including LS, LAS, SVS, and CES [15]. Out of each type of ischemic stroke measured, only LAS was found to have a significant link to constipation. The discrepancy between these two MR studies regarding large artery atherosclerosis may be due to differing methodological choices, such as the genetic variants chosen or varying sample sizes. Nonetheless, these findings continue to promote a broader understanding of overall cardiovascular risk.

To expand on the consistency of these outcomes, it's important to recognize that there is no universally accepted definition of constipation. As a result, there is an intrinsic inconsistency when attempting to compare constipation research. Each study also chooses to evaluate CVD in a different way, with some studies narrowing in on ischemic stroke, and others investigating a more comprehensive list of subtypes. Generalizability may also be limited, as the majority of the data from the featured cohort studies was sampled from those of European descent. Despite this, major findings from the Danish study and the UK Biobank study were still valuable in providing simple associations between constipation and various CVD outcomes of interest [4] [6]. Alone, these studies are inherently limited in avoiding reverse causality bias and unmeasured confounding variables such as inactivity, diet, obesity, medication, and immobilization [4]. To mitigate these limitations, MR studies are critical because genetic variables are mostly fixed. When MR results corroborate the findings of observational studies, suspected associations can be strengthened and deemed causative. With that being said, AF and ischemic stroke should be highlighted as having the most notable associations

with constipation. Individual cardiovascular disease subtypes need to be explored in greater depth to gain a better understanding of the impact of constipation on cardiovascular health.

5. Constipation and Specific Cardiovascular Conditions

Myocardial Infarction (MI)

The relationship between constipation and myocardial infarction (MI) has been increasingly substantiated by population-based studies. A Danish cohort study involving over 83,000 participants demonstrated a significantly elevated hazard ratio (HR) of 1.24 (95% CI: 1.15 - 1.34) for MI in individuals with constipation after adjusting for cardiovascular risk factors [4]. This shows a modest yet clinically relevant association between constipation and MI, highlighting the potential importance of gastrointestinal health in cardiovascular outcomes.

Mechanistically, chronic straining during defecation may provoke transient surges in blood pressure and sympathetic nervous system activation, thereby elevating myocardial oxygen demand and predisposing to ischemic events [16]. Low dietary fiber has been shown to independently increase the risk of ischemic heart disease. Low dietary fiber intake which is a common underlying contributor to constipation is independently linked with a higher risk of coronary artery disease [17]. This highlights the fact that dietary habits may confound the relationship between constipation and cardiovascular health.

Recent studies suggest a potential dose-response relationship between constipation severity and the risk of myocardial infarction (MI). More severe or chronic constipation may increase this risk, although further detailed analyses are required to confirm this pattern [18]. Constipation's impact on cardiovascular health underscores the importance of managing gastrointestinal health to potentially mitigate cardiovascular risks. Understanding these associations could lead to better preventive strategies for cardiovascular diseases in individuals with chronic constipation.

Atrial Fibrillation (AF)

Emerging studies indicate a link between constipation and increased risk of atrial fibrillation (AF). Sundbøll *et al.* cited earlier found a significant association between constipation and AF (aHR 1.27; 95% CI: 1.19 - 1.35) (95% CI: 1.20 - 1.35) [4]. One proposed mechanism is autonomic imbalance. Straining induces vagal stimulation, followed by reflex sympathetic activation, potentially disrupting cardiac electrophysiological stability [6]. A population-based cohort study from Australia also reported an increased risk of AF among elderly patients with chronic constipation [19]. The act of straining can lead to transient vagal stimulation followed by sympathetic overactivity, a combination known to trigger atrial arrhythmias.

Autonomic dysfunction is common in patients with chronic constipation, particularly those with coexisting diabetes or neurogenic bowel disorders, further supporting a shared pathophysiological basis. Gut-brain axis alterations and mi-

crobial dysbiosis may also modulate atrial substrate via systemic inflammation and autonomic tone [20]. Sun *et al*. discuss how gut dysbiosis may influence atrial remodeling and dysfunction, contributing to the pathogenesis of atrial fibrillation [21]. Gut dysbiosis, characterized by an imbalance in microbial composition, leads to increased production of pro-inflammatory metabolites such as trimethylamine N-oxide (TMAO) and lipopolysaccharides (LPS). These metabolites can activate inflammatory pathways, notably the NLRP3 inflammasome, resulting in atrial fibrosis and electrical remodeling—key substrates for AF initiation and maintenance [22]. Gut-derived LPS has been shown to modulate autonomic nervous system activity, enhancing sympathetic tone and reducing vagal influence, thereby promoting arrhythmogenesis [21]. These studies highlight the possible autonomic and inflammatory mechanisms at play in AF.

Peripheral Artery Disease

Peripheral artery disease (PAD) and constipation appear to share overlapping etiologic pathways, particularly systemic inflammation and endothelial dysfunction. A cross-sectional study in patients with type 2 diabetes revealed a significantly higher prevalence of vascular complications, including PAD, among those with comorbid constipation [23]. Inflammatory cytokines such as TNF-α and IL-6, which impair vascular health, are also implicated in the pathogenesis of functional bowel disorders. Inflammatory cytokines implicated in bowel dysmotility, such as TNF-α and IL-6, also contribute to endothelial damage and arterial plaque formation [24]. Furthermore, sedentary behavior may function as a shared behavioral risk factor. Reduced mobility can compound atherosclerotic risk, particularly in elderly and diabetic cohorts [23]. The relationship between constipation and PAD is likely multifactorial.

Stroke (Particularly Ischemic Stroke)

Several meta-analyses have confirmed a significant association between constipation and increased risk of stroke, especially ischemic subtypes. Constipation appears to carry an elevated risk for ischemic stroke, with a meta-analysis reporting a pooled relative risk (RR) of 1.41 (95% CI: 1.17 - 1.69) for stroke overall, and a 50% increased risk for ischemic stroke specifically [14]. Straining during defecation can induce abrupt changes in cerebrovascular dynamics. Physiological strain during defecation can result in transient spikes in systemic blood pressure and intrathoracic pressure (Valsalva maneuver), increasing the likelihood of thromboembolism and cerebrovascular events in predisposed individuals [25]. It is important to note that shared risk factors, such as advanced age, sedentary lifestyle, and diabetes, may compound the association. In patients with atrial fibrillation, the overlap of constipation-related autonomic changes and proarrhythmic conditions may further elevate the stroke risk.

Heart Failure and Major Adverse Cardiac Events (MACE)

Constipation has been independently associated with worsened outcomes in patients with heart failure (HF). Ishida *et al*. demonstrated that comorbid constipation significantly increased all-cause mortality and readmission rates in patients

with HF [26]. The physiological burden of constipation can exacerbate fluid imbalance and impact medication efficacy, notably in patients on diuretics [27]. Bowel dysfunction may affect fluid balance, especially in those using osmotic laxatives that alter intravascular volume or electrolytes, leading to hemodynamic instability. Also, frequent use of magnesium-containing laxatives in this population could precipitate electrolyte disturbances further compromising cardiac conduction [28]. Impaired gastrointestinal perfusion due to low cardiac output may worsen gut dysbiosis and perpetuate inflammation, creating a vicious cycle.

Constipation is also linked with increased risk of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal MI, and stroke. A separate analysis of the UK Biobank reported a significant association between constipation and increased incidence of MACE, even after adjusting for common confounders [6]. The findings suggest that constipation may be an independent risk factor for MACE and may warrant further investigation into its role in cardiovascular disease. The researchers also noted the need for further research to explore the specific mechanisms by which constipation might increase MACE risk.

Conflicting Evidence

Despite the growing body of evidence, not all studies have found a significant association between constipation and cardiovascular disease. A two-sample Mendelian randomization (MR) study found no clear genetic link between constipation and cardiovascular disease, suggesting the association may be confounded by shared lifestyle or clinical factors [13]. The discrepancy may also arise from variation in the definition and severity of constipation across studies, residual confounding, and reverse causality. These discrepancies may stem from heterogeneity in defining constipation, varying follow-up durations, or inadequate adjustment for confounders such as physical inactivity, depression, and medication side effects. The reliance on self-reported data in some studies also introduces the risk of misclassification bias.

Li *et al*., using NHANES data, reported no statistically significant association between self-reported constipation and cardiovascular mortality after adjusting for age, sex, comorbidities, and medication use [29]. These discrepancies may stem from heterogeneity in defining constipation, varying follow-up durations, or inadequate adjustment for confounders such as physical inactivity, depression, and medication side effects. The reliance on self-reported data in some studies also introduces the risk of misclassification bias.

Itano *et al*. suggested that drug use for constipation may itself be associated with increased cardiovascular mortality, reflecting possible reverse causality or confounding by severity [30]. The use of over-the-counter laxatives, which are often unreported, may independently affect cardiovascular parameters, further complicating interpretation.

Future research should focus on clarifying causality through longitudinal designs, standardized definitions, and Mendelian randomization studies. Investigating the impact of treating constipation on cardiovascular outcomes may further

elucidate the directionality of this relationship.

6. Biological Mechanisms Linking Constipation to Cardiovascular Risk

The medical community tends to view constipation as a trivial digestive issue, yet research shows it creates a hidden relationship between gut health and heart function [7]. Research now shows that persistent constipation acts as a cardiovascular risk factor through gradual changes in inflammation levels and autonomic signaling and vascular dynamics and electrolyte balance [31]. The observed links between constipation and cardiovascular disease appear in two forms: statistical patterns in large population data and biological mechanisms at the tissue, molecular, and microbial levels. The following analysis separates observational connections from experimental evidence that supports causality in these mechanisms. Studies show that extended constipation causes systemic inflammation and affects autonomic function, vascular dynamics, and electrolyte balance, which together may result in atherosclerosis, arrhythmias, and other cardiac events. The primary cardiovascular risk link between constipation exists through gut dysbiosis, which describes modifications in the gut microbiota.

Gut Dysbiosis

Gut dysbiosis refers to the condition where the gut microbiota loses its equilibrium between microbial populations and metabolic operations. The gut microbiota imbalance in constipated individuals presents two primary characteristics, which involve elevated trimethylamine N-oxide (TMAO) production and reduced short-chain fatty acid (SCFA) levels. The biologically active metabolites influence cardiovascular system functions. TMAO oxidation occurs in the liver following gut microbial conversion of dietary nutrients, including choline and L-carnitine [16]. Experimental studies show that this change leads to an increase in trimethylamine N-oxide (TMAO), which is produced by microbial digestion of choline and carnitine, and a decrease in short-chain fatty acids (SCFAs), including butyrate and propionate. TMAO accelerates atherosclerosis, disrupts cholesterol transport, increases platelet aggregation, and induces endothelial dysfunction in animal models. These findings move beyond suggestion—they form mechanistic evidence that gut microbes, through their metabolic signatures, help write the vascular fate of the host. SCFAs, by contrast, are guardians of vascular calm [7]. They tighten the gut barrier, lower blood pressure, and dampen inflammation [31]. When constipation reduces fiber fermentation, these protectors vanish like sentinels abandoning their posts. In humans, elevated TMAO and low SCFA levels have been consistently associated with cardiovascular events across prospective cohorts, painting a strong but still correlational picture [31].

Research indicates that elevated TMAO levels directly increase the risk of atherosclerosis while causing adverse cardiovascular effects [31]. The study by Zheng *et al.* (2024) found that TMAO causes endothelial dysfunction through increased oxidative stress and decreased nitric oxide availability, produces foam cells during

cholesterol metabolism, disrupts reverse cholesterol transport, and results in platelet hyperreactivity, which increases thrombosis risk [6]. The fermentation of dietary fiber by the gut microbiota produces beneficial metabolites, which include acetate, propionate, and butyrate that form the SCFAs. The molecules work to maintain gut barrier strength while reducing inflammation and regulating blood pressure levels. The decreased SCFA production in constipated individuals with disturbed gut flora results in elevated gut permeability and systemic inflammation and hypertension, which serve as cardiovascular disease risk factors [7]. The proatherogenic environment developed from constipation-induced gut dysbiosis with elevated TMAO and reduced SCFAs activates multiple disease pathways that include inflammation, endothelial dysfunction, and thrombosis. The link between persistent constipation and elevated cardiovascular risk becomes clearly apparent because of this relationship.

Systemic Inflammation

The connection between constipation and cardiovascular risk exists mainly through chronic low-grade inflammation, which occurs because of increased gut permeability. The delayed movement of intestines in constipation causes changes in microbial environments and damage to gut lining structures. The weakened gut barrier allows bacterial fragments, including lipopolysaccharides (LPS), to pass through into the bloodstream [32]. The circulating molecules activate the immune system to produce inflammatory cytokines after they enter the bloodstream. The prolonged immune system activation from this process leads to blood vessel damage, which results in the formation of atherosclerosis [33]. Research conducted recently discovered that chronic constipation leads to the accumulation of linoleic acid metabolites, which trigger inflammation. The compounds disrupt immune regulation through their suppression of regulatory T cells and their attraction of pro-inflammatory macrophages [34]. The inflammatory process enhances the risk of developing colitis while simultaneously making the body more susceptible to this condition. The reduction of gut function triggers multiple biological reactions that damage gut barriers while creating inflammation and raising cardiovascular risks.

The prolonged stasis in constipation causes changes in microbial composition and damages the intestinal lining, which enables lipopolysaccharides (LPS) and other bacterial fragments to pass through the mucosal wall much like a fortress collapsing from within [32]. Animal research demonstrates that dysbiosis caused by constipation leads to increased gut permeability and elevated circulating cytokines and inflammatory markers, which worsens the severity of encephalomyelitis and colitis [34]. The human evidence base consists mainly of observational studies. The connection between constipation-related systemic inflammation and cardiovascular events remains unclear because researchers have not established definitive proof.

Vagal Nerve and Straining Effects

Constipation triggers heart rhythm risks through straining mechanisms, which

many people perform during bowel movements. The Valsalva maneuver that occurs during straining produces similar effects as bowel movements do. The simple action creates noticeable effects on heart rhythms through vagus nerve activation, which may lead to bradyarrhythmias or severe cardiac incidents. The act of straining leads to an initial fast rise of chest pressure, which then reduces heart blood return for a brief period. The body reacts to maintain blood pressure stability by initiating a brief increase of sympathetic nervous system activity, which activates the "fight-or-flight" response [35]. The prolonged pressure increase activates baroreceptors that function as specialized pressure sensors located in the carotid artery and aorta. The protective reflex of baroreceptors causes the vagus nerve to activate and slow down the heart rate through the parasympathetic ("rest-and-digest") nervous system. Vagal-induced bradycardia represents the heart rate reduction that occurs from this slowing [35]. Studies conducted on animals have clearly shown this phenomenon. The researchers in Hotta *et al*. (2009) used vagus nerve stimulation to observe major heart rate deceleration in rats along with occasional cardiac arrest [36]. According to Thompson *et al*. (1998), strong vagal activation of dogs and pigs through electrical stimulation resulted in substantial heart rate reductions that could produce dangerous cardiac arrhythmias [37]. Studies have shown that the relationship between sympathetic and parasympathetic systems becomes complex during changes in blood pressure. Research conducted by Kollai *et al*. (1978) showed that heart atria stretching resulted in initial sympathetic activation, which later shifted to increased parasympathetic (vagal) activity [38]. The relative strength between different branches of the nervous system determines the probability of dangerous cardiac events from straining. Straining due to constipation leads to vagus nerve activation, which causes dramatic heart rate slowing. Such vagal activation occurs mostly without consequences, yet it may cause fatal cardiac problems in individuals with cardiovascular problems.

The process of straining during bowel movements represents a four-stage physiological process which most people overlook. The process starts when intra-thoracic pressure increases before venous return decreases and sympathetic activation occurs. The baroreceptors located in the carotid and aortic arches trigger a vagal counter-response, which leads to heart rate deceleration [35]. Studies involving animals demonstrate that vagal stimulation produces severe heart rate slowing, which can result in complete cardiac stoppage [36] [37]. Research conducted on humans supports the physiological mechanisms that the American Heart Association has identified as a primary cause of arrhythmias in vulnerable patients [39]. The vagus nerve functions as both a conductor and a culprit because it maintains rhythm or creates arrhythmia [40].

Increased Intra-Abdominal Pressure

Constipation creates cardiovascular health risks through its effect on increasing the pressure inside the abdomen, which medical science defines as intra-abdominal pressure (IAP). The constant straining associated with constipation produces elevated abdominal pressure that reaches substantial levels. The medical

community considers abdominal pressure to be normal at low levels, yet they start to worry when it exceeds 12 mmHg. A pressure higher than 20 mmHg results in abdominal compartment syndrome, which causes organs to malfunction due to compression [41]. The mechanism operates as follows: Your abdominal pressure increase forces pressure into your chest cavity, which in turn increases the pressure surrounding your heart and lungs (intrathoracic pressure). The increased pressure makes it difficult for veins to send blood to your heart, thus decreasing the heart's pumping ability [42]. This elevated pressure has the potential to affect brain vein pressure among other things [43] [44]. Your abdomen contains veins, with the inferior vena cava being the largest, which gets compressed by increased pressure. This compression blocks blood circulation, which results in blood congestion. Fluid retention and deteriorating blood pressure occur because kidney function declines when they become congested [45]. High abdominal pressure in your body triggers the release of vasopressin hormones, which tighten blood vessels to increase blood pressure levels. The body responds through the Cushing reflex, which functions as a protective but dangerous mechanism because elevated abdominal pressure causes head pressure to increase [46]. The act of repeated straining from constipation produces changes in abdominal and chest pressure, which intensifies the strain on heart blood vessels. The management of abdominal pressure holds critical importance for people with heart disease risk factors.

The repeated strain on the body produces more than short-term pain because it leads to increasing intra-abdominal pressure (IAP), which modifies cardiovascular patterns. The increasing abdominal pressure compresses the inferior vena cava, which reduces venous return and cardiac output in a manner similar to how stepping on a garden hose reduces water flow [42]. Research involving human subjects and animals demonstrates that elevated IAP generates thoracic pressure while impairing renal perfusion and triggering neurohormonal responses through vasopressin release and Cushing reflex activation [47]. The cardiovascular system and brain experience increased stress because of these changes, especially among patients who have unstable hemodynamics.

Electrolyte Abnormalities Acquired from Medications

Patients who take laxatives and diuretics to treat constipation or fluid retention experience hypokalemia when their potassium levels drop below 3.5 mmol/L. A slight decrease in potassium levels seems harmless, yet it elevates the risk of developing dangerous heart rhythms, which are called arrhythmias. The electrical activity of heart cells depends heavily on potassium to function properly. The heart becomes more susceptible to arrhythmias when potassium levels decrease below a certain threshold. The sodium-potassium pump (Na/K-ATPase) operates as a vital controller to maintain heart cell electrical stability. The weakened operation of this pump by hypokalemia leads to sodium accumulation inside the cells [45]. The sodium accumulation triggers more calcium entry into the cells by activating another exchanger mechanism. When heart cells contain too much calcium, they generate abnormal electrical signals known as early afterdepolariza-

tions (EADs) and delayed afterdepolarizations (DADs), which create dangerous heart rhythms [48]-[50]. Low potassium levels create electrical instability in heart cells, which becomes a serious problem. The heart cells need longer to recover from each heartbeat when potassium levels are low because action potential duration extends in such conditions. The heart's electrical signals get stuck in a continuous loop because of this phenomenon, which produces severe arrhythmias, including ventricular tachycardia and ventricular fibrillation [51]. According to the American Heart Association clinical guidelines, hypokalemia directly causes severe heart rhythm problems that include premature ventricular contractions (PVCs), ventricular tachycardia (VT), torsades de pointes (TdP), and ventricular fibrillation (VF) [52]. The development of these arrhythmias elevates the risk of cardiac arrest and sudden death, particularly among patients who already have heart conditions. The common laxatives and diuretics prescribed for constipation have the unintended side effect of creating dangerously low potassium levels in patients. When potassium levels decrease, heart cells develop electrical instability, which creates conditions that can result in severe, life-threatening arrhythmias.

Constipation exists as a solitary condition only in rare instances. The use of laxatives and diuretics as treatments leads to a widespread decrease in serum potassium levels below 3.5 mmol/L. The heart's electrical system depends on potassium to maintain stability despite its seemingly insignificant nature [48]. Research conducted on animals and cells demonstrates that low potassium levels damage the sodium-potassium pump (Na^+/K^+-ATPase) and disrupt calcium homeostasis while producing early and delayed afterdepolarizations, which may develop into ventricular tachycardia or fibrillation [50]. The American Heart Association identifies hypokalemia as a primary cause of dangerous arrhythmias, which include torsades de pointes and sudden cardiac death [52].

7. Methodological Limitations in the Current Evidence Base

Existing literature presents various limitations that can affect the validity of the results achieved. Dong *et al.* reports a study investigating the link of cardiovascular disease and constipation through a Mendelian Randomization study, consisting of an analysis of the method used. This discussion of Mendelian Randomization considers the ability of the method to independently evaluate constipation on outcomes of cardiovascular conditions without confounding variables influencing the results [13]. Drawbacks mentioned include a limited number of genetic markers that were associated with significance along with a population that was Eurocentric, preventing further generalizability [13]. Thus, such Mendelian Randomization studies are beneficial to use for providing causal association of constipation and cardiovascular conditions, however, significance and wider application must be considered.

Studies performed on a population with pre-existing conditions were also analyzed for a connection among constipation and cardiovascular risk. For instance, the condition of post-menopausal women was chosen as a point of interest in an-

alyzing constipation and cardiovascular risk. However, the study conducted by Salmoraigo-Botcher *et al*., indicated that there were several confounding variables that may have been attributed to hormonal changes or other physiological changes that can contribute to cardiac conditions [53]. Additionally, certain self-reported data in regards to family history, diet, and physical activity were unverified or reduced to a "yes or no" option, limiting the scope and reliability of the information gathered [53]. Continuing the discussion of diet, physical activity, and pre-existing conditions, the investigators retrieved the information from participants and utilized it as a baseline to reduce potential for covariates. Additional factors affecting cardiovascular risk such as demographics, mental health, and family history were recorded from responses to an initial questionnaire, taken at baseline, and accounted for in analysis and presentation of results by statistical means of chi-square and Kruskal-Wallis tests. While the study adjusted for certain factors that were confounding, not all factors were mentioned and accounted for.

Most clinical studies performed in examination of constipation and cardiovascular conditions are centered around a particular population. In assessing the risk of constipation in a cohort study, the focus remained on the Danish population, within a specific hospital, providing difficulties when considering the applicability of the results in a broader scale [4]. The study adjusted for cardiac and constipation conditions, lifestyle factors, and medications associated with the aforementioned, improving validity of the results. However, physical inactivity and dietary habits were not adjusted for, impacting the reliability of the results and reducing generalizability in application to a wider population. Lifestyle factors such as obesity were deemed as in weak association with constipation and was not considered impactful to the results, despite its known correlation to cardiovascular disease. Additionally, the presence of surveillance and detection bias can skew findings considerably. Acknowledgement of the bias was accompanied with minimization of the bias due to acute onset and severe clinical course, yet a majority of the conditions tested for are characterized by those very terms, making it difficult to assign validity to the claims mentioned.

Consistently, the studies conducted have maintained a focus on European and American populations, which have a vast diversity from populations across the globe. A significant issue that arises from global scale studies is the large amount of variances that can occur in terms of lifestyle and environment, ultimately resulting in potential for increased or maintained confounding variables.

8. Clinical Implications and Management Approaches

Constipation has been associated with multiple cardiovascular events. Intestinal microbiota changes can induce blood pressure rise, atherosclerosis, congestive heart failure, atrial fibrillation, acute coronary disease, and aortic dissection [16]. The mechanism by which constipation induces hypertension is through increased water absorption and inflammation, as well as excessive straining, acutely increasing blood pressure by up to 70 mm Hg [19].

Fiber plays an important role in improving gastrointestinal and cardiovascular outcomes. Soluble fiber foods include gums, pectin, starches, and fructans, which are mainly present in fruits, vegetables, barely, and oats [54]. Soluble fiber exerts its effect by improving gut health as well as regulating blood sugar. Soluble fibers undergo fermentation, which regulates blood sugar levels via production of short term fatty acids such as butyrate, which can stimulate insulin secretion and insulin sensitivity in tissues, subsequently decreasing risk of diabetes [55]. Soluble fiber fermentation also leads to the production of glucagon-like peptide 1 (GLP-1) and peptide YY hormones, which inhibit glucagon release and increase insulin sensitivity [56]. Additionally, soluble fiber reduces LDL cholesterol levels by binding to bile acids and cholesterol in the digestive tract, which promotes their excretion and prevents absorption in the bloodstream (Purnima Gunness, 2010). Soluble fiber delays digestion time, which reduces total absorption of fats and cholesterol. Insoluble fibers mainly comprise cellulose, hemicellulose, brans, whole grains, seeds and nuts [54]. Insoluble fiber aids in promoting regular bowel movements and has been shown to help reduce risk of colorectal cancer [55]. Digestive regularity is promoted through rapid gastric emptying, which leads to decreased transit time and increased fecal bulk. Insoluble fibers inhibit the growth of cancer cells via detoxification of carcinogens [57]. Adequate hydration is another key factor that aids in preventing constipation. Water increases intestine volume, which aids in bowel movement stimulation. Hydrating with about 1.5 - 2.0 liters/day along with daily fiber intake of 25 g can increase stool frequency [58].

Osmotic laxatives aid stool passage by drawing water into the intestines to make the stool softer. Common osmotic laxatives include polyethylene glycol (PEG), lactulose, glycerin, magnesium hydroxide (milk of magnesia), sorbitol, magnesium phosphate, sodium phosphate, and castor oil. Generally, these agents work within 6 - 12 hours and commonly cause bloating, diarrhea, and gas [59]. Compilations of osmotic laxative use include electrolyte imbalance and dehydration. Hypokalemia (low potassium) as a result of osmotic laxative use can lead to dangerous arrhythmias including, atrial flutter, atrial fibrillation, torsades de pointes, ventricular fibrillation, and ventricular tachycardia [60]. Excessive dehydration as a result of osmotic laxative use causes the heart to work harder, which can lead to elevated heart rate and palpitations. Additionally, lowered blood volume from decreased fluid intake leads to thicker blood, which causes increased work on the heart to pump blood. Stimulant laxatives stimulate large intestine nerves, which aids muscle contraction to push stool through the colon. Common stimulant laxatives include senna, bisacodyl, and sodium picosulfate. These agents induce bowel movements within 6 - 12 hours and the most common side effect is abdominal pain. Hypokalemia is a complication of stimulant laxative use as well, which poses risk for serious cardiac adverse events. Agents that contain sodium should be used with caution in patients with heart failure because sodium causes water retention, which increases blood volume and pressure. The heart has to work harder to pump blood and the overall strain leads to further exacerbation of heart failure.

Physical activity plays a role in relieving constipation by decreasing time food is spent in the large intestine. This limits excessive body absorption of water from the stool, allowing softer stools to pass [60]. Acupuncture relieves constipation through peristalsis stimulation, stress reduction, colonic smooth muscle thickening, and vagus nerve stimulation [61].

Ultimately, shared decision making between patients and their providers is essential to maintaining trust. Patients should be informed of risks and benefits of treatment with anti-constipation agents and each plan should be uniquely tailored to the patient's medical history. Elderly patients with constipation that have comorbid cardiac conditions are at even greater risk of complications with medical therapy and should be given alternative therapy options that do not pose serious risk of cardiac events, such as acupuncture.

9. Research Priorities and Future Directions

The presence of current ongoing studies to investigate the relationship between constipation and cardiovascular disease is essential. However, there is still a lack of randomized controlled trials and high-quality Mendelian randomization (MR) studies to draw a clear conclusion. Previous data includes MR studies that suggest associations between constipation and the risk of atrial fibrillation but not other CVDs, such as coronary artery disease [13]. Further studies can continue measuring constipation and CVD as Mendelian randomization, supplying more data to replicate the current studies. A limitation of many of these previous studies includes underlying diseases that may lead to CVD that do not include constipation, as well as patient self-reporting that may not be standardized among all participants.

Future mechanistic studies can help us better understand the gut microbiome's role in constipation and cardiovascular risk. Previous case studies have indicated that pathogenic gut microbiota can lead to an increased risk of hypertension and eventual cardiovascular events [62]. Clinical studies and the utilization of fecal tests that measure the amount of pathogenic microbiota can help standardize the microbiome and test for inflammatory cytokines caused by bacteria, parasites, or viruses. A longitudinal study can help determine a clinical correlation between constipation and CVD. Additionally, more studies that include fecal transplantation can potentially reduce constipation and, therefore, potentially reduce the risk of CVD [61]. Treatment of gut dysbiosis may prove functional in reducing the risk of constipation and other adverse effects. Other causal links, including vascular effects of constipation, may also explain changes to the intestinal microbiome [16]. Overall, it is essential to continue mechanistic studies of the gut microbiome to determine if constipation and gut dysbiosis influence various organ systems.

Further investigation can also include studying target populations that are at risk of cardiovascular disease, including older populations, diabetics, those with hypertension, and those with current CVD. For example, those with Type 2 diabetes had an increased risk of cardiovascular disease if they also had constipation,

where 27 percent of those with constipation had CVD, and 13% without constipation had CVD [23]. To further this study, examining intervention outcomes, such as the treatment of constipation reducing cardiovascular events or mortality, would be beneficial. Data can be collected as a longitudinal study, where patients with Type II diabetes or any target population, such as older populations or hypertensives, are examined over time to determine if reducing constipation symptoms early leads to decreased cardiovascular events. Finally, it is crucial to standardize uniform criteria in defining constipation and cardiovascular outcomes. To achieve this, the duration of the constipation event can be monitored, as well as Rome criteria. Cardiovascular events can also be standardized, including lab cholesterol values or troponin values during a myocardial infarction. These efforts will help to better understand the clinical correlations and intervention outcomes between constipation and cardiovascular disease, emphasizing the importance of gut health.

Conflict of Interest Statement

The authors of this manuscript declare that they have no conflicts of interest that are directly or indirectly related to the work submitted for publication. Specifically:

1) Financial Interests: None of the authors has received any financial compensation, funding, grants, or other monetary support that could be perceived as influencing the research, analysis, or conclusions presented in this work.

2) Professional Relationships: The authors have no employment, consultancy, board membership, or other professional relationships with organizations that could be perceived as influencing the work presented here.

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References

[1] Diaz, S., Bittar, K., Hashmi, M.F. and Mendez, M.D. (2023) Constipation. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK513291/

[2] Bharucha, A.E. and Lacy, B.E. (2020) Mechanisms, Evaluation, and Management of Chronic Constipation. *Gastroenterology*, **158**, 1232-1249.e3. https://doi.org/10.1053/j.gastro.2019.12.034

[3] Dennison, C., Prasad, M., Lloyd, A., Bhattacharyya, S.K., Dhawan, R. and Coyne, K. (2005) The Health-Related Quality of Life and Economic Burden of Constipation. *PharmacoEconomics*, **23**, 461-476. https://doi.org/10.2165/00019053-200523050-00006

[4] Sundbøll, J., Szépligeti, S.K., Adelborg, K., Szentkúti, P., Gregersen, H. and Sørensen, H.T. (2020) Constipation and Risk of Cardiovascular Diseases: A Danish Population-Based Matched Cohort Study. *BMJ Open*, **10**, e037080. https://doi.org/10.1136/bmjopen-2020-037080

[5] Sumida, K., Molnar, M.Z., Potukuchi, P.K., Thomas, F., Lu, J.L., Yamagata, K., *et al*. (2019) Constipation and Risk of Death and Cardiovascular Events. *Atherosclerosis*, **281**, 114-120. https://doi.org/10.1016/j.atherosclerosis.2018.12.021

[6] Zheng, T., Camargo Tavares, L., D'Amato, M. and Marques, F.Z. (2024) Constipation Is Associated with an Increased Risk of Major Adverse Cardiac Events in a UK Population. *American Journal of Physiology-Heart and Circulatory Physiology*, **327**, H956-H964. https://doi.org/10.1152/ajpheart.00519.2024

[7] Peng, Y., Liu, F., Qiao, Y., Wang, P., Ma, B., Li, L., *et al*. (2022) Association of Abnormal Bowel Health with Major Chronic Diseases and Risk of Mortality. *Annals of Epidemiology*, **75**, 39-46. https://doi.org/10.1016/j.annepidem.2022.09.002

[8] Sharma, A., Rao, S.S.C., Kearns, K., Orleck, K.D. and Waldman, S.A. (2021) Review Article: Diagnosis, Management and Patient Perspectives of the Spectrum of Constipation Disorders. *Alimentary Pharmacology & Therapeutics*, **53**, 1250-1267. https://doi.org/10.1111/apt.16369

[9] Bouras, E. and Vazquez-Roque, M. (2015) Epidemiology and Management of Chronic Constipation in Elderly Patients. *Clinical Interventions in Aging*, **10**, 919-930. https://doi.org/10.2147/cia.s54304

[10] Forootan, M., Bagheri, N. and Darvishi, M. (2018) Chronic Constipation. *Medicine*, **97**, e10631. https://doi.org/10.1097/md.0000000000010631

[11] Talley, N.J., Jones, M., Nuyts, G. and Dubois, D. (2003) Risk Factors for Chronic Constipation Based on a General Practice Sample. *American Journal of Gastroenterology*, **98**, 1107-1111. https://doi.org/10.1111/j.1572-0241.2003.07465.x

[12] Simren, M., Palsson, O.S. and Whitehead, W.E. (2017) Update on Rome IV Criteria for Colorectal Disorders: Implications for Clinical Practice. *Current Gastroenterology Reports*, **19**, 15. https://doi.org/10.1007/s11894-017-0554-0

[13] Dong, Q., Chen, D., Zhang, Y., Xu, Y., Yan, L. and Jiang, J. (2023) Constipation and Cardiovascular Disease: A Two-Sample Mendelian Randomization Analysis. *Frontiers in Cardiovascular Medicine*, **10**, Article ID: 1080982. https://doi.org/10.3389/fcvm.2023.1080982

[14] Suenghataiphorn, T., Yanpiset, P., Xanthavanij, N., Srikulmontri, T., Thiravetyan, B., Tribuddharat, N., *et al*. (2024) Increased Risk of Stroke in Constipation Patients: Systematic Review and Meta-Analysis. *Journal of Clinical Gastroenterology*. https://doi.org/10.1097/mcg.0000000000002127

[15] Du, W., Yang, S., Zhou, H., Wu, Y., Cai, Y., Meng, H., *et al*. (2023) The Association between Constipation and Stroke Based on the NHANES and Mendelian Randomization Study. *Frontiers in Neuroscience*, **17**, Article ID: 1276032. https://doi.org/10.3389/fnins.2023.1276032

[16] Ishiyama, Y., Hoshide, S., Mizuno, H. and Kario, K. (2019) Constipation-Induced Pressor Effects as Triggers for Cardiovascular Events. *The Journal of Clinical Hypertension*, **21**, 421-425. https://doi.org/10.1111/jch.13489

[17] Threapleton, D.E., Greenwood, D.C., Evans, C.E.L., Cleghorn, C.L., Nykjaer, C.,

Woodhead, C., *et al*. (2013) Dietary Fibre Intake and Risk of Cardiovascular Disease: Systematic Review and Meta-Analysis. *BMJ*, **347**, f6879. https://doi.org/10.1136/bmj.f6879

[18] Wang, J.Y., Hart, S.L., Lee, J., Berian, J.R., McCrea, G.L. and Varma, M.G. (2009) A Valid and Reliable Measure of Constipation-Related Quality of Life. *Diseases of the Colon & Rectum*, **52**, 1434-1442. https://doi.org/10.1007/dcr.0b013e3181a51196

[19] Judkins, C.P., Wang, Y., Jelinic, M., Bobik, A., Vinh, A., Sobey, C.G., *et al*. (2023) Association of Constipation with Increased Risk of Hypertension and Cardiovascular Events in Elderly Australian Patients. *Scientific Reports*, **13**, Article No. 10943. https://doi.org/10.1038/s41598-023-38068-y

[20] Yan, Q., Zhai, W., Yang, C., Li, Z., Mao, L., Zhao, M., *et al*. (2021) The Relationship among Physical Activity, Intestinal Flora, and Cardiovascular Disease. *Cardiovascular Therapeutics*, **2021**, Article ID: 3364418. https://doi.org/10.1155/2021/3364418

[21] Sun, T., Song, B. and Li, B. (2025) Gut Microbiota and Atrial Cardiomyopathy. *Frontiers in Cardiovascular Medicine*, **12**, Article ID: 1541278. https://doi.org/10.3389/fcvm.2025.1541278

[22] Li, N., Wang, L., Li, L., Yang, M., Wang, Q., Bai, X., *et al*. (2023) The Correlation between Gut Microbiome and Atrial Fibrillation: Pathophysiology and Therapeutic Perspectives. *Military Medical Research*, **10**, Article No. 51. https://doi.org/10.1186/s40779-023-00489-1

[23] Ito, H., Ito, K., Tanaka, M., Hokamura, M., Tanaka, M., Kusano, E., *et al*. (2022) Constipation Is a Frequent Problem Associated with Vascular Complications in Patients with Type 2 Diabetes: A Cross-Sectional Study. *Internal Medicine* (*Tokyo*, *Japan*), **61**, 1309-1317. https://doi.org/10.2169/internalmedicine.7676-21

[24] Evans, B.R., Yerly, A., van der Vorst, E.P.C., Baumgartner, I., Bernhard, S.M., Schindewolf, M., *et al*. (2022) Inflammatory Mediators in Atherosclerotic Vascular Remodeling. *Frontiers in Cardiovascular Medicine*, **9**, Article ID: 868934. https://doi.org/10.3389/fcvm.2022.868934

[25] Ordookhanian, C., Barseghian, C., Amidon, R.F. and Kaloostian, P. (2022) Intricate Connection among the Valsalva Maneuver, Gastrointestinal Tract, and Hemodynamics: A Rare Case Presentation. *Cureus*, **14**, e24474. https://doi.org/10.7759/cureus.24474

[26] Ishida, T., Kawada, K., Jobu, K., Hamada, T., Kubo, T., Okazaki, M., *et al*. (2025) Impact of Comorbid Constipation on the Survival of Patients with Heart Failure: A Multicenter, Prospective Cohort Study Conducted in Japan. *Frontiers in Cardiovascular Medicine*, **11**, Article ID: 1470216. https://doi.org/10.3389/fcvm.2024.1470216

[27] Namiuchi, S., Tanita, A., Sunamura, S., Onodera, K., Ogata, T., Noda, K., *et al*. (2023) Effect of Constipation on Readmission for Heart Failure in Patients with Acute Heart Failure. *ESC Heart Failure*, **11**, 819-825. https://doi.org/10.1002/ehf2.14650

[28] Eiraku, K., Uozumi, Y., Hieda, M., Maruyama, T. and Nomura, H. (2022) A Senile Case of Heart Failure Associated with Hypermagnesemia Induced by Magnesium-containing Laxative Agent. *Geriatrics & Gerontology International*, **22**, 897-899. https://doi.org/10.1111/ggi.14478

[29] Li, X., Wen, H., Ke, J. and Zhao, D. (2024) Association of Constipation with All-Cause Mortality among Individuals with Type 2 Diabetes: A Retrospective Cohort Study. *Journal of Diabetes Investigation*, **16**, 501-509. https://doi.org/10.1111/jdi.14375

[30] Itano, S., Honda, Y., Kubo, E., Yamada, Y., Ikenoue, T. and Kimachi, M. (2020) P1440 Association between the Use of Drugs for Constipation and Mortality in Hemodial-

ysis Patients; from Japan-Dialysis Outcomes and Practice Patterns Study (J-DOPPS). *Nephrology Dialysis Transplantation*, **35**, gfaa142.P1440. https://doi.org/10.1093/ndt/gfaa142.p1440

[31] Nesci, A., Carnuccio, C., Ruggieri, V., D'Alessandro, A., Di Giorgio, A., Santoro, L., *et al*. (2023) Gut Microbiota and Cardiovascular Disease: Evidence on the Metabolic and Inflammatory Background of a Complex Relationship. *International Journal of Molecular Sciences*, **24**, Article No. 9087. https://doi.org/10.3390/ijms24109087

[32] Martel, J., Chang, S., Ko, Y., Hwang, T., Young, J.D. and Ojcius, D.M. (2022) Gut Barrier Disruption and Chronic Disease. *Trends in Endocrinology & Metabolism*, **33**, 247-265. https://doi.org/10.1016/j.tem.2022.01.002

[33] Sandys, O. and te Velde, A. (2022) Raising the Alarm: Environmental Factors in the Onset and Maintenance of Chronic (Low-Grade) Inflammation in the Gastrointestinal Tract. *Digestive Diseases and Sciences*, **67**, 4355-4368. https://doi.org/10.1007/s10620-021-07327-1

[34] Zhang, Y., Song, F., Yang, M., Chen, C., Cui, J., Xing, M., *et al*. (2024) Gastrointestinal Dysmotility Predisposes to Colitis through Regulation of Gut Microbial Composition and Linoleic Acid Metabolism. *Advanced Science*, **11**, e2306297. https://doi.org/10.1002/advs.202306297

[35] Cooke, W.H., Reynolds, B.V., Yandl, M.G., Carter, J.R., Tahvanainen, K.U.O. and Kuusela, T.A. (2002) Effects of Exercise Training on Cardiovagal and Sympathetic Responses to Valsalva's Maneuver. *Medicine & Science in Sports & Exercise*, **34**, 928-935. https://doi.org/10.1097/00005768-200206000-00004

[36] Hotta, H., Lazar, J., Orman, R., Koizumi, K., Shiba, K., Kamran, H., *et al*. (2009) Vagus Nerve Stimulation-Induced Bradyarrhythmias in Rats. *Autonomic Neuroscience: Basic & Clinical*, **151**, 98-105. https://doi.org/10.1016/j.autneu.2009.07.008

[37] Thompson, G.W., Levett, J.M., Miller, S.M., Hill, M.R.S., Meffert, W.G., Kolata, R.J., *et al*. (1998) Bradycardia Induced by Intravascular versus Direct Stimulation of the Vagus Nerve. *The Annals of Thoracic Surgery*, **65**, 637-642. https://doi.org/10.1016/s0003-4975(97)01351-9

[38] Kollai, M., Koizumi, K., Yamashita, H. and Brooks, C.M. (1978) Study of Cardiac Sympathetic and Vagal Efferent Activity during Reflex Responses Produced by Stretch of the Atria. *Brain Research*, **150**, 519-532. https://doi.org/10.1016/0006-8993(78)90817-x

[39] Mehra, R., Chung, M.K., Olshansky, B., Dobrev, D., Jackson, C.L., Kundel, V., *et al*. (2022) Sleep-Disordered Breathing and Cardiac Arrhythmias in Adults: Mechanistic Insights and Clinical Implications: A Scientific Statement from the American Heart Association. *Circulation*, **146**, e119-e136. https://doi.org/10.1161/cir.0000000000001082

[40] Shen, M.J. and Zipes, D.P. (2014) Role of the Autonomic Nervous System in Modulating Cardiac Arrhythmias. *Circulation Research*, **114**, 1004-1021. https://doi.org/10.1161/circresaha.113.302549

[41] Arcieri, T.R. and Meizoso, J.P. (2025) Intraabdominal Hypertension and Abdominal Compartment Syndrome—What You Need to Know. *Journal of Trauma and Acute Care Surgery*. https://doi.org/10.1097/ta.0000000000004603

[42] Persichini, R., Lai, C., Teboul, J., Adda, I., Guérin, L. and Monnet, X. (2022) Venous Return and Mean Systemic Filling Pressure: Physiology and Clinical Applications. *Critical Care*, **26**, Article No. 150. https://doi.org/10.1186/s13054-022-04024-x

[43] Xu, X., He, Z., Shan, Y., Mao, Q., Feng, J. and Gao, G. (2021) Intra-Abdominal Pressure Measurements in Neurocritical Patients. *Journal of Visualized Experiments*.

https://doi.org/10.3791/62557

[44] Depauw, P.R.A.M., Groen, R.J.M., Van Loon, J., Peul, W.C., Malbrain, M.L.N.G. and De Waele, J.J. (2019) The Significance of Intra-Abdominal Pressure in Neurosurgery and Neurological Diseases: A Narrative Review and a Conceptual Proposal. *Acta Neurochirurgica*, **161**, 855-864. https://doi.org/10.1007/s00701-019-03868-7

[45] Dreesen, P., Schoutteten, M.K., Vande Velde, N., Kaminski, I., Heylen, L., De Moor, B., *et al*. (2020) Increased Intra-Abdominal Pressure during Laparoscopic Pneumoperitoneum Enhances Albuminuria via Renal Venous Congestion, Illustrating Pathophysiological Aspects of High Output Preeclampsia. *Journal of Clinical Medicine*, **9**, 487. https://doi.org/10.3390/jcm9020487

[46] Montorfano, L., Dip, F., Lo Menzo, E., Agrawal, N., Phillips, E.H., Liang, H., *et al*. (2022) The Role of Cushing's Reflex and the Vasopressin-Mediated Oligoanuric Response to Intracranial Hypertension in Patients with Abdominal Compartment Syndrome. *Surgery*, **171**, 399-404. https://doi.org/10.1016/j.surg.2021.08.046

[47] Cavaliere, F., Cina, A., Biasucci, D., Costa, R., Soave, M., Gargaruti, R., *et al*. (2011) Sonographic Assessment of Abdominal Vein Dimensional and Hemodynamic Changes Induced in Human Volunteers by a Model of Abdominal Hypertension. *Critical Care Medicine*, **39**, 344-348. https://doi.org/10.1097/ccm.0b013e3181ffe0d2

[48] Tazmini, K., Frisk, M., Lewalle, A., Laasmaa, M., Morotti, S., Lipsett, D.B., *et al*. (2020) Hypokalemia Promotes Arrhythmia by Distinct Mechanisms in Atrial and Ventricular Myocytes. *Circulation Research*, **126**, 889-906. https://doi.org/10.1161/circresaha.119.315641

[49] Skogestad, J. and Aronsen, J.M. (2018) Hypokalemia-Induced Arrhythmias and Heart Failure: New Insights and Implications for Therapy. *Frontiers in Physiology*, **9**, Article No. 1500. https://doi.org/10.3389/fphys.2018.01500

[50] Aronsen, J.M., Skogestad, J., Lewalle, A., Louch, W.E., Hougen, K., Stokke, M.K., *et al*. (2014) Hypokalaemia Induces Ca^{2+} Overload and Ca^{2+} Waves in Ventricular Myocytes by Reducing Na^{+},K^{+}-ATPase α_2 Activity. *The Journal of Physiology*, **593**, 1509-1521. https://doi.org/10.1113/jphysiol.2014.279893

[51] Osadchii, O.E. (2010) Mechanisms of Hypokalemia-Induced Ventricular Arrhythmogenicity. *Fundamental & Clinical Pharmacology*, **24**, 547-559. https://doi.org/10.1111/j.1472-8206.2010.00835.x

[52] Sandau, K.E., Funk, M., Auerbach, A., Barsness, G.W., Blum, K., Cvach, M., *et al*. (2017) Update to Practice Standards for Electrocardiographic Monitoring in Hospital Settings: A Scientific Statement from the American Heart Association. *Circulation*, **136**, e273-e344. https://doi.org/10.1161/cir.0000000000000527

[53] Gettes, L.S. (1992) Electrolyte Abnormalities Underlying Lethal and Ventricular Arrhythmias. *Circulation*, **85**, I70-I76.

[54] Salmoirago-Blotcher, E., Crawford, S., Jackson, E., Ockene, J. and Ockene, I. (2011) Constipation and Risk of Cardiovascular Disease among Postmenopausal Women. *The American Journal of Medicine*, **124**, 714-723. https://doi.org/10.1016/j.amjmed.2011.03.026

[55] Soliman, G.A. (2019) Dietary Fiber, Atherosclerosis, and Cardiovascular Disease. *Nutrients*, **11**, Article No. 1155. https://doi.org/10.3390/nu11051155

[56] Alahmari, L.A. (2024) Dietary Fiber Influence on Overall Health, with an Emphasis on CVD, Diabetes, Obesity, Colon Cancer, and Inflammation. *Frontiers in Nutrition*, **11**, Article ID: 1510564. https://doi.org/10.3389/fnut.2024.1510564

[57] Ağagündüz, D., Şahin, T.Ö., Yılmaz, B., Ekenci, K.D., Duyar Özer, Ş. and Capasso, R. (2022) Cruciferous Vegetables and Their Bioactive Metabolites: From Prevention to

Novel Therapies of Colorectal Cancer. *Evidence-Based Complementary and Alternative Medicine*, **2022**, Article ID: 1534083. https://doi.org/10.1155/2022/1534083

[58] Anti, M., Pignataro, G., Armuzzi, A., *et al*. (1998) Water Supplementation Enhances the Effect of High-Fiber Diet on Stool Frequency and Laxative Consumption in Adult Patients with Functional Constipation. *Hepato-Gastroenterology*, **45**, 727-732. https://pubmed.ncbi.nlm.nih.gov/9684123/

[59] Bashir, A. and Sizar, O. (2024) Laxatives. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK537246/

[60] Castro, D. and Sharma, S. (2025) Hypokalemia. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK482465/

[61] Astudillo, A.A. and Mayrovitz, H.N. (2021) The Gut Microbiome and Cardiovascular Disease. *Cureus*, **13**, e14519. https://doi.org/10.7759/cureus.14519

[62] Muchtar, N.J., Helianthi, D.R. and Nareswari, I. (2020) Effectiveness of Acupuncture for Management in a Hospitalized Geriatric Patient with Constipation. *Medical Acupuncture*, **32**, 116-120. https://doi.org/10.1089/acu.2019.1401