SYSTEMATIC REVIEW AND META-ANALYSIS

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Constipation and Risk of Acute Myocardial Infarction: A Systematic Review and Meta-Analysis of Cohort Studies

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ABSTRACT

Background & Aims: Constipation is commonly seen among patients with cardiovascular diseases and is linked to adverse outcomes. However, the association between constipation and the risk of acute myocardial infarction (AMI) remains conflicting. Therefore, we aimed to conduct a systematic review and meta-analysis to summarize the available data on this topic.
Method: We identified potentially eligible studies from the MEDLINE and EMBASE databases, searching from inception to May 2024, to investigate the association between constipation and the risk of developing AMI. To be included, studies needed to compare incidence of AMI between cohorts with and without constipation. Effect size and 95% confidence intervals (CIs) were combined using the generic inverse variance method. All statistical analyses were performed by Review Manager 5.4.
Results: Our meta-analysis included seven studies that met the eligibility criteria. There were 5,351,976 participants, with a mean age of 57.8 years and 74% were males. We found that patients with constipation had a 14% increased risk of AMI with a pooled risk ratio (RR) of 1.14 (95%CI: 1.08-1.14; I^2=85%; p<0.001) compared to those without constipation.
Conclusions: Our study revealed that constipation is associated with a higher risk of AMI. Emphasizing and addressing gastrointestinal health, including constipation, as an important issue is essential for comprehensive cardiovascular care.

Key words: constipation – acute myocardial infarction – systematic review – meta-analysis.

Abbreviations: AMI: acute myocardial infaction; CI: confidence interval; HR: hazard ratios; RR: relative risk.

INTRODUCTION

Constipation is one of the most common conditions, which generates a disturbing quality of life for patients. Estimates range from 10-25%, with in the United States population and worldwide are affected with constipation [1]. The burden of care of constipation is demonstrated in various dimensions, such as personal and work-related or school-related impact [2], cognitive impairment [3] or costs more than US $230 million per annum [4]. As the majority of patients do not seek healthcare [5], more severe conditions that arises from constipation can be underdiagnosed. Increasingly, constipation patients have been linked to hypertension [6], heart failure [7] and other diseases [8]. Cardiovascular events are expected to be responsible for 32% of the global deaths [9], and with over 23 million patients impacted with heart failure [10], understanding a critical cardiovascular condition such as acute myocardial infarction (AMI) remains crucial to reduce mortality for the general public.

Acute myocardial infaction is one of the most common cardiovascular disease with serious consequences in mortality, morbidity, and cost to the society [11]. Current incidence projection of this high mortality disease is expected to double in 25 years, due to various multifactorial factors [12]. Beyond the rising trends of obesity, metabolic syndrome and smoking, exploring other risk factors can provide additional clues to combating this deadly disease. Both AMI and constipation have various common risk factors, such as age [13], usage of some medications [14] or even nutritional intake [15]. Current literature has linked constipation to AMI [16-18], but information on the association between constipation and

AMI is conflicting. Thus, we conducted a systematic review and meta-analysis of studies examining the impact of constipation on the risk of AMI event.

METHODS

This manuscript was written according to PRISMA 2020 guidelines [19], in which the PRISMA checklist is available in the supplementary material of this manuscript.

Search Strategy

Three investigators (P.Y., T. Srikulmontri and N.T.) independently conducted searches in Medline and Embase databases from inception through May 2024 using search terms as specified in the Supplementary file. No language restrictions were applied. The same investigators independently assessed the eligibility of the retrieved records, with further discussions involving one investigator (T. Suenghataiphorn) to resolve any conflicts.

Eligibility Criteria

The eligibility criteria were as follows: Included studies must be cohort studies published as original research, assessing the association between constipation and risks of AMI. There is no standard definition of constipation [20], and the definition is defined differently by each authors, as identified either by ICD-10 codes or self-reporting of frequency of stools or symptoms as similar to the more recent Rome IV criteria of the functional constipation disorder [21]. Therefore, studies must include a group of individuals with constipation and another group without constipation and must provide effect estimates representing the association between constipation and the risk of AMI in the form of relative risk (RR) or hazard ratios (HR), accompanied by 95% confidence intervals (CIs) or survival curves. Raw data adequate for calculation for the effect sizes is acceptable. Exclusion criteria comprise studies that are abstracts or poster presentations, other types of research such as reviews or randomized controlled trials, and studies without a comparator arm.

Data Extraction

We employed a standardized data collection protocol to extract the following information: last name of the first author, study country, study design, publication year, total number of participants, study participants recruitment protocol, constipation diagnosis, myocardial infarction diagnosis, follow-up duration, age, gender and variables adjusted for in multivariate analysis.

Three investigators (P.D., N.K. and V.P.) applied the Newcastle-Ottawa Scale for cohort studies to evaluate research quality, focusing on the quality of participant recruitment, comparability between groups, and accuracy of outcome ascertainment [22].

Statistical Analysis

Data analysis was conducted using Review Manager 5.4 software from the Cochrane Collaboration. Point estimates with standard errors from each study were combined using DerSimonian and Laird's generic inverse variance method [23]. Due to heterogeneous background populations and protocols among the studies, a random-effects model was employed. Statistical heterogeneity was assessed using the Cochran's Q test, supplemented by I^2 statistics to quantify the proportion of total variation across studies attributable to heterogeneity rather than chance. I^2 values categorize heterogeneity as insignificant (0–25%), low (26–50%), moderate (51–75%), or high (>75%) [24]. The Egger regression test will be conducted using Stata BE 18 (StataCorp LP, College Station, TX, USA) for the regression analysis.

RESULTS

Our search strategy identified 11,658 studies (9,742 from EMBASE and 1,916 from MEDLINE). After removing 415 duplicates, we reviewed those studies by title and abstract, excluding 11,231 studies that did not meet the eligibility criteria related to study design, participants, or article type. Subsequently, we thoroughly reviewed 12 articles and excluded 5 [15, 25-28] for not reporting the relevant outcome (such as non-AMI outcomes, unavailable effect size and reporting only mortality outcomes). Ultimately, seven studies met the eligibility criteria for our meta-analysis [16-18, 29-32]. Fig. 1 illustrates our search methodology and selection process, and Table I details the characteristics and quality assessment of the included studies.

A total of seven cohort studies with 5,351,976 participants investigated the association between constipation and AMI [16-18, 29-32]. The average participant age was 57.8 years old and 74% were male as shown in Table I. Four of the studies came from the United States, whereas one Australian, United Kingdom and Denmark were included in our final analysis.

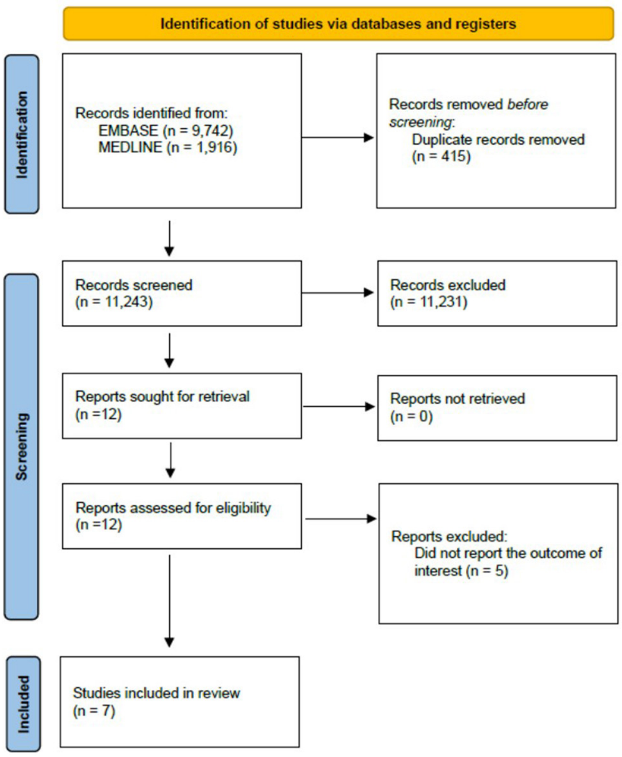

Fig. 1. Search methodology and selection process.

Table I. Baseline characteristics of all eligible studies included in the meta-analysis

	Blotcher et al. [30]	Ma et al. [29]	Sumida et al. [18]	Sundbøll et al. [17]
Year of publication	2011	2016	2019	2020
Country of origin	United States	United States	United States	Denmark
Study design	Prospective Cohort Study	Prospective Cohort Study	Retrospective cohort study	Retrospective cohort study
Study participants	Postmenopausal women were recruited from the Women's Health Initiative, a long-term national health study in the United States, with baseline characteristics collected from 1994 to 1998.	Female registered nurses from The Nurse's Health Study were recruited in 1982 and analyzed thereafter. Patients with a history of cardiovascular disease were excluded.	Patients were recruited from the Racial and Cardiovascular Risk Anomalies in CKD study between October 2004 and September 2006. All outcomes were defined as the first occurrence after October 1, 2006.	Patients were recruited from the Danish National Patient Registry database between July 2004 and November 2013.
Number of participants	Constipated group: 5,391 Non-Constipated group: 47,699	Constipated group: 6,348 Non-constipated group: 54,264	Constipated group: 237,855 Non-constipated group: 3,121,798	Constipated group: 83,239 Non-constipated group: 832,384
Diagnosis of constipation	Constipation was defined by a self-administered questionnaire as difficulty having bowel movements in the previous four weeks. We selected a cohort of individuals whose constipation symptoms somewhat interfered with their usual activities.	Constipation was defined as having a bowel movement every 3-4 days, based on self-reported, self-administered questionnaires. The comparator group included individuals with daily bowel movements.	Constipation was defined as having at least two diagnoses for constipation, identified by ICD-9-CM code 564.0x, that were at least 60 days apart, as well as having at least two prescriptions for laxatives, each with a supply of 30 days or more.	Constipation was defined using ICD-8 to ICD-10 codes from both primary and secondary diagnoses in inpatient and outpatient settings, as well as having at least two prescriptions for laxatives.
Diagnosis of myocardial infarction	Myocardial infarction was defined as a new event using ICD-9-CM codes found in discharge summaries, hospital face sheets, and/or physician attestations.	Myocardial infarction was defined as symptomatic nonfatal myocardial infarction or fatal coronary heart disease (CHD) using ICD-8 codes and cardiac enzymes if available.	Myocardial infarction was defined as the first occurrence of a new event, documented as a any of the following: acute myocardial infarction, CABG or PCI.	Myocardial infarction was defined as the first diagnosis of myocardial infarction, identified using ICD-8 to ICD-10 codes, as a new event.
Follow up time	6.9 years	30 years	6.7 years	10-20 years
Age	63 years	48 years	59 years	46 years
Gender	Female: 100%	Female: 100%	Male: 93%	Male: 41%
Confounder adjusted in the multivariate analysis	Age group, race/ethnicity, education, marital status, previous history of cardiovascular disease, log baseline heart rate, family history of MI, BMI, diabetes, high cholesterol, smoking, physical activity, hypertension, dietary factors, medications log depression score, optimism score, frailty score and log WBC count	Age, ethnicity, menopausal status, smoking status, physical activity, family history of myocardial infarction, hypertension, cholesterolemia, ulcerative colitis, cholecystectomy, medications intake, alcohol, dietary fiber, energy intake, body mass index and diabetes	Age-adjusted, sex, race, and baseline eGFR, diabetes mellitus, hypertension, CHD, congestive heart failure, cerebrovascular disease, peripheral vascular disease, peptic ulcer disease, rheumatic disease, malignancy, dementia, Parkinson's disease, depression, liver disease, chronic lung disease, HIV/AIDS, and bowel disorders, Charlson comorbidity index, baseline body mass index, systolic and diastolic blood pressure, and total cholesterol, socioeconomic parameters, indicators of sickness and quality of care, VA healthcare region and medications	Age, sex, calendar year, hypothyroidism, hyperthyroidism, pregnancy within 90 days before the index date, depression, Parkinson's disease, multiple sclerosis, colon, rectal and anal cancer, other gastrointestinal cancers, Crohn's disease, ulcerative colitis, paralytic ileus, chronic pulmonary disease, valvular heart disease, diabetes mellitus, hypertension, hypercholesterolemia, obesity, chronic kidney disease, liver disease, alcoholism-related disorders, medications associated with constipation and cardiovascular drugs
Newcastle-Ottawa score	Selection: 3 stars Comparability: 2 stars Outcome: 3 stars	Selection: 2 stars Comparability: 1 star Outcome: 2 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars

Follow-up time ranged from 6.9 to 30 years, with most of the research utilized ICD code system or questionnaire to define constipation and outcomes. The pooled analysis revealed that individuals with constipation had an increased risk of AMI, with a pooled RR of 1.14 (95%CI: 1.08-1.14; $p<0.001$, Fig. 2), when compared to individuals without constipation. High statistical heterogeneity was observed (I^2=85%). Subgroup analysis revealed combined gender group had an increased risk of AMI, with a pooled RR of 1.16 (95%CI: 1.10-1.22; $p<0.001$, I^2=89%), but for the female-only subgroup, we did not find statistically significant results. The Egger regression test (p=0.937) confirms the absence of publication bias.

Table I (continued)

	Peng et al [32]	Judkins et al. [16]	Zheng et al. [31]
Year of publication	2022	2023	2024
Country of origin	United States	Australian	United Kingdom
Study design	Prospective Cohort study	Retrospective Cohort Study	Retrospective cohort study
Study participants	Patients were recruited from the National Health and Nutrition Examination Survey (NHANES), a national survey designed to assess the health and nutritional status of adults and children in the United States, conducted from 2005 to 2010.	Patients were recruited from the Centre for Victorian Data Linkage, part of the Department of Health and Human Services of Victoria, which includes all public and private hospitalizations in Victoria, Australia. This statewide cohort study was conducted in Victoria from July 2000 to June 2020.	Patients were recruited from the UK Biobank, which includes a cohort of individuals from hospital inpatient admissions and collects questionnaire data on general health and lifestyle, as well as self-reported medical conditions and medication usage, from 2006 to 2010.
Number of participants	Constipated group: 1,486 Non-constipated group: 11,986	Constipated group: 270,586 Non-constipated group: 270,586	Constipated group: 23,814 Non-constipated group: 384,540
Diagnosis of constipation	Constipation was defined using the following criteria: Bristol Stool Form Scale type 1 or 2, or fewer than three bowel movements per week.	Constipation was defined using the ICD-10 code K59.0.	Constipation was identified through medical records with any encounters of the ICD-10 code K59.0 and among patients who routinely consumed laxatives.
Diagnosis of myocardial infarction	Myocardial infarction was defined by a self-reported questionnaire by in which patients indicated that a doctor or healthcare provider had diagnosed them with myocardial infarction.	Myocardial infarction was defined using the following ICD-10 codes: I21, I22, I23, I24, and I25.	Myocardial infarction was defined using the following ICD-10 codes: I20.0, I21, I24.8, and I24.9.
Follow up time	7.7 years	20 years	10 years
Age	46 years	73 years	56 years
Gender	Male: 51%	Male: 45%	Male: 46%
Confounder adjusted in the multivariate analysis	Age, gender, race, PIR, BMI, physical activity, smoking status, alcohol, prescription, hypertension, dyslipidemia, diabetes, cancer (excluding non-melanoma skin cancer), cardiotoxic drugs	Age, sex, cardiovascular risk factors (hypertension, obesity, smoking, diabetes, sleep apnea, COPD, kidney disease, endocrine disorders, metabolic disorders, PAOD, atrial fibrillation and cardiac arrhythmia), gastrointestinal disorders (irritable bowel syndrome, ulcerative colitis, Crohn's disease and other gastrointestinal disorders) and metropolitan residence.	Age, sex, body mass index, Calcium Channel Blocker usage, Hypertension, Diabetes, Hypercholesterolemia and Smoking
Newcastle-Ottawa score	Selection: 3 stars Comparability: 2 stars Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars

Table I. The characteristics and quality assessment of the included studies.

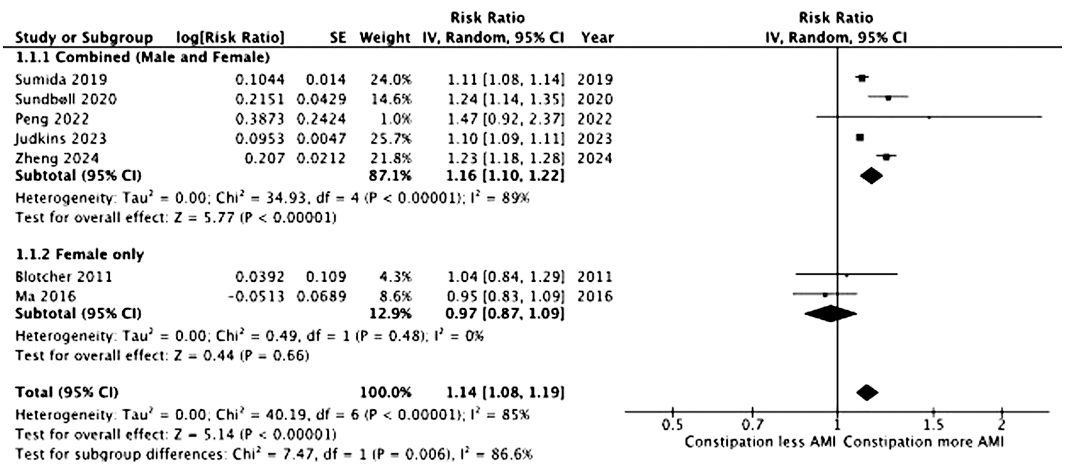

Fig. 2. The pooled analysis: constipation and risk of acute myocardial infarction.

DISCUSSION

This current study is the first systematic review and meta-analysis to consolidate data on how constipation affects risk of AMI incidents. The pooled analysis indicated that constipated patients have 14% higher risk of AMI event compared to individuals without constipation. The strength of the study lies from the pooled amount data, which increases the statistical power, as shown in other researches [33]. Regarding the differences in subgroup analyses, the relatively smaller study size from the only two studies, as well as wide confidence interval observed, may explain the difference in our results. Furthermore, studies have shown that female had a lower risk of acute myocardial infarction event [34], as well as lower prevalence of acute myocardial infarctions [35], and thus may contribute to the non-statistically significance in our results.

Although the exact process is unknown, several potential explanations exist for our findings. First, there is a significant association between serum levels of modulating inflammatory cytokines and age-related constipation [36]. These inflammatory molecules, such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-l), and interleukin 6 (IL-6), are directly linked to coronary artery disease and AMI events [37], and may explain our results. Interestingly, recent studies has shown an imbalance of gut microbiota, in which constipation patients had difference levels of gut microbiota than from non-constipated patients [38, 39]. The *Bifidobacterium* and *Bacteroidetes* are found to be higher levels in both the AMI group [40] and the constipation group [41, 42], suggesting further exploration in these subpopulation species. Imbalance microbiota has resulted in higher NF-kB phosphorylation and plasma lipopolysaccharide (LPS) concentration, and a decrease in intestinal barrier resistance and Akt, in which the size of infarction is influenced [43]. The LPS levels, as well as trimethylamine N-oxide (TMAO), in which imbalance microbiota generates, is considered to be pro-atherosclerotic molecule [44]. A higher risk baseline, due to more pro-atherosclerotic status, coupled with transient event from straining feces, may have resulted in more AMI events seen in our results.

Transient events during constipation such as straining, in similar to Valsalva maneuver [45], may explain our results. Prior study indicated that the Valsalva maneuver resulted in diminished oxygen consumption and may induced ischemia [46]. Furthermore, defecation syncope, which is a well-recognized cause and results from a repeated Valsalva-like event [47], may induce AMI during this period and may explain why constipated patients encounter more AMI events. Another proposed mechanism includes serotonin involvement, in which constipation is associated with higher serotonin synthesis and released [48]. Serotonin is a vasoconstrictor, known to promote thrombus formation [49] and is directly associated with coronary artery disease and occurrence of cardiac events [50]. Understanding the relationship behind constipation, serotonin and myocardial infarction may provide additional clues for preventive strategies in the future [51].

The current meta-analysis has several limitations. Firstly, the included meta-analysis showed high heterogeneity, possibly influenced by differences in baseline characteristics such as prevalence of constipation, characteristics of constipation as defined by each author, and follow-up duration. Secondly, since all studies were conducted mainly with Western country population, the findings may not be generalizable to other populations. Furthermore, constipation and AMI are a common disease, in which numerous confounders and factors may influence its development. In addition, the number of available studies is low, and may require additional studies to verify the relationship. Lastly, as all of the studies included in our meta-analyses are observational study designs, the results would not be able to confirm the causality relationship between constipation and AMI. Despite that our study utilizes numerous adjustment factors and similar population group, due to study limitations in adjusting more comprehensive confounders, the pooled results may be skewed from those unadjusted factors in the pooled study. As such, future research should include a global population, as AMI is increasingly seen worldwide [52], as well as exploring longitudinal research study, to understand the true impact of constipation in contributing towards AMI conditions.

CONCLUSIONS

Our meta-analysis found that constipation was associated with a higher risk of AMI. As constipation is highly prevalent in general population, understanding its mechanism and pathophysiology is crucial to reduce incidence of AMI as well as improving long-term survival outcomes. In addition, routine screening and management of constipation may be considered to be one of the strategies to reduce cardiovascular risk in the future.

Conflicts of interest: None to declare.

Authors' contributions: T. Suenghataiphorn and P.W. conceived the study. T. Suenghataiphorn designed the methodology. P.Y., T. Srikulmontri, N.T. performed the literature research. T. Suenghataiphorn and T. Sodsri collected data. T. Suenghataiphorn and P.W. analysed the data. P.D., N.K., and V.P. performed the Ottawa scoring. T. Suenghataiphorn, P.W., N.X. drafted tge manuscript. T. Suenghataiphorn and P.W. revised the manuscript. All the authors read and approved the final version.

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