Diverticulosis and nine connective tissue disorders: epidemiological support for an association

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**ABSTRACT**

**Purpose:** An underlying connective tissue disorder (CTD) may predispose to formation of intestinal diverticula. We assess the association of diverticulosis with nine selected CTDs, to inform the pathophysiology of diverticula.

**Methods:** A population-based period-prevalence study. Individuals (3.5 million New Zealand residents born 1901–1986) with a health system record 1999–2016 were grouped into those with a hospital diagnosis of diverticulosis or diverticulitis (ICD-10-AM K57), and those without. Also recorded were any hospital diagnoses of nine selected CTDs. The association of exposure to diverticulosis and each CTD was assessed using logistic regressions adjusted for age, gender, ethnicity and region.

**Results:** In all, 85,958 (2.4%) people had a hospital diagnosis of diverticulosis. Hospitalisation with diverticulosis was highly significantly associated with rectal prolapse (adjusted odds ratio [OR] = 3.9), polycystic kidney disease (OR = 3.8), heritable syndromes (Marfan or Ehlers-Danlos) (OR = 2.4), female genital prolapse (OR = 2.3), non-aortic aneurysm (OR = 2.3), aortic aneurysm (OR = 2.2), inguinal hernia (OR = 1.9) and dislocations of shoulder and other joints (OR = 1.7), but not subarachnoid haemorrhage (OR = 1.0).

**Conclusion:** People with diverticulosis are more likely to have colonic extracellular matrix (ECM)/connective tissue alterations in anatomical areas other than the bowel, suggesting linked ECM/connective tissue pathology. Although biases may exist, the results indicate large-scale integrated studies are needed to investigate underlying genetic pathophysiology of colonic diverticula, together with fundamental biological studies to investigate cellular phenotypes and ECM changes.

**Background**

Diverticulosis is one of the most common age-related health conditions in the western world, experienced by over 60% of people aged 65+ and with annual numbers of emergency department (ED) visits rising. The reasons for the formation of diverticula are poorly understood. Clinically, lack of clarity about the reasons for the development of diverticula leads to difficulties in counselling patients with chronic symptoms and may influence quality of life, illness perception, and self-management. The lack of knowledge complicates the ongoing search for causes and risk factors that are modifiable. Improved understanding of how diverticula develop could lead to better treatment and management, and also to preventive strategies among those most at risk. In this article, for simplicity, the term diverticulosis is used to include individuals with colonic diverticula, symptomatic or not, and who are therefore at risk of diverticulitis.

Colonic diverticula have been regarded as arising from constipation and strain that in turn result from lack of dietary fibre. These long-held theories are now challenged, with studies de-emphasising the causative role of dietary fibre. Recent studies have presented diverticulosis as a connective tissue disorder (CTD). Biochemical analyses of colonic extracellular matrix (ECM) among people with diverticulosis suggest a disordered collagen metabolism underlies diverticulosis. However, this belief is not yet widely accepted; of the five recent evidence-based guidelines that cover aetiology of diverticulosis, just one mentions collagen or ECM.
microbiome, diet and exercise and other factors may also contribute, but the pathophysiology remains uncertain. Intraluminal pressure is still regarded as playing a key role, with faecal material and/or intraluminal gas thought to push the colonic mucosa and sub-mucosa outwards to form outpouchings.\textsuperscript{14} If pressure does play an important role, questions remain as to why the colonic walls of some people, and not others, succumb to this pressure.

Evidence is mounting regarding heritability of diverticulosis. At least six studies independently report that heritability accounts for about 50% of the risk for diverticulosis.\textsuperscript{15–20} In Europe, a recent human genome-wide association study tested 32.4 million sequence variants and found three, \textit{ARHGAP15}, \textit{COLQ} and \textit{FAM155A}, were associated with diverticulosis.\textsuperscript{21} Another study by Coble et al. identified a rare single nucleotide variant in the laminin \(\beta 4\) gene (\textit{LAMB4}) that segregated with diverticulosis in a dominant pattern.\textsuperscript{22} Because these sequence variants did not overlap with previously known signals in risk loci for immune-mediated and inflammatory diseases, the authors concluded that the genetic link seemed to be through connective tissue more generally. If this is so, then demonstrating that people with diverticulosis are at higher risk of CTDs could offer epidemiological support for a link between diverticulosis and connective tissue morphology more generally. This population-based period-prevalence study aimed to compare the risk of the selected CTDs in people with a record of diverticulosis, and those without, and thereby contribute to the discussion about pathophysiology of diverticulosis.

\section*{Methods}

This study is a nationwide period-prevalence study of the New Zealand (NZ) population aged 30 years and over. Individuals were included if born between 1901 and 1986 and active in the national health system between July 1999 (when use of International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification [ICD-10-AM] was mandated) and June 2016 when data were extracted. A person was regarded as active in the health system if any record existed in the following records: any hospital discharge diagnoses coded using the ICD-10-AM recorded following each discharge from a public-funded hospital stay or hospital visit of over 3-h duration. Diverticulosis was identified if any diagnosis code (principal or other relevant diagnoses), was coded to chapter K57 (diverticular disease of the intestine whether acute/non-acute, colonic/small intestinal, uncomplicated/complications). Each related stay was classified during routine clinical coding as either an acute presentation (emergency department stay of 3 h or more or admission to surgical or medical ward) or as a non-acute admission (planned or waitlisted, for example, for a colonoscopy or surgery). Nine CTDs were pre-selected, purposefully choosing disorders from abdominal and non-abdominal locations, selected for being relatively clearly diagnosed and coded in a hospital setting, and thus more likely to be noted in the databases. The CTDs [and ICD-10-AM code] included: heritable syndromes (Ehlers-Danlos syndrome [Q79.6] and Marfan syndrome [Q87.4]), subarachnoid haemorrhage [I60], joint dislocations (including shoulder girdle [S43] and other specific joint derangements [M24]), aortic aneurysm and dissection, thoracic or abdominal [I71], other aneurysm, for example, of the carotid, renal or iliac arteries [I72], polycystic kidney disease (PKD) [Q61], inguinal hernia [K40], female genital prolapse [N81] and rectal prolapse [K62.3]. Following each discharge, diagnosis coding is undertaken routinely, by trained clinical coders using hospital discharge summaries and clinical notes. Date of birth, gender, self-identified ethnicity and region of domicile are also taken from the encounter record.

Odds ratios (ORs) for each CTD were derived for those with a diverticulosis diagnosis versus those without, including all eligible participants, using multi-variable logistic regression methods. Those with diverticulosis differed from those without diverticulosis by gender (male, female), year of birth, self-identified ethnicity (European/others, Māori, Pacific and Asian) and region of residence (Northern, Midland, Central and South Island), so models adjusted for these factors. Statistically significant associations between diverticulosis and CTDs may not necessarily reflect related aetiology. Although models adjusted for these potential confounders, there may be other confounders. One possibility is that ORs

in NZ, if gender or year of birth was not recorded, or if date of last contact or address was invalid. A single record for each eligible individual was derived, including sex, year of birth, self-identified ethnicity, year of death (if dead), geographic region of residence, and the date(s) of first discharge record of diverticulosis and the nine CTDs. Any hospital diagnosis of (a) diverticulosis or diverticulitis, and (b) any of nine CTDs recorded during the study period was noted, as described below.

Diagnoses of interest were identified by the hospital discharge diagnoses coded using the ICD-10-AM recorded following each discharge from a public-funded hospital stay or hospital visit of over 3-h duration. Diverticulosis was identified if any diagnosis code (principal or other relevant diagnoses), was coded to chapter K57 (diverticular disease of the intestine whether acute/non-acute, colonic/small intestinal, uncomplicated/complications). Each related stay was classified during routine clinical coding as either an acute presentation (emergency department stay of 3 h or more or admission to surgical or medical ward) or as a non-acute admission (planned or waitlisted, for example, for a colonoscopy or surgery). Nine CTDs were pre-selected, purposefully choosing disorders from abdominal and non-abdominal locations, selected for being relatively clearly diagnosed and coded in a hospital setting, and thus more likely to be noted in the databases. The CTDs [and ICD-10-AM code] included: heritable syndromes (Ehlers-Danlos syndrome [Q79.6] and Marfan syndrome [Q87.4]), subarachnoid haemorrhage [I60], joint dislocations (including shoulder girdle [S43] and other specific joint derangements [M24]), aortic aneurysm and dissection, thoracic or abdominal [I71], other aneurysm, for example, of the carotid, renal or iliac arteries [I72], polycystic kidney disease (PKD) [Q61], inguinal hernia [K40], female genital prolapse [N81] and rectal prolapse [K62.3]. Following each discharge, diagnosis coding is undertaken routinely, by trained clinical coders using hospital discharge summaries and clinical notes. Date of birth, gender, self-identified ethnicity and region of domicile are also taken from the encounter record.

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are artefactually elevated because investigations for some symptoms find previously unsuspected conditions. To explore whether this was so, when both diverticulosis and a CTD were recorded for an individual, we compared the first date of the CTD to the first (“index”) date of diverticulosis, and classified the pairing according to (a) whether prior to 6 months before the index date, (b) within 6 months of index date, or (c) 6 or more months following the index date.

Although the models adjusted for year of birth, it is possible that people with diverticulosis were simply older than those with CTDs, and thus more likely to report hospitalisations. In sensitivity analyses, we modelled interaction terms between diverticulosis and year of birth for each different CTD. Subgroup analyses were performed using three periods of year of birth (1901–1940, 1941–1960, 1961–1986).

Ethics approval was obtained from the University of Auckland Human Participants Ethics Committee (#016560), with the requirement for informed consent waived. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

**Results**

In all, 3,564,727 people were identified as meeting the inclusion criteria; 37,070 were excluded as ineligible or because of missing data as described above, leaving 3,527,657 people available for analyses (Figure 1). Of these, 85,958 (2.4%) had at least one hospital record that included a diverticulosis or diverticulitis diagnosis. At the first presentation, 38,239 (44.5%) of these diagnoses were from an acute admission, 35,914 (41.8%) as the primary diagnosis. Those with a diagnosis of diverticulosis were more likely to be women, of older age, of NZ European ethnicity and living in more northern regions (Table 1).

Overall, 140,668 (4.0%) people had at least one hospital record for one or more of the nine CTDs, as follows: inguinal hernia \((n = 58,508)\), female genital prolapse \((n = 29,848)\), aneurysm (aortic = 19,939, other = 5943), joint dislocations \((n = 19,548)\), subarachnoid haemorrhage \((n = 6982)\), rectal prolapse \((n = 4642)\), PKD \((n = 1527)\) and heritable syndromes \((n = 470)\). Among all participants, 6428 (0.18%) had multiple CTDs, 875 (1.02%) of those with diverticulosis and 5553 (0.16%) of those without.

Figure 2 shows the association between diverticulosis and each selected CTD during the whole study period. After adjustment for gender, year of birth, ethnic group and region, there were strong associations between a diverticulosis diagnosis and both rectal prolapse \((OR = 3.9, 95\% \text{ confidence interval } [95\%\text{CI} ] 3.6–4.3)\) and PKD \((OR = 3.8, 95\%\text{CI } 3.2–4.4)\) (Figure 2). Four

![Figure 1. Flow chart of included people with and without diverticulosis.](connectivetissue-research-figure1.png)
Weakening of the colonic wall increased collagen crosslinking. The evidence while Oma et al. concluded that con-

| Year of birth (years), n (%) | Diverticulosis participants (n = 85,958) | Non-diverticulosis participants (n = 3,441,699) |
|----------------------------|----------------------------------------|------------------------------------------------|
| 1901–1930                  | 24,790 (28.8)                         | 1,653,362 (48.0)                         |
| 1931–1940                  | 20,773 (24.2)                         | 1,653,362 (48.0)                         |
| 1941–1950                  | 19,520 (22.7)                         | 1,653,362 (48.0)                         |
| 1951–1960                  | 12,696 (14.8)                         | 1,653,362 (48.0)                         |
| 1961–1970                  | 6144 (7.1)                            | 1,653,362 (48.0)                         |
| 1971–1980                  | 4198 (4.9)                            | 1,653,362 (48.0)                         |
| 1981–1986                  | 297 (0.3)                             | 1,653,362 (48.0)                         |

| Ethnic group, n (%)        | Diverticulosis participants (n = 85,958) | Non-diverticulosis participants (n = 3,441,699) |
|----------------------------|----------------------------------------|------------------------------------------------|
| European/others            | 76,554 (89.1)                         | 2,597,916 (75.5)                         |
| Māori                      | 5458 (6.3)                             | 341,264 (9.9)                             |
| Pacific                    | 2121 (2.5)                             | 185,622 (5.4)                             |
| Asian                      | 1823 (2.1)                             | 316,897 (9.2)                             |

| Region, n (%)              | Diverticulosis participants (n = 85,958) | Non-diverticulosis participants (n = 3,441,699) |
|----------------------------|----------------------------------------|------------------------------------------------|
| Northern                   | 33,584 (39.1)                         | 1,653,362 (48.0)                         |
| Midland                    | 23,690 (27.6)                         | 1,653,362 (48.0)                         |
| Central                    | 16,118 (18.8)                         | 1,653,362 (48.0)                         |
| South Island               | 12,566 (14.6)                         | 1,653,362 (48.0)                         |

CTDs had ORs lying between 2.0 and 2.5: heritable syndromes (OR = 2.4), female genital prolapse (OR = 2.3), non-aortic aneurysm (OR = 2.3) and aortic aneurysm (OR = 2.2). Weaker positive associations were found with inguinal hernia, joint dislocations of shoulder or other joint derangements. Other than those with subarachnoid haemorrhage, all associations were statistically significant with p-values <0.001.

Comparisons of the date of first recorded diagnosis of each of the selected CTDs and the first record of diverticulosis varied by disorder (Table 2). In some, for example, shoulder dislocations and female genital prolapse, the date of first hospital diagnosis appeared unrelated to the timing of the first diverticulosis diagnosis. In contrast, more than 30% of aortic aneurysms and rectal prolapses were diagnosed during the period within six months of the index date, thus some clinical investigations may have found either the diverticulosis or CTD diagnosis incidentally (Table 2).

In the sensitivity analyses we found reduced associations between CTDs and diverticulosis in general among older people, and stronger associations of diverticulosis with three CTDs (rectal prolapse, female genital prolapse and other aneurysm) in younger people (see appendix Table 1). Stronger associations in the younger cohort lend strength to a possible genetic causal pathway.

**Discussion**

In this large population-based study, those with diverticulosis have greater likelihood, during their observable lifetime, of eight of the nine pre-selected CTDs, with ORs ranging from a high of 3.9 (95%CI 3.6–4.3) for rectal prolapse, to 1.7 (95%CI 1.6–1.8) for shoulder joint and other dislocations. Some of these associations were known, including Ehlers-Danlos syndrome (EDS), Williams-Beuren syndrome, PKD, Coffin-Lowry syndrome, and Marfan syndrome,18 PKD,22,23 and aortic aneurysm.24

Although there is potential for uncontrolled confounding, we believe that the higher ORs, in combination, support the theory that diverticula arise from a disorder of connective tissue. Studies of diverticulosis demonstrate changes in the organisation of collagen within the colonic wall,4,25,26 with increased tissue inhibitor of metalloproteinase expression,10 increased collagen crosslinking17 and elastin deposition.28 Weakening of the colonic wall may arise from the increased collagen component,12,29,30 thus allowing diverticula to form.7 Wrafter et al. argued that diverticula form as a result of a disorder similar to cystic conditions,9 while Oma et al. concluded that connective tissue alterations observed in diverticulosis shared aetiology with abdominal hernial disease.8 The evidence for a connective tissue disorder is strong and growing.

**Strengths and limitations**

This is a large population-based observational study, recording diagnoses over many years. The databases used for diagnoses are those of the national universal-coverage health system in NZ that include all publicly funded hospital admissions or stays of 3 h or more. Most acute medicine in NZ is practised in public hospitals, with established hospital medical coders having national training systems, standards and audits. Because cases and controls together form a whole population and the CTDs are rare, the ORs will approximate diverticulosis-related risks ratios unless there is bias (discussed below). The large population dataset suggests the results are likely generalisable, at least to western populations of predominantly Caucasian descent.

Measurement error in the form of under-reporting will have occurred, for example, if diverticulosis or a CTD was diagnosed in a setting not covered by these national hospital databases (such as in primary care, in private specialist care or overseas), or if a relevant hospitalisation occurred before 1999 and again not included in the database we used. Further, under-reporting will exist if a condition led directly to death (cause of death data were not examined).

Two sources of error are particularly relevant. Firstly, in a study population of this size, it is impossible to identify all individuals with asymptomatic diverticulosis because investigations tend to occur only after symptoms arise. Studies show that diverticula form at a young age and that the likelihood of symptomatic diverticulosis in those with diverticula detected during CT-scans is only 4–20%.31–33 A substantial number of people with existing but as yet...
### Connective tissue disorders

| Condition                      | Diverticulosis (n=85958) | Non-diverticulosis (n=3441699) | Adjusted odds ratio (95% CI) (Diverticulosis vs Non-diverticulosis) |
|--------------------------------|--------------------------|-------------------------------|---------------------------------------------------------------|
| Rectal prolapse                | 768 (0.89)               | 3874 (0.13)                   | 3.9 (3.6, 4.3)                                               |
| Polycystic kidney disease      | 197 (0.23)               | 1330 (0.04)                   | 3.8 (3.2, 4.4)                                               |
| Heritable syndromes           | 18 (0.02)                | 452 (0.01)                    | 2.4 (1.5, 3.8)                                               |
| Female genital prolapse        | 2527 (5.42)              | 27321 (1.53)                  | 2.3 (2.2, 2.4)                                               |
| Other aneurysm                 | 609 (0.71)               | 5334 (0.17)                   | 2.3 (2.1, 2.5)                                               |
| Aortic aneurysm                | 2218 (2.58)              | 17721 (0.57)                  | 2.2 (2.1, 2.3)                                               |
| Inguinal hernia                | 3956 (4.60)              | 54552 (1.66)                  | 1.9 (1.9, 2.0)                                               |
| Dislocations                   | 855 (0.99)               | 18693 (0.54)                  | 1.7 (1.6, 1.8)                                               |
| Subarachnoid haemorrhage       | 279 (0.32)               | 6703 (0.20)                   | 1.0 (0.9, 1.2)                                               |

**Figure 2.** Association of diverticulosis with selected connective tissue disorders.

ORs were adjusted for gender, year of birth, ethnic group and region. Female genital prolapse analysis included female participants only.
Table 2. Occurrence of first diverticulosis diagnosis and selected connective tissue disorder diagnoses.

| Disorders of interest | No. of people with a hospital diagnosis of the disorder | Age this condition was first recorded: median (Q1, Q3) | Percentage of first hospital diagnoses for disorders of interest that occur within period |
|-----------------------|--------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------------------------------------|
|                       | In whole population | In those with HDD | >6 months prior to index HDD | ± 6 months of index HDD | >6 months after index HDD |
| Diverticulosis        | 85,958               | 85,958             | 70 (59, 78) | - | 100.0 | - |
| Rectal prolapse       | 4,642                | 768                | 69 (54, 81) | 21.1 | 37.9 | 41.0 |
| Polycystic kidney disease | 1,527          | 197                | 58 (46, 73) | 54.8 | 25.4 | 19.8 |
| Heritable syndromes   | 470                  | 18                 | 38 (28, 51) | 66.6 | 16.7 | 16.7 |
| Female genital prolapse | 29,848          | 2,527              | 61 (49, 71) | 54.8 | 11.9 | 33.3 |
| Other aneurysm        | 5,943                | 609                | 70 (59, 78) | 37.4 | 19.9 | 42.7 |
| Aortic aneurysm       | 19,939               | 2,218              | 75 (68, 82) | 34.1 | 31.1 | 34.8 |
| Inguinal hernia       | 58,508               | 1,956              | 62 (48, 73) | 46.4 | 15.8 | 37.8 |
| Shoulder dislocations | 19,548               | 855                | 48 (32, 68) | 40.4 | 8.8  | 50.8 |
| Subarachnoid haemorrhage | 6,982           | 279                | 58 (48, 71) | 40.9 | 11.1 | 48.0 |

Q1, Q3 are the first and third quartiles about the median.
HDD = hospital diagnosis of diverticulosis (ICD-10-AM K57)
Heritable syndromes is the combination of Marfan syndrome and Ehlers-Danlos syndrome.
Shoulder dislocation is the combination of shoulder girdle or other specific joint derangements.
Other aneurysm includes carotid, renal, iliac and other arteries.

non-troublesome and unrecognised diverticula will thus be misclassified as without diverticulosis in our analyses. The bias thereby introduced will vary according to the true (unknown) rate, but statistically, if those with unrecognised diverticulosis have CTDs at rates even slightly higher than the population as a whole, our ORs will underestimate, rather than overestimate, the diverticulosis-related risk.

Secondly, in this study, CTDs are probably under-reported if typically identified at younger age than diverticulosis. For example, the two heritable syndromes are often detected in childhood, potentially even before our datasets were established. If no further hospitalisation has occurred since 1999 the CTD may be under-reported. Alternatively, if CTDs are identified as adults they may be more completely recorded in our data than is diverticulosis if not treated in hospital. In either case the ORs may be biased.

Finally is the question of incidental diagnoses, for which the order (in life), and timing of diagnoses is potentially informative. This is a question for each disorder separately, given its location within the body, similarity of signs and symptoms with those of diverticulosis, typical age at onset and/or diagnosis, and whether investigations to detect one, might incidentally detect another. Accordingly, we considered whether or not the CTD diagnosis preceded, corresponded with, or followed, the first diverticulosis diagnosis. We report median age and the period of diagnosis and discuss the potential for biases for each CTD separately.

Rectal prolapse

Rectal prolapse was the condition most associated with diverticulosis (OR = 3.9; 95%CI 3.6–4.3). There is clear potential for co-diagnosis because of similar location within the body and related symptoms. Several small case series have reported diverticulosis coincident with rectal prolapse, but we found no epidemiological reports of this association. Although straining and constipation may be regarded as a potential shared cause for both conditions, recent independent studies report that, contrary to prior belief, constipation and diverticulosis are unrelated. In our study, analysis by date of diagnosis shows that as many as 38% of CTDs are diagnosed within 6 months of the diverticulosis diagnosis, strongly suggesting co-diagnosis. The ORs reported may, therefore, overstate the true association.

Polycystic kidney disease

PKD is a CTD that is clearly genetic. It is associated with cyst formation in other organs, such as the liver and arachnoid membranes, as well as other abnormalities including intracranial aneurysms, aortic aneurysms, and abdominal wall hernias. PKD may feasibly involve connective tissue failure that extends to the colon, and hence to diverticulosis.

The adjusted odds of having PKD among those with diverticulosis were almost four times (OR = 3.8, 95%CI 3.2–4.4) greater than those without diverticulosis. Previous reports are inconsistent. In patients undergoing abdominal CT scans, three-fold rates of renal cysts were reported in diverticulosis patients (53.4%) versus controls (18.7%). Among renal transplant patients, those with renal failure due to PKD experienced a significantly higher risk of diverticulitis than did other patients with end-stage renal disease. Patients with chronic renal failure due to PKD have a high incidence of diverticulosis in one study, but two smaller studies found no increased risk. At first glance the present findings lend compelling support for an association between the two conditions. Examination of the time periods, however, showed...
that 25% of the two diagnoses (PKD and diverticulosis) occurred within a relatively short period, so it is possible that investigating one set of symptoms incidentally discovered another condition, leading to odds ratios that may overstate the real associations.

**Heritable syndromes**

The associations between diverticulosis and two heritable CTDs, Marfan syndrome and Ehlers-Danlos syndrome, are well recognised.\(^\text{18,41}\) While a review by Beckers et al. demonstrated a CTD link between generalised joint hypermobility (including Ehlers-Danlos syndrome), gut dysmotility, rectal prolapse, female genital prolapse and hiatal hernia, that review did not include diverticulosis.\(^\text{42}\) However in a Danish population-based study, diverticulosis hospitalisation rates for those with Ehlers-Danlos syndrome were almost three times those of controls.\(^\text{43}\) In the present study, the reverse relationship is slightly weaker but remains strong (OR = 2.4, 95%CI 1.5–3.8), but the confidence interval is relatively wide, with power low because the conditions are rare and perhaps under-reported as described. Further, because survival to older age, when diverticulosis becomes more common, is less likely in people with these syndromes, so diverticulosis is less likely to be observed.

**Female genitourinary prolapse**

Higher odds (OR = 2.3, 95%CI 2.2–2.4) of female genitourinary prolapse were observed for those with diverticulosis. The timing of first diagnosis of prolapse is less associated temporally with diverticulosis than either PKD or rectal prolapse, with only about 12% occurring around the time of diverticulosis diagnosis, and the median age first recorded (61 years) is younger than that for diverticulosis (70 years). Thus, the ORs may be subject to little bias.

**Aneurysms**

When examining the association for aneurysms, we chose to investigate aortic and other aneurysms separately; both were positively associated with diverticulosis (OR = 2.2 and 2.3, respectively). We did not distinguish between thoracic or abdominal aortic aneurysms. The high percentage of aortic aneurysms was diagnosed around the time of diverticulosis diagnosis possibly because both diverticulosis and an abdominal aortic aneurysm were found during a single abdominal CT scan, and the ORs may be upwardly biased in consequence. However, the ORs are similar for aneurysms elsewhere.

**Inguinal hernia**

Over 60 years ago, Saint’s triad (the concurrence of gallstones, abdominal hernia and diverticulosis) linked colonic diverticula and abdominal hernia.\(^\text{7,44}\) More recently a large study of colonoscopies in Denmark concluded that colonic diverticulosis was associated with hernia repair.\(^\text{8}\) In the present study, although both diverticulosis and inguinal hernia are abdominal, inguinal hernia is not first detected near the diverticulosis index date, suggesting little bias in the ORs (1.9) and thus supporting the potential for a linked pathology with diverticulosis.\(^\text{7,8,45}\)

**Shoulder joint hypermobility**

Shoulder joint hypermobility has been described as a CTD.\(^\text{46,47}\) It is typically detected at a much younger age than diverticulosis, and unlikely to be detected during DD-related investigations, and therefore is reasonably unbiased. While the OR (1.7) was slightly lower than for other CTDs studied, it was statistically significant.

**Subarachnoid haemorrhage**

Subarachnoid haemorrhage was the only CTD investigated that appeared unrelated to diverticulosis (OR = 1.00). Both familial and collagen links are acknowledged for subarachnoid haemorrhage, with previous studies showing linkages to abdominal aortic aneurysm, PKD and heritable syndromes.\(^\text{48}\) Hypothetically, the current study may miss a real association because of relatively poor survival following subarachnoid haemorrhage leaving some diverticulosis cases unidentified.

Taken singly, these results contribute little to the understanding of diverticular formation. In combination, however, the overall odds of having one of these nine CTDs diagnosed in people with diverticulosis are about twice those without diverticulosis, suggesting that a common factor may exist. ECM pathologies have been observed in each of eight of the nine CTDs studied. Those pathologies include excessive and uncontrolled collagen deposition, imbalances of collagen type I to collagen type III, increased collagen cross-linking and increased elastin levels in the ECM. Should ECM/connective tissue alterations in other anatomical areas be indeed linked, then a shared, potentially genetic, origin may contribute to diverticular aetiology.

While our findings are not conclusive proof that diverticulosis is a CTD nor in themselves confirm a shared causal pathway, they support and bring together several current theories on pathophysiology of diverticulosis based upon basic science and physiological studies—that a predisposition towards connective tissue dysfunction,
Exposure to a diverticulosis hospitalisation was associated with abdominal symptoms involving connective tissue and, of particular interest to those with a family history of the disease. Until the causes and risk factors for diverticulosis are understood, counselling patients with chronic or persistent symptoms regarding management will remain difficult and leave self-management poorly informed.

Key messages

- Risk of hospitalisation for nine connective tissue disorders among people with a diagnosis of diverticulosis was compared to those without in a population of 3.5 million adults.
- Exposure to a diverticulosis hospitalisation was strongly associated with a hospital diagnosis of rectal prolapse and polycystic kidney disease, with odds ratios over 3.5.
- Increased odds were also found for female genital prolapse, heritable syndromes (Marfan and Ehlers-Danlos), non-aortic aneurysm, inguinal hernia, aortic aneurysm and dislocated shoulder, but not subarachnoid haemorrhage.
- The findings are consistent with diverticulosis and other connective tissue conditions being disorders with some shared origins, potentially genetic. Studies from a range of disciplines are required to advance knowledge about the formation of diverticula.

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References

1. Bollom A, Austrie J, Hirsch W, Nee J, Friedlander D, Ellingson K, Cheng V, Lembo A. Emergency department burden of diverticulitis in the USA, 2006–2013. Dig Dis Sci. 2017;62(10):2694–2703. [published Online First: 2017/03/24], doi:10.1007/s10620-017-4525-y
2. Vather R, Broad JB, Jaung R, Robertson J, Bissett IP. Demographics and trends in the acute presentation of diverticular disease: a national study. ANZ J Surg. 2015;85:744–748. doi:10.1111/ans.13147
3. Walker MM, Harris AK. Pathogenesis of diverticulosis and diverticular disease. Minerva Gastroenterol Dietol. 2017; 63(2):99–109. doi:10.23736/S1121-421X.16.02360-6
4. Wedel T, Barreneschee M, Lange C, Cossais F, Böttner M. Morphologic basis for developing diverticular disease, diverticulitis, and diverticular bleeding. Viszeralmedizin. 2015; 31(2):76–82. doi:10.1159/000381431
5. Strate LL, Modi R, Cohen E, Spiegel BMR. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 2012; 107(10):1486–1493. doi:10.1038/aaj.2012.194
6. Strate LL. Diverticulosis and dietary fiber: rethinking the relationship. Gastroenterol. 2012; 142(2):205–207. doi:10.1053/j.gastro.2011.12.019
7. Hauer-Jensen M, Bursac Z, Read RC. Is herniosis the single etiology of Saint’s triad? Hernia. 2009; 13(1):29–34. doi:10.1007/s10029-008-0421-x
8. Oma E, Jorgensen LN, Meisner S, Henriksen NA. Colonic diverticulosis is associated with abdominal wall hernia. Hernia. 2017; 21(4):525–529. doi:10.1007/s10029-017-1598-7
9. Wrafter PF, Connelly TM, Khan JS, Lucey BC, Berg A, Koltun W, Joyce WP. Diverticular disease is associated with benign intra-abdominal cystic disease. Expert Rev

Author contributions

JBB conceived the study, obtained funding, data and ethical approval, had oversight of analyses, and prepared all versions of the manuscript. ZW conducted analyses, prepared figures and tables, and provided critical review. All other authors provided specialist background knowledge and critical academic review. All authors gave approval of the final manuscript version for submission.
32. Loffeld RJ. Long-term follow-up and development of diverticulitis in patients diagnosed with diverticulosis of the colon. Int J Colorectal Dis. 2016;31(1):15–17. [published Online First: 2015/09/28]. doi:10.1007/s00384-015-2397-1

33. Strate LL. Lifestyle factors and the course of diverticular disease. Dig Dis. 2012;30(1):35–45. [published Online First: 2012/05/11]. doi:10.1159/000335707

34. Braunschmid T, Stift A, Mittlbock M, et al. Constipation is not associated with diverticular disease - Analysis of 976 patients. Int J Surg. 2015;19:42–45. [published Online First: 2015/05/20]. doi:10.1016/j.ijsu.2015.04.045

35. Peery AF, Sandler RS, Ahnen DJ, Galanko JA, Holm AN, Shaukat A, Mott LA, Barry EL, Fried DA, Baron JA. Constipation and a low-fiber diet are not associated with diverticulosis. Clin Gastroenterol Hepatol. 2013;11(12):1622–1627. [published Online First: 2013/07/31]. doi:10.1016/j.cgh.2013.06.033

36. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet. 2007; 369 (9569):1287–1301. doi:10.1016/S0140-6736(07)60601-1

37. Luciano RL, Dahl NK. Extra-renal manifestations of autosomal dominant polycystic kidney disease (ADPKD): considerations for routine screening and management. Nephrol Dial Transplant. 2014; 29 (2):247–254. doi:10.1093/ndt/gft437

38. Morris-Stiff G, Coles G, Moore R, Jurewicz A, Lord R. Abdominal wall hernia in autosomal dominant polycystic kidney disease. Br J Surg. 1997;84(5):615–617.

39. Lederman ED, Conti DJ, Lempert N, Singh TP, Lee EC. Complicated diverticulitis following renal transplantation. Dis Colon Rectum. 1998;41 (5):613–618. [published Online First: 1998/05/21].

40. Scheff RT, Zuckerman G, Harter H, Delmez J, Koehler R. Diverticular disease in patients with chronic renal failure due to polycystic kidney disease. Ann Intern Med. 1980;92(2 Pt 1):202–204. [published Online First: 1980/02/01].

41. Malfait F, De Paepe A. Molecular genetics in classic Ehlers-Danlos syndrome. Am J Med Genet C Semin Med Genet. 2005; 139C(1):17–23. doi:10.1002/ajmg.c.30070

42. Beckers AB, Keszthelyi D, Fikree A, et al. Gastrointestinal disorders in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type: A review for the gastroenterologist. Neurogastroenterol Motil. 2017;29(8). [published Online First: 2017/01/14]. doi:10.1111/nmo.13013

43. Leganger J, Soborg MLK, Mortensen LQ, Gregersen R, Rosenberg J, Burchart J. Association between diverticular disease and Ehlers-Danlos syndrome: a 13-year nationwide population-based cohort study. Int J Colorectal Dis. 2016; 31(12):1863–1867. doi:10.1007/s00384-016-2650-2

44. Simic AP, Skrobic OM, Djuric-Stefanovic A, Stojakov D, Peiko PM. From Ockham’s razor to Hickam’s dictum and back-Saint’s theory and the insights in herniosis. Eur Surg. 2015; 47(1):9–14. doi:10.1007/s10353-014-0292-6

45. Henriksen NA, Mortensen JH, Lorentzen L, Ågren MS, Bay-Jensen AC, Jorgensen LN, Karsdal MA. Abdominal wall hernias-A local manifestation of systemically impaired quality of the extracellular matrix. Surgery. 2016; 160(1):220–227. doi:10.1016/j.surg.2016.02.011

46. Zarate N, Farmer AD, Grahame R, Mohammed SD, Knowles CH, Scott SM, Aziz Q. Unexplained gastrointestinal symptoms and joint hypermobility: is connective tissue the missing link? Neurogastroenterol Motil. 2010; 22(3):252–e78. doi:10.1111/j.1365-2982.2009.01421.x

47. Knuuti E, Kauppila S, Kotila V, Risteli J, Nissi R. Genitourinary prolapse and joint hypermobility are associated with altered type I and III collagen metabolism. Arch Gynecol Obstet. 2011; 283 (5):1081–1085. doi:10.1007/s00404-010-1518-x

48. Zhang B, Fugleholm K, Day LB, Ye S, Weller RO, Day INM. Molecular pathogenesis of subarachnoid haemorrhage. Int J Biochem Cell Biol. 2003;35 (9):1341–1360. [published Online First: 2003/06/12].

49. Maguire LH, Handelman SK, Du X, Chen Y, Pers TH, Speliotes EK. Genome-wide association analyses identify 39 new susceptibility loci for diverticular disease. Nat Genet. 2018;50(10):1359–1365. [published Online First: 2018/09/05]. doi:10.1038/s41588-018-0203-z