The IDEA Journal
International Digestive Experts Articles

Year IV - N. 4, December 2022

Editorial
Updates on Literature

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mediAbout

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Editorial
Updates on Literature 5

Low FODMAP diet or medication in primary care patients with IBS 7

Post-polypectomy endoscopic surveillance: more doubts than answers 10

How Good Is Screening Colonoscopy? Comment on the NordICC Trial 13

How much *Helicobacter Pylori* eradication therapy prevents gastric cancer after 26 years? 16

A link between the gut microbiome and long-standing type 1 diabetes 20

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EDITORIAL STANDARDS

AIMS AND SCOPE

The International Digestive Experts Articles Journal is a peer-reviewed journal on prevention, diagnosis and management of gastrointestinal disorders. The journal is primarily intended for the update of gastroenterologists, hepatologists, and all medical doctors focusing their practice on digestive pathologies.

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Editorial

Updates on Literature

In this fourth number of *The IDEA Journal 2022*, five new studies from the gastroenterology literature are discussed.

In the first editorial contribution, Bredenoord discusses the finding of a recent study investigating and proving the beneficial effect of the FODMAP-lowering diet in patients with *irritable bowel syndrome*. Importantly, patients in this study were recruited by primary care physicians, thus providing the first evidence that this type of diet can have benefits on patients' symptoms even in primary care. Despite the study limitations, this result opens for the possibility of considering this type of diet as first-line treatment.

In the second editorial contribution, Antonelli, Sharma, and Hassan give a critical perspective on a recent study evaluating a large cohort of UK patients undergoing endoscopic surveillance. Specifically, participants were stratified according to the updated criteria adopted by the ESGE and the UK guidelines on surveillance. This study gives further insight on surveillance after *polypectomy*, by providing a description of colonoscopy practice in real life in the past 15 years.

Antonelli, Sharma, and Hassan also comment another recent publication on the subject of screening colonoscopy, which is currently the main technique to diagnose *colorectal cancer*. The study, ongoing since 2009, is the first long-standing randomized controlled trial measuring the incidence and mortality of colorectal cancer to estimate colonoscopy effectiveness. Although not exceptional as expected, at the 10-year follow-up, colonoscopy still showed a high effect in reducing colorectal cancer incidence and mortality.

In the fourth editorial contribution, the focus is on the results of the 26.5-year follow-up of a Chinese randomized, placebo-controlled trial on Helicobacter Pylori and eradication therapy. This technique was found to reduce the risk of *gastric cancer*, and the beneficial effects were more prominent among patients with precancerous gastric lesions, or with successful eradication and no re-infection.

The final editorial contribution of this year reports the results of a study addressing the potential link between the gut microbiome and *long-standing type 1 diabetes mellitus*. Patients affected by this pathology are at risk of developing micro- and macrovascular complications, and there is evidence that the gut microbiome may play a role in the development of immune-mediated diseases. First, patients' gut microbiome, as compared to controls', was enriched of opportunistic pathogens and depleted of commensal species. Moreover, not only the glycaemic control explained a significant portion of the variation in species and pathways, but so did both micro- and macrovascular complications, calling for increasing attention on the matter.

We hope you enjoy the reading,
The Editorial Board

Low FODMAP diet or medication in primary care patients with IBS

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Comment to: Carbone, F., van den Houte, K., Besard, L., Tack, C., Arts, J., Caenepeel, P., Piessevaux, H., Vandenberghe, A., Matthys, C., Biesiekierski, J., Capiau, L., Ceulemans, S., Gernay, O., Jones, L., Maes, S., Peetermans, C., Raat, W., Stubbe, J., van Boxstael, R., ... Tack, J. (2022). Diet or medication in primary care patients with IBS: The DOMINO study - A randomised trial supported by the Belgian Health Care Knowledge Centre (KCE Trials Programme) and the Rome Foundation Research Institute. Gut. https://doi.org/10.1136/gutjnl-2021-325821

The irritable bowel syndrome (IBS) is defined by the Rome IV criteria as recurrent abdominal pain associated with a change in stool frequency and/or form or abdominal pain associated with defecation (see the in-depth Box 1). Other symptoms in IBS are bloating, abdominal distention, diarrhea, constipation and flatulence. IBS exists in a large range of severity, from occasional mild symptoms to severe daily incapacitating symptoms. Patients with milder or less frequent symptoms usually seek care via internet and relatives and friends, while patients with more severe phenotypes seek medical care and consult their primary care physician. A small proportion of IBS patients is eventually referred to gastroenterologists and undergoes additional testing such as endoscopy, lab, and radiological testing. Given this, the majority of patients have mild to moderately severe phenotypes and only occasionally consult their general practitioner (1,2).

Multiple treatments have been proposed for IBS, but most have limited therapeutic gain and a large number needed to treat. Spasmodic agents are often prescribed and are seen as standard treatment (3). Otilonium bromide is a calcium channel blocker that has been shown to improve abdominal pain and bloating. Other recommendations are peppermint oil, iberogast, psyllium fibers and, sometimes, antidepressants to treat the pain. Constipation and diarrhea are treated with laxatives and loperamide, respectively.

The **FODMAP-lowering diet** has been proven to be effective for the treatment of the **irritable bowel syndrome**, as shown in tertiary care patients. In this study, patients with irritable bowel syndrome and recruited by **primary care** physicians were randomized to either undergo a treatment with otilonium bromide or with a FODMAP-lowering diet for 24 weeks. The resulting better ability of the FODMAP-lowering diet in reducing patients' symptoms is important especially because it occurred in primary care, suggesting the possibility of being considered as a first-line treatment.

Dietary treatments have been recommended to IBS patients increasingly in secondary and tertiary care, but are not uniformly used in primary care. The low FODMAP diet has been studied the most in the past decade (4). This diet is low in FODMAPs, being fermentable oligosaccharides, disaccharides, monosaccharides and polyols and improves symptoms after 6–8 weeks (Figure 1). However, the low FODMAP diet is complex and requires several visits with an experienced dietitian and it has been associated with decreased caloric intake, with some nutrient inadequacies, as well as with potentially unfavorable effects on gut microbiota composition. Therefore, less stringent FODMAP-lowering dietary interventions have been explored, with good results.

Figure 1

Although most IBS patients are found in primary care, the effects of low FODMAP diets have not been studied in that particular population yet.

In this newly published study by Carbone and colleagues, 459 IBS patients, recruited by primary care physicians, were randomized to 8 weeks of either otilonium bromide 40 mg three times a day or FODMAP-lowering diet and followed for 24 weeks. Patients randomized to diet were instructed to download an application on their smartphone, those without smartphone (2% of total) could use a booklet for instructions. The dietary intervention was set up as a mobile application with instructions written in French and Dutch. The design of the mobile application was based on the self-determination theory to stimulate a change in dietary behaviour. Strikingly, in the treatment, no dietitian was involved. The diet was not a strict low FODMAP diet, but rather a less stringent diet designed as a FODMAP-lowering diet in combination with dietary recommendations from National Institute for Health and Care Excellence/the British Dietetic Association (NICE/BDA) guidelines for IBS.

The results show that the responder rate after 8 weeks was significantly higher with FODMAP-lowering diet compared with otilonium bromide (71% vs 61%). Patients allocated to FODMAP-lowering diet were more often adherent to their treatment (93%)

Rome IV Criteria

C. BOWEL DISORDERS

C1. IRRITABLE BOWEL SYNDROME

*Diagnostic criteria**

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with **two or more** of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Source: https://theromefoundation.org/rome-iv/rome-iv-criteria/

Box 1.

compared with otilonium bromide (73%). The significantly higher response rate with FODMAP-lowering diet was already observed after 4 weeks and a high symptom response persisted during follow-up. These results implicate that FODMAP-lowering diets can also be effective in primary care IBS patients. It also shows it is feasible and it suggests that this could be considered the first-line treatment for IBS in primary care.

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Post-polypectomy endoscopic surveillance: more doubts than answers

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Comment to: Cross, A. J., Robbins, E. C., Pack, K., Stenson, I., Rutter, M. D., Veitch, A. M., Saunders, B. P., Duffy, S. W., & Wooldrage, K. (2022). Post-polypectomy surveillance interval and advanced neoplasia detection rates: A multicenter, retrospective cohort study. Endoscopy. https://doi.org/10.1055/a-1795-4673

Colonoscopy and polypectomy of pre-malignant polyps represent the intervention of choice for the prevention of colorectal cancer (CRC) (1). Patients undergoing resection of pre-malignant polyps may be at increased risk of developing metachronous advanced neoplasia and CRC and are usually suggested to undergo endoscopic surveillance with another colonoscopy after a certain period of time. However, there are no high-quality studies, especially no randomised controlled trials, evaluating the impact of different surveillance strategies on hard outcomes like CRC incidence or mortality. Available recommendations are based mostly on studies with different designs but with a low level of evidence (2). In fact, endoscopic surveillance accounts for up to 20% of the colonoscopies performed, with a limited benefit on CRC reduction when compared with participation in CRC screening programs.

During the past 15 years, two significant changes have modified surveillance strategies. First, CRC screening programs have spread throughout much of the Western world. As a result, the number of subjects with premalignant lesions has increased significantly (3). The second great change is the introduction of quality indicators in colonoscopy (4). The culture of quality improvement in colonoscopy has been embraced by most endoscopists and endoscopy units. Consequently, the proportion of colonoscopies with premalignant polyps has increased and the risk of CRC during surveillance has been reduced. In addition, the performance of the endoscopist, measured by the adenoma detection rate, is critical in determining the long-term CRC incidence (1). To date, available guidelines are based only on endoscopic findings and do not consider endoscopists' quality indicators.

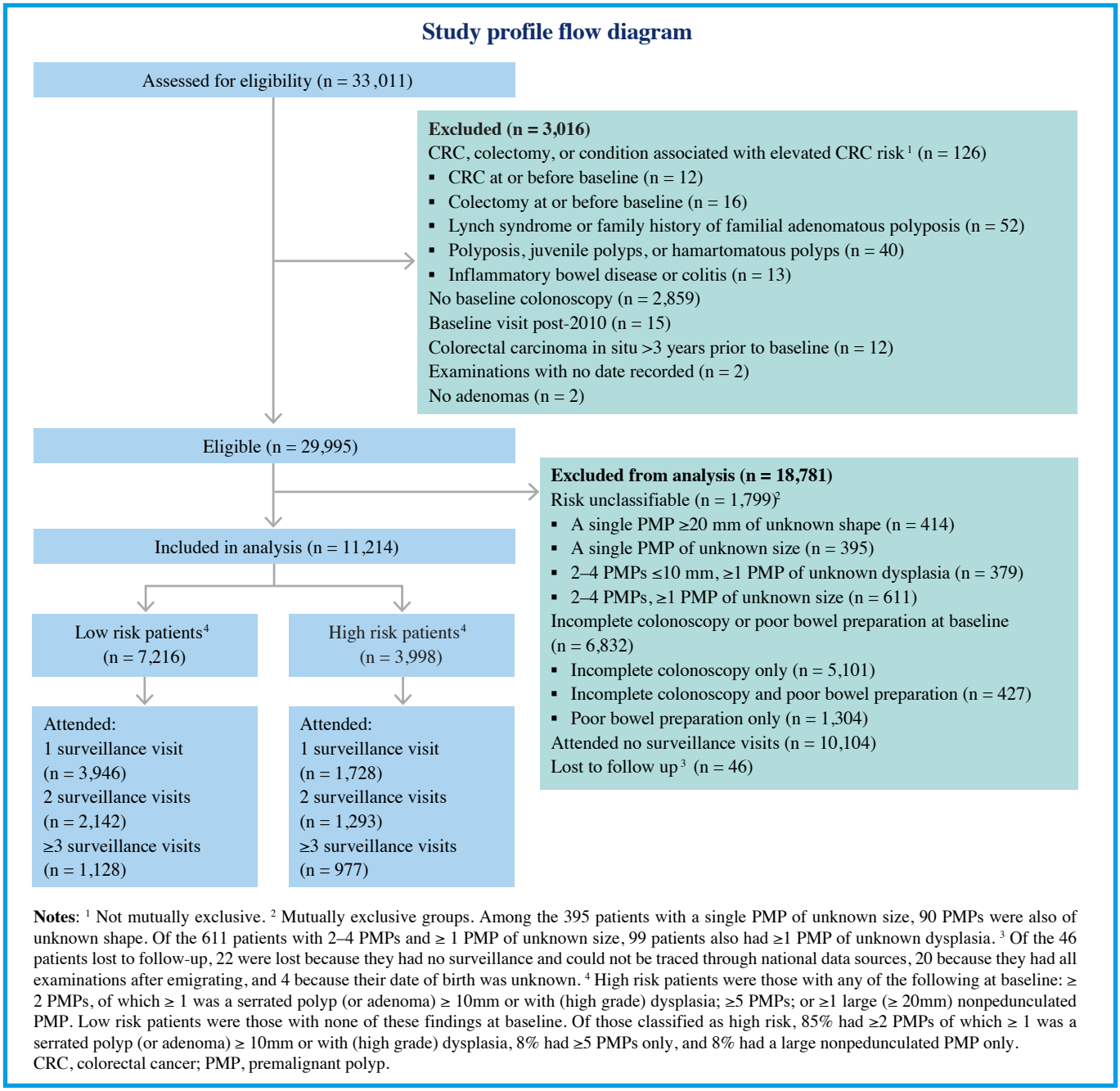
In the last 2 years, both European and US guidelines have been updated (5,6). European guidelines have re-shaped the concept of a high-risk individual, with

The authors discuss the results of a recent study evaluating a large group of UK patients undergoing **endoscopic surveillance**, stratified according to the updated criteria adopted both by the ESGE and the UK guidelines on surveillance. Despite considerable limitations, this study increases knowledge on surveillance after **polypectomy**, giving a well descripted "real-life" scenario of **colonoscopy** practice in the past 15 years.

the intent of reducing the magnitude of patients sent to surveillance endoscopy. In addition, it must be underlined that all low-risk individuals are not recommended to undergo no surveillance, but to return to the screening program, meaning that they will nonetheless undergo a FIT in 5 to 10 years.

A group of large, European randomised trials investigating the impact of different surveillance strategies are on the way, and are expected to greatly increase our knowledge on endoscopic surveillance (7). The current study by Cross et al., in the meantime, sheds more light on this topic by analysing a large group of UK patients undergoing endoscopic surveillance stratified according to the "new" criteria adopted both by the European Society of Gastrointestinal Endoscopy (ESGE) and the UK guidelines on surveillance (see Supplementary Figure 1).

The authors confirm the low CRC incidence (1.1%) in the "expanded" low-risk group in UK and ESGE guidelines irrespective of the surveillance interval. This result confirms that patients meeting these



Notes: [1] Not mutually exclusive. [2] Mutually exclusive groups. Among the 395 patients with a single PMP of unknown size, 90 PMPs were also of unknown shape. Of the 611 patients with 2–4 PMPs and ≥ 1 PMP of unknown size, 99 patients also had ≥1 PMP of unknown dysplasia. [3] Of the 46 patients lost to follow-up, 22 were lost because they had no surveillance and could not be traced through national data sources, 20 because they had all examinations after emigrating, and 4 because their date of birth was unknown. [4] High risk patients were those with any of the following at baseline: ≥ 2 PMPs, of which ≥ 1 was a serrated polyp (or adenoma) ≥ 10mm or with (high grade) dysplasia; ≥5 PMPs; or ≥1 large (≥ 20mm) nonpedunculated PMP. Low risk patients were those with none of these findings at baseline. Of those classified as high risk, 85% had ≥2 PMPs of which ≥ 1 was a serrated polyp (or adenoma) ≥ 10mm or with (high grade) dysplasia, 8% had ≥5 PMPs only, and 8% had a large nonpedunculated PMP only.
CRC, colorectal cancer; PMP, premalignant polyp.

Supplementary Figure 1

criteria should return to the CRC screening program. On the other hand, the authors have found an increased risk of CRC incidence if surveillance intervals are lengthened in the high-risk group of both guidelines, from 1.0% at a 3-year interval to 2.4% at a 6-year interval, supporting existing recommendations to undergo the first surveillance colonoscopy at 3 years. Although reassuring, this study comes with considerable limitations. First, only about 1/3 of eligible participants were actually included in this study, owing to incomplete or insufficient data. Second, all baseline colonoscopies were performed before 2010, when high-definition colonoscopy was not as universally spread as today, and when quality indicators for colonoscopy were still a rare topic of conversation. Third, majority of available data were retrospective, introducing a serious risk of selection bias. This is particularly evident when looking at the different choices in terms of surveillance intervals that did not follow existing recommendations and are probably due to many uncontrolled factors (bowel prep, endoscopist "feeling", etc.).

In conclusion, this study increases knowledge on surveillance after polypectomy giving a well descripted "real-life" scenario of colonoscopy practice in the last 15 years. It reassures both patients and endoscopists on the right direction that guidelines have undertaken, reducing the burden of unnecessary endoscopic surveillance on already fully saturated endoscopy services. The colonoscopists' community awaits with trepidation and enormous interest the results of the European Polyp Surveillance (EPOS) trials, which will empower us with high quality evidence to make even more informed and evidence-based choices. The current era of personalised medicine will then arrive also in post-polypectomy surveillance, tailoring the right interval to the right patient.

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How Good Is Screening Colonoscopy? Comment on the NordICC Trial

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Comment to: Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death (2022) M. Bretthauer, M. Løberg, P. Wieszczy, M. Kalager, L. Emilsson, K. Garborg, M. Rupinski, E. Dekker, M. Spaander, M. Bugajski, Ø. Holme, A.G. Zauber, N.D. Pilonis, A. Mroz, E.J. Kuipers, J. Shi, M.A. Hernán, H.-O. Adami, J. Regula, G. Hoff, and M.F. Kaminsk. 10.1056/NEJMoa2208375

Colorectal cancer (CRC) accounts for approximately 10% of all annually diagnosed cancers and cancer-related death worldwide. It is the second most common cancer diagnosed in women and third most in men. In women, incidence and mortality are approximately 25% lower than in men. These rates also vary geographically, with the highest rates seen in the most developed countries (1) (see the in-depth Box 1).

In the Western world, different methodologies for CRC screening have been implemented. The ideological pillar of cancer screening is that the detection of tumours at an earlier and more treatable stage, and the removal of precancerous lesions (polyps) results in a reduction of CRC incidence and mortality, and a reduction in costs related to late-stage cancer treatment (2).

The mainstay of CRC screening is colonoscopy, which however is far from representing an ideal screening test. It is a costly and invasive procedure, it is strongly operator-dependent and it has a limited availability. In a screening setting, colonoscopy is either offered as primary upfront colonoscopy, in which individuals are invited to undergo a colonoscopy at a certain age, regardless of symptoms or any other discriminatory factor, or after a positive, first-round non-invasive screening test such as the Faecal Immunochemical Test, that detects a certain level of faecal haemoglobin and is correlated with an increased risk of colorectal neoplasia and advanced neoplasia (3). Both approaches have strengths and pitfalls, but it could be (and has been) argued that in an ideal setting, offering colonoscopy to every individual in screening age is more effective than other indirect tests and should result in an increased protection against colorectal cancer and death.

However, high quality evidence indicating which CRC screening strategy is superior has been

To date, **colonoscopy** is the main technique to diagnose **colorectal cancer**. The study in object, the first long-standing randomized controlled trial, still ongoing since 2009, measures as primary endpoint the incidence and mortality of colorectal cancer to estimate colonoscopy effectiveness. Other endpoints are all cause mortality and tumour stage at diagnosis.

lacking, and in particular, the absence of randomised controlled trials stating the superiority of the primary colonoscopy screening strategy has limited the uptake of this method in many regions of the world.

In this recent article published in The New England Journal of Medicine, Bretthauer et al. report the first round of results of the first long-standing randomised controlled trial investigating the effect of primary colonoscopy screening in a population-based screening program across four different European countries. This is the first report after a 10-year follow-up.

The medical and organisational endeavour behind this trial is enormous. This was a pragmatic randomised trial starting in 2009 and still ongoing, with the last planned analysis in 5 years' time reporting the 15 years outcomes. This trial was started in regions where primary colonoscopy screening programs were not yet in operation, and the investigators randomised individuals to undergo colonoscopy screening or no screening. Individuals randomised to the screening group were invited to undergo colonoscopy and could of course refuse. This trial was ethically possible since no screening programs were active at the time, and individuals randomised to the usual care were not invited to participate but followed up over time to ensure the maintenance of trial and randomisation integrity.

Primary endpoint of the trial was colorectal cancer incidence and mortality at 10 and 15 years of follow-up. Other endpoints were all cause mortality, tumour stage at diagnosis. Primary analysis was conducted following the intention-to-treat principle, but also per protocol analysis and per protocol estimation of the effect of screening if all participants invited to screening had participated.

A total of nearly 85,000 individuals were included, 28,220 in the invited group and 56,365 in the no screening group. The median follow-up for the analysis was 10.0 years in both groups (interquartile range, 9.9 to 10.0; maximum follow-up, 10.0 years). The percentage of participants who underwent screening varied among the countries (from 33.0% in Poland to 60.7% in Norway) and was higher overall among men than among women and among older participants than among younger participants.

The risk of colorectal cancer at 10 years was 0.98% (259 cases) in the invited group and 1.20% (622 cases) in the usual-care group, for a risk ratio of 0.82 (95% confidence interval (CI), 0.70 to 0.93). Among the participants with cases of colorectal cancer for which staging information was available, 0.38% in the invited group and 0.44% in the usual-care group received a diagnosis of early-stage (stage A or B) colorectal cancer, whereas 0.40% in the invited group and 0.50% in the usual-care group received a diagnosis of late-stage (stage C or D) colorectal cancer.

The risk of colorectal cancer-related death at 10 years was 0.28% (72 deaths) among participants in the invited group and 0.31% (157 deaths) among those in the usual-care group (risk ratio, 0.90; 95% CI, 0.64 to 1.16).

In adjusted analyses to estimate the effect of screening if all the participants who were randomly assigned to screening had actually undergone screening, the risk of colorectal cancer at 10 years was decreased from 1.22% to 0.84%, corresponding to an estimated risk ratio of 0.69 (95% CI, 0.55 to 0.83). The risk of death from colorectal cancer was 0.15% in the invited group and 0.30% in the usual-care group. The estimated risk ratio was 0.50 (95% CI, 0.27 to 0.77).

The results of this trial are extremely relevant for a number of reasons and have caused a great debate in the endoscopy community worldwide. They show that on population level, invitation to undergo screening colonoscopy is not enough to ensure a high adherence to the treatment, and that the adherence varies considerably across different countries.

The protective effect of colonoscopy was lower than expected and this can be for a number of reasons. First, the overall mortality rate for CRC in the western world has shown an overall reduction, probably linked to the increased availability of different treatment options and early diagnosis. Second, the follow-up period for mortality may be too low to detect a significant difference, and for this reason the 15-year follow-up analysis will be much more informative on this aspect.

However, it must be noted that a reduction in incidence and mortality was observed and was greater in the Per Protocol Analysis. Although more prone to selection bias, this analysis just took into

consideration the actual individuals who underwent colonoscopy, who were found to be less at risk for CRC incidence and death.

This trial also shows the differences between Intention-To-Treat and Per Protocol Analysis, and the importance of reporting both when reporting the results of a randomised trial. Although not as exceptional as expected, colonoscopy still showed a high effect in reducing CRC incidence and mortality, probably the highest across all cancer screenings currently in use.

According to the International Agency for Research on Cancer (IARC, World Health Organization), colorectal cancer (CRC) is the third most common cancer type worldwide: almost 2 million cases were diagnosed in 2020 and its global burden is estimated to increase to more than 3 million new cases per year (equivalent to 56%) between 2020 and 2040. CRC is the second most common cause of cancer death, leading to almost 1 million deaths recorded per year, even if screening techniques, effective in reducing the number of deaths from this disease, are available. The estimated increase in the number of deaths from the disease amounts to about 1.6 million (69%) deaths worldwide in 2040. Most of the increase is expected to occur in Countries with a high Human Development Index − "a summary measure of average achievement in key dimensions of human development: a long and healthy life, being knowledgeable and have a decent standard of living" (https://hdr.undp.org/data-center/human-development-index#/indicies/HDI). Colon, rectum, and anus are the three distinct cancer types referred to collectively as CRC, whose burden is highest in Asia (more than half of all cases and deaths are recorded there), with China accounting alone for more than half a million new cases and more than 280,000 deaths per year, and Japan with the second highest number of deaths (almost 60,000 per year). Among risk factors, alcohol consumption was responsible, in 2020, for more than 160,000 new cases of CRC, 8% of all cases of the disease diagnosed that year. Tobacco smoking (which causes lung cancer) and human papillomavirus (HPV) infection (which causes cervical cancer) also contribute to the burden of CRC. Another factor increasing the risk of developing CRC is obesity, which is responsible for more than 85,000 cases of colon cancer and 25,000 cases of rectal cancer diagnosed in 2012, and ~23% of all cases of CRC diagnosed that year. IARC thus recommends intentional weight loss, physical activity, and diets rich in fish, fruits, and vegetables to reduce the risk of developing CRC. Moreover, attending organized screening increases the chance of detecting CRC when it is at an earlier, and potentially more manageable and treatable, stage.

Source: https://www.iarc.who.int/featured-news/colorectal-cancer-awareness-month-2022/#colorectal-screening

Box 1.

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How much *Helicobacter Pylori* eradication therapy prevents gastric cancer after 26 years?

Written by the Editorial Secretariat

Comment to: Yan L, Chen Y, Chen F, Tao T, Hu Z, Wang J, You J, Wong BCY, Chen J, Ye W. Effect of Helicobacter pylori Eradication on Gastric Cancer Prevention: Updated Report From a Randomized Controlled Trial With 26.5 Years of Follow-up. Gastroenterology. 2022 Jul;163(1):154-162.e3. doi: 10.1053/j.gastro.2022.03.039. Epub 2022 Mar 29. PMID: 35364066.

Gastric cancer is the fifth most common cancer and the third leading cause of cancer deaths worldwide. ***Helicobacter Pylori (H. Pylori)*** **is a gastric pathogen whose infection is considered one of the triggering factors of gastric carcinogenesis** – progressing from superficial gastritis, chronic atrophic gastritis, intestinal metaplasia and dysplasia, to adenocarcinoma (see Supplementary Figure 1). Infection by these bacteria is associated with an approximately 3-fold increase in the risk of noncardia gastric cancer (1,2).

Nonetheless, the extent of *H. Pylori* eradication efficacy in the prevention of gastric cancer and its long-term effects remain unclear. Heterogeneous findings and disparities in the methodology of the studies that were conducted on the topic have contributed to such uncertainty, as even no favorable effect was noted in some reports.

This article presents the results of the **26.5-year follow-up** of a randomized, placebo-controlled trial conducted in Changle of Fuzhou, Fujian Province, China, in July 1994. Interestingly, Eastern Asia has the highest incidence rates of stomach cancer (3).

1,630 subjects carrying *H. Pylori* infection were included in the study; the pathogen presence was detected by both rapid urease test and histopathologic examination. 817 patients were assigned to the *H. Pylori* eradication therapy (2-week course of 20 mg omeprazole, 750 mg of a combination product of amoxicillin and clavulanate potassium, and 400 mg metronidazole, all twice daily), while 813 were assigned to the placebo (Figure 1). Regular follow-ups and endoscopic check-ups (in 1999, 2006, and 2020) were performed by a local team that was blind to the treatment status of the participants. The primary outcome of the study was the incidence of gastric cancer during follow-ups.

A first 7.5-year follow-up has been published in 2004 (4): the authors found a similar incidence of gastric cancer development between participants receiving *H. Pylori* eradication treatment and those receiving placebo (treatment: 7 cases of gastric cancer vs. placebo: 11; n.s.). In the subgroup of *H. Pylori* carriers without precancerous lesions, eradication of *H. Pylori* significantly decreased the development of

Helicobacter Pylori is a gastric pathogen whose infection is considered one of the triggering factors of gastric carcinogenesis. So far, only heterogeneous findings of helicobacter pylori eradication on the prevention of **gastric cancer** were observed across populations. Moreover, its long-term effect among high-risk populations remains unclear. The present study found that Helicobacter Pylori eradication reduced gastric cancer risk after 26.5-year follow-up, and the beneficial effects were more prominent among those without precancerous gastric lesions, or with successful eradication and no re-infection.

gastric cancer (treatment: 0 cases of gastric cancer vs. placebo: 6; P<0.001).

In the follow-up at 26.5 years, recently published, the authors reported **a significant protective effect of *H. Pylori* eradication accounting for a 43% reduction in gastric cancer risk.** The cumulative incidence of gastric cancers in the two groups is shown in Figure 1. Among a total of 56 cases of diagnosed gastric cancer, 21 (2.57%) were in the *H. Pylori* treatment group and 35 (4.31%) were in the placebo group. The crude incidence rate accounted for 115 per 100,000 person-years in the treatment

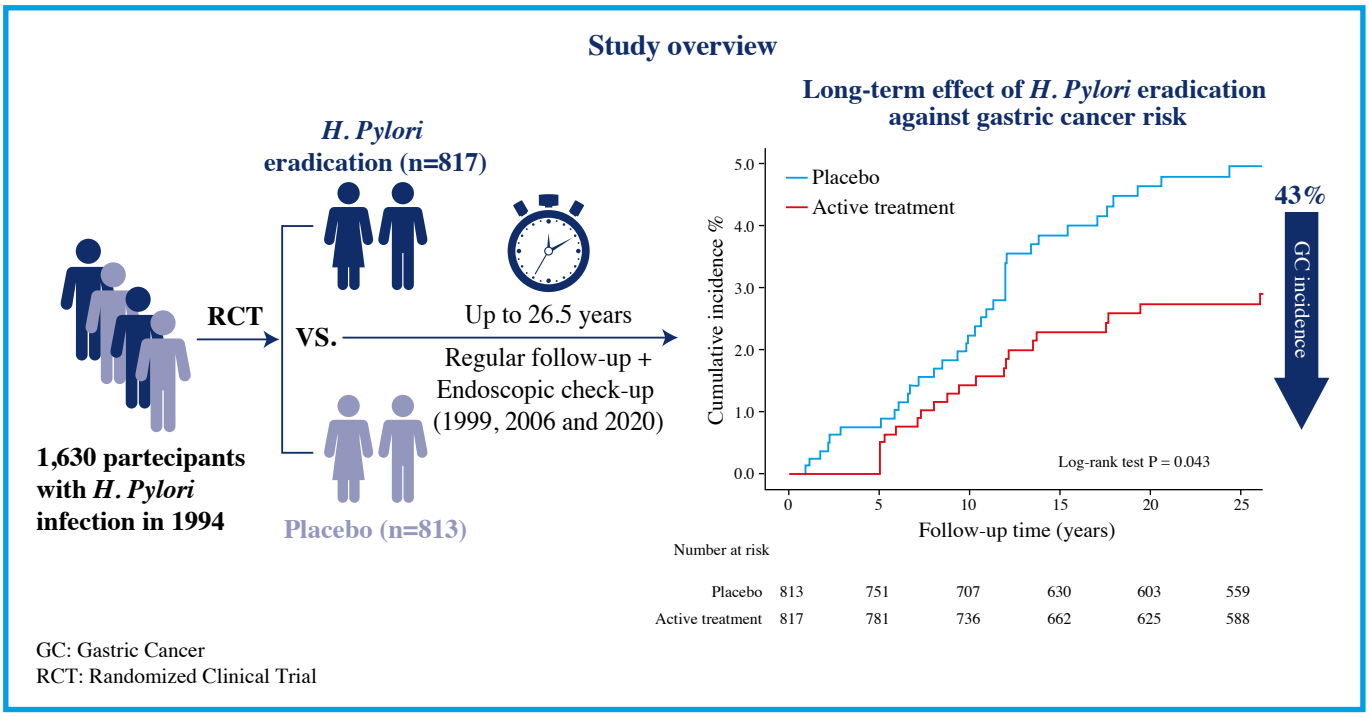


Figure 1

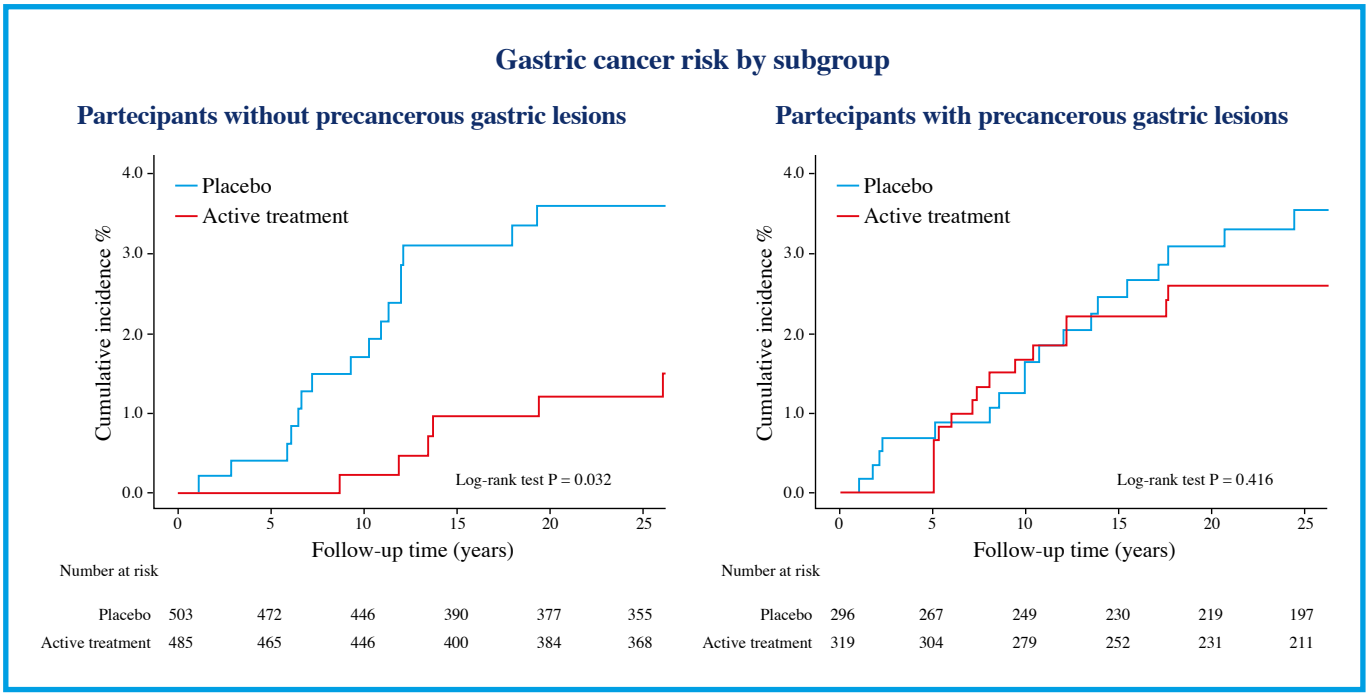


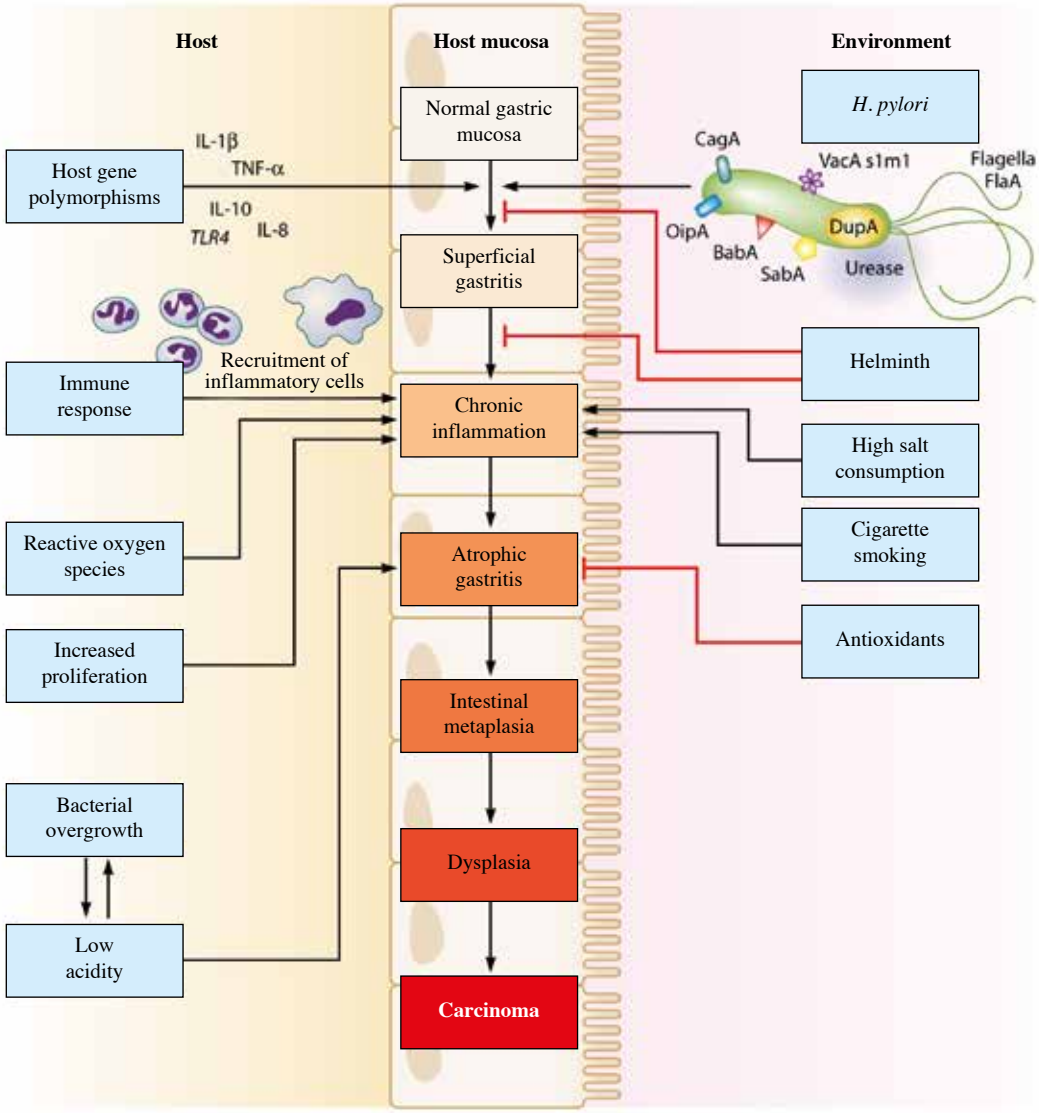
Figure 2

arm compared to 198 per 100,000 person-years in the placebo arm. An increasing incidence of gastric cancer was observed after nearly 1 year from the beginning of the study in the placebo group, whereas in the treated group this increase occurred from the fifth year onwards. Comparing histopathologic diagnoses at baseline and at following follow-ups, authors observed a significantly decreased risk of gastric lesion progression in subjects who received *H. Pylori* treatment compared with the placebo group at different checkup time points.

An even more pronounced risk reduction was observed in the stratified analysis, which compared subjects displaying or not gastric lesions at the baseline histopathology evaluation: **a significantly lower incidence was found in those who displayed no precancerous lesion compared to those who did** (Figure 2). Similarly, a statistically significant protective effect was observed in those without dyspepsia symptoms at baseline. However, no significant difference was observed in separating patients by anatomic subsite of cancer (cardia vs. noncardia) and comparing the treated vs. the placebo group.

An additional analysis was performed comparing

Multifactorial pathway leading to gastric carcinoma



Many host, bacterial, and environmental factors act in combination to contribute to the precancerous cascade leading to development of gastric cancer.

Modified from (8)

Supplementary Figure 1

individuals according to their *H. Pylori* status (presence or absence of persisting bacterial infection). At the 7.5-year follow-up, 47 out of 574 participants in the group receiving placebo were *H. Pylori*-negative (8.19%) vs. 625 out of 758 participants (82.45%) in the group receiving the active treatment. **32 patients with persistent *H. Pylori* infection were diagnosed with gastric cancer in the placebo group, whereas gastric cancer occurred in only 16 of those whose infection was successfully eradicated in the active treatment arm** (6.07% vs. 2.56% respectively; P<0,05). The follow-up at 11.5 years showed that the risk of gastric cancer was still significantly decreased exclusively among those successfully eradicated in the active treatment arm.

Mortality was evaluated as a secondary outcome. At the most recent follow-up, 253 participants had died for all-cause reasons (15.52%): 116 from cancer, 51 from cardiovascular diseases, and 86 from other causes. Among cancer deaths, 32 accounted for gastric cancer, 7 for esophageal cancer, 26 for liver cancer, 24 for lung cancer, ands 27 for other types of cancer. Although a decrease of 24% in mortality in the treated group compared to the placebo was observed, **the difference did not reach statistical significance either for all-cause mortality or for cause-specific mortality.**

In conclusion, **this study found that *H. Pylori* eradication therapy effectively prevents gastric cancer in *H. Pylori*-infected patients and its beneficial effects are more prominent in those who did not display precancerous lesions or dyspepsia symptoms at baseline, or whose *H. Pylori* eradication was successful** (with no re-infection). No significant difference in the overall mortality was observed and a similar risk-reduction effect was found for both cardia and noncardia cancer.

Overall these results are consistent with those of another long-term study (5) that described a reduction of 39% in gastric cancer risk upon *H. Pylori* eradication therapy over a 14.7-year follow-up. However, it is worth noting that, since all subjects in this study were H. Pylori-positive at the start, the present findings do not prove the need for H. Pylori testing. Moreover, considering that in Western countries the prevalence of H. Pylori has become very low (6), and that the number needed to test-and-treat (7) is probably very high to see any effect in this population, whether or not test-and-treat is helpful cannot be determined by this study.

Finally, the generalizability of these results to low-risk populations is still unknown.

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A link between the gut microbiome and long-standing type 1 diabetes

Written by the Editorial Secretariat

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Hyperglycemia is an important risk factor in the development of several diabetes-related complications (1), and poor glycaemic control is associated with systemic low-grade inflammation (1,2). While several studies have indicated that the gut microbiome may play a role in the development of immune-mediated diseases, including type 1 diabetes (3–5) (see Supplementary Figure 1), only a few studies have investigated its role in long-standing type 1 diabetes. Furthermore, studies focusing on the differences in the gut microbial composition in long-standing type 1 diabetes in larger cohorts and on the potential link with diabetes-associated complications are lacking.

In the study in object, the gut microbiome was characterized using whole-genome shotgun sequencing in a cohort of 240 patients with long-standing type 1 diabetes with a large range of glucose control, diabetes duration, and complications. Patients with type 1 diabetes in the final sample had an average age of 52 ± 16 years, an average HbA1c (glycosylated haemoglobin as index of glycaemic control) of 8% (63.6 mmol/mol), and an average disease duration of 28 ± 15 years. These patients were compared to a large (n = 2,937), age-, sex-, and BMI-matched, healthy control group to identify whether the microbiome composition is in fact associated with type 1 diabetes-related traits.

Patients with type 1 diabetes are at risk for developing micro- and macrovascular complications. Since there is evidence that the gut microbiome may play a role in the development of immune-mediated diseases, the present study investigated the potential link between the gut microbiome and long-standing type 1 diabetes.

The authors characterized the gut microbiome of all participants. In brief, faecal samples from the two cohorts were collected and processed using a uniform workflow (6), and metagenomic sequencing data were analysed using standardized methods (6). To define the impact of diabetes-associated characteristics on the gut microbiome composition, microbiome variance per phenotype was determined, and microbial taxonomy was associated with type 1 diabetes–related characteristics and vascular complications.

Results showed that no differences in alpha-diversity of microbial taxa between patients with diabetes and healthy participants emerged, while patients with diabetes showed a small but significant increase in α-diversity of microbial biochemical pathways. Concerning the gut microbiome composition, 37 bacterial species (including *Clostridiaceae,*

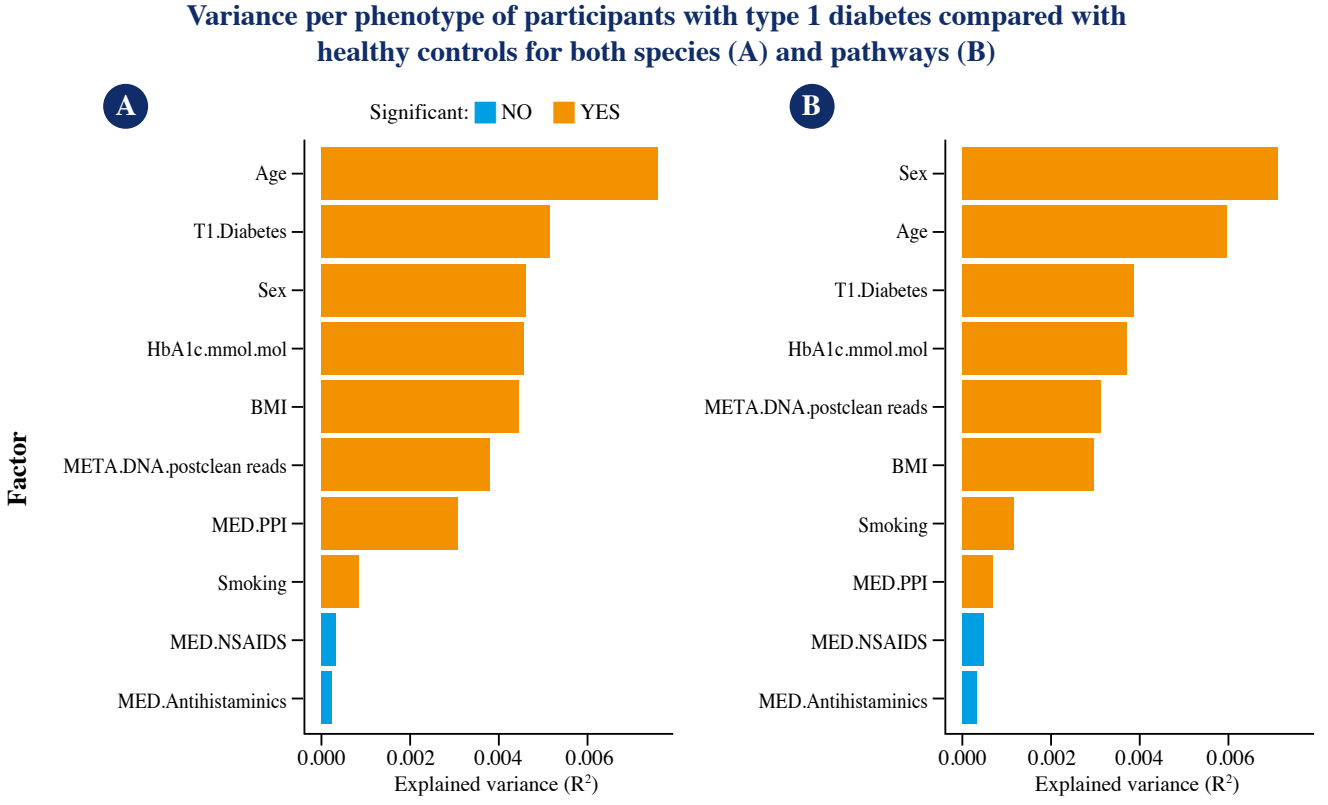
Clostridiales, and genus *Oscillibacter*) were significantly enriched in patients with diabetes, while 43 bacterial taxa (including *Alistipes putredinis, Prevotella copri*, and *Bifidobacterium longum*) were significantly depleted. Worth noting, **in patients with type 1 diabetes, enriched species consisted mainly of opportunistic pathogens, whereas depleted ones consisted mainly of commensal species.**

Via a principal component analysis, leaving out that patients had diabetes and control participants did not, HbA1c explained a significant portion of the variation in species (explained variance $R^2 > 0.004$) and pathways (explained variance $R^2 > 0.003$) (Figure 1). Considering the diabetes-associated characteristics that had an impact on the microbiome variation, they included duration of diabetes, age of onset, HbA1c levels/glycaemic load, and medication use. Age explained the largest amount of variation in microbiome composition, followed by the use of proton pump inhibitors − PPIs, widely used to treat gastric diseases − or platelet aggregation inhibitors and HbA1c.

Concerning species-specific associations, HbA1c showed the strongest positive association with *Dorea formicigenerans* and the strongest negative associations with genus *Fecalibacterium*. Disease duration and HbA1c showed positive associations with bacteria from the family Ruminococcaceae, and disease duration showed a negative association with *Roseburia intestinalis*.

More importantly, **both micro- and macrovascular complications explained a significant portion of the variance in the gut microbiome** ($R^2 > 0.0075$) (Figure 1). Diabetic nephropathy, retinopathy, and neuropathy were strongly associated with several microbial species, with the most significant associations found for diabetic nephropathy. On the other hand, the presence of peripheral arterial disease and myocardial infarction (i.e. macrovascular complications) were strongly associated with the same microbial species.

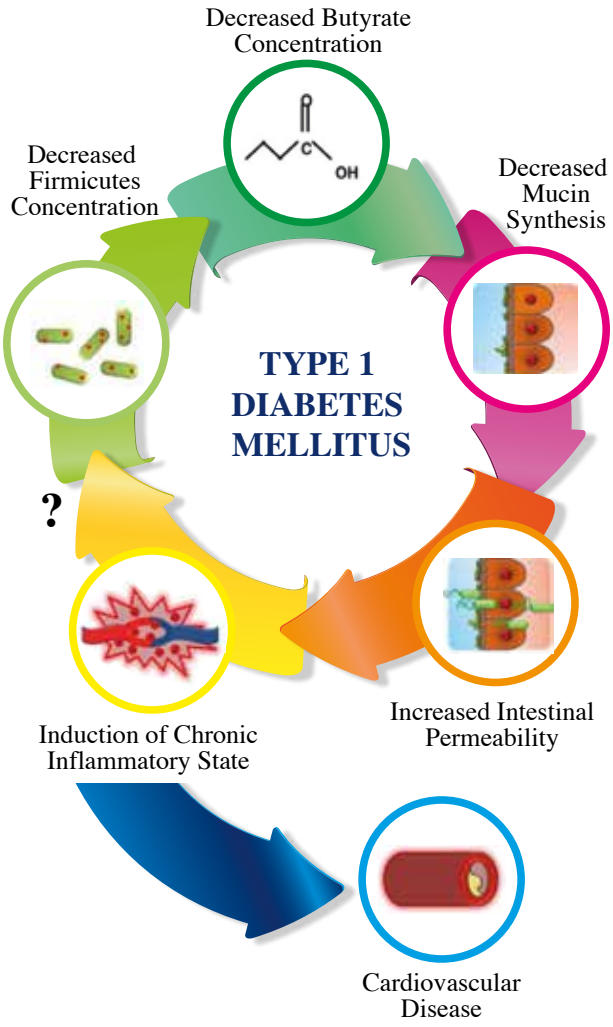
The finding that the gut microbiome composition differed between participants with long-standing type



Orange bars are significant (FDR < 0.005). MED, medication; NSAIDs, nonsteroidal anti-inflammatory drugs.

Figure 1

1 diabetes and healthy control subjects, and that this difference could be related to glycaemic control, opens up to the possibility that a causal link between the two might exist, although this cannot be stated based on the present study. Moreover, this finding suggests that a change in diversity can occur over time. The altered gut microbiome composition may affect glycaemic control and thereby drive the risk of developing complications, especially cardiovascular ones, which calls for increasing attention on the matter (7).



Supplementary Figure 1

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