Microscopic colitis (MC) is a chronic, inflammatory bowel disorder, characterised by watery, non-bloody diarrhoea. Typically, no endoscopic abnormalities are observed during colonoscopy, although the biopsies show clear signs of chronic inflammation. Two major subtypes of MC, i.e. lymphocytic colitis (LC) and collagenous colitis (CC), are distinguished based on histological findings. LC is hallmarked by an increased number of lymphocytes in the epithelium, while a thickened subepithelial collagen band is the main feature of collagenous colitis (CC). MC predominantly affects females and the average age at diagnosis is above 60 years of age. The disease can (intermittently) be present for several years. On average, patients report up to 5 bowel movements per day, mostly of watery consistency.

Worldwide, the incidence of MC has increased markedly over the last two decades. Until recently, Dutch incidence data were lacking, but the data of our national incidence study confirmed an increasing incidence in the Netherlands as well, rising from a mean annual incidence rate of 1.9 to 5.4 per 100,000 person years between 2000-2012. In line with the literature, highest incidence rates of MC in the Netherlands were observed for females (male:female ratio 1:3) and subjects above 60 years of age. The rising incidence rates can, in part, be attributed to an increased awareness for this condition among general practitioners, clinicians and pathologists, but may also be due to changes in (yet unknown) risk factors. Over time, the mean annual incidence rates are expected to rise even further, considering the increasing proportion of elderly in westernized populations together with the increased performance of colonoscopies (e.g. via the general practitioner and as part of population based screening on colorectal cancer) leading to more frequent detection of MC. As a consequence, clinicians will be confronted with patients suffering from MC more often. Therefore, it is of relevance that they recognize the symptoms, general patient characteristics and possible risk factors, in order to adequately identify subjects with a possible diagnosis of MC. The significant impact of MC on patients’ wellbeing is an additional reason for adequate patient identification. Although MC is not associated with a clear increase in mortality or morbidity, MC clearly impairs the health-related quality of life. In MC patients with active disease, quality of life is reported to be as impaired as in patients with classical inflammatory bowel disease (IBD). This is mainly attributed to the chronic and watery aspect of the diarrhoea, which hinders patients to perform daily activities, to attend work and social events, and it makes them feel insecure about their body. This negative impact on the quality of life should be the driving force for physicians to timely identify these patients, in order to prevent for example, work absenteeism, social isolation and physical decline.

The clinical characteristics of MC such as diarrhoea, abdominal pain/discomfort, weight loss and a normal endoscopic appearance of the mucosa are however unspecific for the disease and show large overlap with symptoms of e.g. irritable bowel syndrome (IBS). As
the optimal treatment strategy differs largely between these entities, it is of relevance to adequately set a diagnose in patients with chronic diarrhea. Where diarrhea predominant IBS is mainly treated with anti-diarrheal medication, peppermint oil, antidepressants, nutritional changes, stress reduction and/or psychological interventions, MC is generally effectively treated with the oral corticosteroid budesonide. Budesonide is highly effective in the majority of patients with MC, but after cessation of therapy symptoms return in approximately 60-80% of patients. It is unclear why this happens and it stresses the importance of better understanding of potential triggers for this disease. Consequently, the majority of patients requires maintenance treatment, implying long-term exposure to corticosteroids, with an enhanced risk on e.g. osteoporosis and related complications. Besides oral budesonide, no evidence-based treatment strategy is available.

What currently impedes timely detection of patients possibly suffering of MC, is the relative ignorance of risk factors and the underlying pathophysiological mechanisms of MC. Further insight in these factors would accelerate diagnosis of MC patients and better discriminate them from those with for example IBS. Furthermore, identification of new and confirmation of presumed risk factors for MC is of relevance for implementing preventive strategies.

Currently, the number of established risk factors is limited, i.e. an age >60 years, female gender, smoking, the presence of autoimmune disorders such as celiac disease or rheumatoid arthritis, and the use of certain drugs. Furthermore, these factors explain only a small part of the incident cases. With this thesis we aimed to contribute to the knowledge on MC risk factors, by confirmation of the established and exploration of new potential risk factors for MC. A relevant contribution in this sense, was the confirmation that non-steroid anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) are indeed associated with an increased risk of MC. In addition, we showed that this risk rises markedly, when both drugs are used simultaneously. Interestingly, we found that the risk of MC depends on the recency and the duration of drug use, in respect to the moment of diagnosis. The risk of MC clearly decreases when the time between the last prescription and the diagnosis was more than 6 months and when the drugs had been continuously used since more than 1 year. In our opinion, this is relevant information for both clinicians and pharmacists in order to better assess the chance of a possible MC diagnosis in a patient with chronic diarrhea, but also to determine whether drug use might play a causative role. If a causal relationship between the diarrhoeal symptoms and MC is expected based on the characteristics of the drug use, withdrawal of the drug should be considered as a first treatment strategy. This might discard, or at least postpone, the need for further anti-inflammatory treatment strategies. It should be noted that NSAIDs and PPIs are frequently prescribed by clinicians and are often freely available as over-the-counter drugs. In the Netherlands, over 10% of the national population is exposed to a PPI and over 20% to an NSAID at least once a year. In the
population above 65 years of age, the proportion of PPI users increased to up to 33%. This stresses the relevance for users and prescribers to be aware of the potential risks of these drugs. Though, it should be noted that only a small fraction of these users ultimately develops MC, which raises questions about e.g. genetic susceptibility and the possible pathophysiological mechanisms involved. Given the frequency of use, further studies on drug-induced MC and host-susceptibility are urgently needed. Hypothetically, a two-hit model might be applicable to MC, in which exposure to generally common drugs, leads to a clinically manifest phenotype, but only in (genetically) susceptible hosts. Genetic variations in for instance intestinal barrier function, immune function or a different composition and/or activity of the intestinal microbiota may increase the susceptibility to develop MC. However, how this relates to the onset of MC in later life is yet unclear. At the moment, a European collaborative project focussing on genetic variations in MC patients is ongoing, and patient material of our Dutch cohort will be included in this study.

Following the conclusion that NSAID and PPI exposure cannot explain all MC cases, other possible risk factors for the disease should be explored, as was done in this thesis. The only factor that was consistently associated with an increased risk of MC was smoking. Although the clinical benefit of stopping to smoke on MC symptoms is yet unknown, it has repeatedly been shown in our and other studies that smokers tend to develop their disease about 10 years earlier than non-smokers. MC is an additional condition in the long list of disorders on which smoking has a negative impact and should be considered in smoking patients presenting with chronic diarrhoea without a clear cause. Unfortunately, the underlying mechanism by which cigarette smoking causes/exacerbates MC symptoms is still unknown. Because smoking is strongly associated with MC, the role of environmental pollution in MC was also assessed, as the general compounds of cigarette smoke (nitrogen oxides, sulfoxides, particulate matter) are also present in polluted air. However, no clear associations between MC and (proxy) markers for ambient air pollution (e.g. the proportion of industrial area, the distance to the nearest highway, the concentration of air pollution components) were observed. The current thesis did not focus on a potential role of the intestinal microbiota or on the immune system. It appears that these mechanisms are likely to be involved in MC. Therefore, further studies should focus on microbial changes in untreated versus treated patients, and in patients versus controls, in order to evaluate the pathophysiological role of alterations in the gut microbiome. Furthermore, additional genetic and immunological studies are urgently needed in order to further unravel the pathophysiology of the disease. Hopefully, the outcomes of such studies can be used to develop preventive strategies and more targeted treatments.

In conclusion, more awareness for MC colitis is warranted given the clear impact on patients’ wellbeing and the globally and nationally increasing incidence rates. The results
of our studies provide additional and new information on clinical characteristics of Dutch MC patients and risk factors for the disease (e.g. NSAID and PPI exposure, smoking). Consideration or elimination of potential risk factors by clinicians will help to reduce the number of patients requiring treatment and those with a relapse after treatment. In addition, the results of this thesis might lead to better, targeted and earlier patient identification by general practitioners and clinicians. Consequently, this will not only improve the general quality of life of patients but will also reduce the costs related to absenteeism and an increased health care consumption in this generally elderly population. Although the contributed social value of the results of this thesis itself is modest, the most relevant and direct spin-off of this research project has probably been the increased regional and national attention for MC. As a consequence of this project, lectures, meetings, and collaborative projects for gastroenterologists, pathologists and GP’s have been initiated in (the south of) the Netherlands and patient data have been and will be included in international collaborative studies like the PRO-MC registry. More awareness for the condition in and outside the scientific world is likely to be the major key to improved patient identification and treatment.