Ambient air quality as risk factor for microscopic colitis - A geographic information system (GIS) study
Peer-reviewed author version

Ambient air quality as risk factor for microscopic colitis – a Geographic Information System (GIS) study

Short title: *Ambient air quality as risk factor for MC*

Authors

Bas P.M. Verhaegh, PhD[1,2]; Esmee M. Bijnens, PhD[3]; Tim R.A. van den Heuvel, PhD[1,2]; Danny Goudkade, MD[4]; Maurice P. Zeegers, Professor[2,5]; Tim S. Nawrot, Professor[3,6]; Ad A.M. Masclee, Professor[1,2]; Daisy M.A.E. Jonkers, Professor[1,2]; Marieke J. Pierik, PhD[1]

[1] Division of Gastroenterology – Hepatology, Dept. Internal Medicine, Maastricht University Medical Center[+], Maastricht, the Netherlands

[2] NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands

[3] Center for Environmental Sciences, Hasselt University, Diepenbeek, Belgium

[4] Department of Pathology, Maastricht University Medical Center[+], Maastricht, the Netherlands

[5] Care and Public Health Research Institute (School CAPHRI), Maastricht University, the Netherlands

[6] Department of Public Health and Primary Care, Leuven University, Leuven, Belgium

Corresponding author

Bas P.M. Verhaegh, PhD

Dept. of Internal Medicine – Division of Gastroenterology-Hepatology

Maastricht University Medical Center+

PO Box 5800

6202 AZ Maastricht, the Netherlands

+31-43-3875021

bas.verhaegh@mumc.nl

Abstract (250/250)

Background: Microscopic colitis (MC) is considered a multifactorial disease, strongly associated with smoking. However, little is known about the role of environmental factors such as ambient air pollution in MC pathophysiology. There is an overlap in components of cigarette smoke and ambient air pollution. Therefore, the aim of this study was to explore an independent association between ambient air quality and MC.

Methods: A case-control study was performed. MC cases in South Limburg, the Netherlands, diagnosed between 2000-2012, were retrieved from the national pathology registry and matched to non-MC controls from the same area based on age (±2 years) and gender. A stable residential address for ≥3 years was required. Residential land use, proximity to major road, and concentrations of air pollution compounds, were determined using a Geographic Information System (GIS). Univariate and multivariable regression analyses were corrected for age, gender and smoking status.

Results: In total, 345 MC cases (78.6% female) and 583 matched controls (77.2% female) were included. In the univariate analyses, the percentage of urban green within a 500m buffer and residential proximity to the nearest highway were associated with MC (both $p<0.10$). On the multivariable level only a higher age at diagnosis (OR 1.02, 95%-CI 1.01-1.04) and current smoking at index date (OR 4.30; 95%-CI 3.01-6.14) were significantly associated with MC.

Conclusion: Based on the current findings, ambient air quality does not seem to be an important risk factor for MC, in contrast to the well-known risk factors age and current smoking.

Key Words: microscopic colitis, epidemiology, risk factors, environmental factors, air pollution

Introduction

Microscopic colitis (MC) is a chronic bowel disorder with frequent watery diarrhoea as primary symptom. Although the aetiology is not clear, MC is considered a multifactorial disease, in which immunological, genetic, microbial, life style and environmental factors play a role (1). Amongst the latter, smoking and drug exposure have repeatedly been associated with MC (2-7). Especially (co)exposure to non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) seems to increase the risk of MC (3, 4). However, in these studies only 20-40% of MC patients were exposed to these drugs in the year before diagnosis, suggesting that drug-exposure does not explain for all MC cases. Other possible risk factors for MC (*e.g.* hormones, alcohol, socio-economic status) have been addressed in a limited number of studies, but the results were either negative or conflicting (2, 8-11). Moreover, there are indications for an altered microbiome in MC patients, compared to healthy controls (12, 13). In other words, further research for possible risk factors is warranted in order to confirm current risk factors and hypotheses on underlying pathophysiological mechanisms, or to find new ones.

Several publications report that smoking is associated with MC (2, 5, 6, 14). Tobacco smoke compounds such as particulate matter (PM), nitric oxides and benzene are also present in polluted air. Therefore, ambient air quality (influenced by *e.g.* industrial, agricultural and traffic related emissions in the residential area) may have a contributory effect to the pathogenesis of MC as well. Furthermore, MC peak incidence rates are observed in the older population (>60 years of age), which might also be supportive for involvement of environmental factors in the pathogenesis to some extent. Considering that people are continuously exposed to polluting sources in the direct environment, such as traffic, industry, urbanized areas or agricultural poisons, ambient air quality might be contributory. Moreover, previous studies reported an association between air pollution and various gastrointestinal conditions, such as gastrointestinal cancer, appendicitis, bowel infections and IBD (15-19). However, the association with MC has never been reported.

Chemicals present in ambient air can reach the gastrointestinal tract by direct ingestion or via ingestion of pulmonary mucus, which clears inhaled air from particles (20). Based on *in vitro* and animal studies, air pollutants are postulated to have various compromising intestinal effects, such as DNA damage, disruption of the epithelial barrier and initiation of an innate immune response by activation of immune cells or cell signalling pathways (21). In individuals with a genetic predisposition for an inflammatory condition, presence of inflammatory cytokines might lead to a more pronounced effect on the epithelial barrier in case of exposure to toxic particles (22). Beside direct effects on the epithelium, air pollutants induce changes in microbial composition or physiology. In mice models, for instance, PM changed the relative amounts of various bacterial strains and reduced the production of butyrate, impairing epithelial permeability (23). In addition, some bacteria are able to metabolize ingested particles into toxic metabolites or reactive oxygen species, affecting mucosal barrier function. In general, environmental factors (in)directly induce epigenetic changes during life. In a genetic susceptible host, the sum of epigenetic changes and environmental influences then may trigger inflammatory activity, not resolving due to the epigenetic changes (24).

In conclusion, there is circumstantial evidence which suggests that ambient air quality may play a role in MC pathophysiology. Therefore, the aim of this study was to assess the effect of ambient air quality on the risk of MC in a population-based cohort of MC patients. We hypothesized that exposure to ambient air pollution increases the risk of MC.

Materials and methods

Study population

A case-control study was performed, including all MC cases in the region of South Limburg, the Netherlands. Cases were identified in PALGA, the Dutch nationwide registry of histo- and cytopathology. All cases aged 18 years or older, with a PALGA registered diagnosis of MC, collagenous colitis (CC), lymphocytic colitis (LC), incomplete CC (CCi) or incomplete LC (LCi) between January 2000 and December 2012, were selected. Hereafter, pathology reports and medical charts

were reviewed to exclude cases which did not meet the histological or clinical criteria for MC. The haematoxylin-eosin stained sections from diagnostic biopsies were retrieved and revised according to the ESP/EMCG diagnostic criteria (25) by an experienced pathologist (D.G.), in order to verify the diagnosis. The pathologist was blinded for any clinical symptoms and the previously established diagnosis.

Non-MC controls were retrieved from the general South Limburg population. Study information letters were sent to randomly selected households within the study area, based on postal code. Per household, informed consent was asked to a maximum of four subjects above 18 years of age. Of this control population (n=1,611), two non-MC controls were matched to each MC case, based on gender and year of birth (± 2 years). If a control was matched, any other member from the same household was excluded for further matching. Frequency matching was applied to ensure that the control population resembled the distribution of the area's background population.

The index date of the cases was defined as the date of histological diagnosis. Non-MC controls were assigned the same index date as their matched case.

Residential data

For each subject, historical and current residential data were retrieved from the national civil registration system (in Dutch: Basisregistratie Persoonsgegevens, https://www.rvig.nl/brp), kept by the Dutch Ministry of Internal Affairs. For each subject, the residential address at index date was recorded. Only subjects with a stable residential address for at least three years before the index date, were considered suitable for inclusion. Residential addresses were geocoded, based on the data provided by the 'Basisregistratie Adressen en Gebouwen', a database maintained by the national Cadastre survey (https://www.kadaster.nl/bag).

Markers for ambient air quality

Both direct and indirect markers for ambient air quality were included in the study, *i.e.* main air pollution components, land use data, population density, urbanity, proximity to major roads, and total road length in the residential area. Based on the geocoded residential addresses, individual exposure to the various variables was assessed, applying geographic information system (GIS) functions (ArcGIS 9.3. Esri, Redlands, CA, USA). Figure 1 (panel C-F) gives an impression on the spatial distribution of some of the included markers for ambient air quality.

Data on regional concentrations of the most common air pollutants according to the World Health Organisation, *i.e.* particulate matter ≤10μm (PM_{10}), nitric dioxide (NO_2), ozone (O_3), sulphur dioxide (SO_2) and benzene (C_6H_6), were obtained from the National Institute for Public Health (RIVM) of the Dutch Ministry of Health, Welfare and Sports (http://www.lml.rivm.nl). Air pollutant concentrations ($\mu g/m^3$) were measured at 60 fixed monitoring stations in the Netherlands. Measured concentrations, added with local and foreign data, were applied in a dispersion model to calculate local concentrations on a 5x5km grid and interpolated to a 1x1km grid (26). A margin of uncertainty of 15% around the interpolated data was calculated by the RIVM. Data were available for each year between 2000 and 2012. In the study analyses, SO_2 and benzene were not included, as rational concentrations were too low to expect any health risks (26).

Land use data were retrieved from CORINE Land Cover, a cartographic database (scale 1:100,000) coordinated by the European Environment Agency (EEA)(27). Each 100x100m was assigned to its major type of land use, being residential (CORINE class 1.1), industrial (class 1.2.1), urban green (class 1.4.1), agricultural (class 2) or natural areas (class 3). Data were available for the years 2000, 2006, and 2012. Within 100m, 500m and 2500m radius buffers from each residential address, the percentages of the various types of land use were determined. Data were not restricted to national borders.

Traffic intensity was reflected by a) the total road length within 100m, 200m, 500m radius buffers from the residential address and b) the residential proximity to the nearest highway or major

road (defined as national roads with >10.000 vehicles per day). The proximity was calculated based on digital street maps and was expressed as a logarithmic function.

Population density (number of inhabitants per km^2) and urbanization rate (number of addresses per km^2) were derived from demographic data of Statistics Netherlands (CBS) (https://www.cbs.nl). Data were available per neighbourhood (an area often smaller than $1km^2$, *e.g.* a small village or a part of a larger village or city district.) for the years 2004, 2009, and 2012.

For all analyses data most close to the concerning index date were applied.

Statistical analysis

Continuous variables were expressed as means with standard deviation (SD). With regard to the patient characteristics, statistical significant differences between cases and controls were calculated using an independent Student's T-test for continuous variables or a Chi^2-test for categorical variables. For all other variables, univariate logistic regression analysis was applied to calculate odds ratios (OR) with 95%-Confidence Intervals (95%-CI). All variables with a p-value <0.10 in the univariate analyses were included in the multivariable logistic regression analysis. Both univariate and multivariable models were corrected for the confounders age, gender and smoking status at index date. In the case population, smoking status at index date was obtained by scrutinizing patient's medical files. Controls were asked for their smoking status (including year of cessation, if applicable) via a brief questionnaire added to the informed consent form. Missing data on smoking status were imputed by applying a fully conditional specification method in SPSS. This method imputes missing data with random values from a multinominal distribution based on the category proportions. Presence of multicollinearity between selected variables was assessed by requesting collinearity diagnostics in the statistical program. Statistical significance was determined as p<0.05.

For all analyses, CCi and LCi cases were included in the CC and LC group, respectively. Furthermore, in case biopsy specimens could not be revised, the diagnosed subtype as recorded in the pathology report was acquired, provided that the diagnosis was set with a high or moderate

likelihood (28). A sensitivity analysis was performed, excluding CCi and LCi cases and cases without a biopsy proven diagnosis.

All analyses were conducted with IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA).

Ethical Considerations

This study was performed according to the revised version of the declaration of Helsinki and approved by the medical ethical committee of Maastricht University Medical Centre[+] (NL44127.068.13 and NL31636.068.10). Written informed consent was obtained from all participants.

Results

Study population

In total, 430 MC cases were selected from the three participating centres, of which 77 cases were excluded for the following reasons: they were living outside the designated study area at index date (n=5), they lived <3 years on the residential address since at index date (n=60), or they were included in two centres at the same time (n=2). In addition, 18 cases were excluded because the diagnosis could not be confirmed upon biopsy revision.

The remaining 345 cases (271 females, 78.6%) consisted of 108 (31.1%) CC, 176 (51.0%) LC, 6 CCi (1.7%) and 28 (8.1%) LCi cases. In 27/345 cases (7.8%, 15 CC and 12 LC), no biopsy material was available for revision (Table1). As all of them had a high likelihood of a positive MC diagnosis based on the pathology report, they were included for further analyses.

All 345 cases were matched to 583 non-MC controls (450 females, 77.2%). The spatial distribution of the included subjects is visualized in Figure 1 (panel A and B). A 1:2 matching ratio was achieved in 69.0% of cases. As presented in Table 1, the mean age at index date was 63.3 ± 13.0

years for the cases and 61.1 ± 12.4 years for the controls (p=0.01). On average, the duration of an unchanged residential address before the index date was 21.3 ± 12.8 and 21.3 ± 12.1 years (p=0.96) for cases and controls, respectively.

In total, the smoking status at index date was missing in 13.0% of the cases and 4.3% of the controls. After imputation, the proportion of current smokers was 43.8% in the case population and 15.3% in the control population (p<0.01) (Table1).

Environmental factors

Univariate analyses

Data on the various measured (proxy) markers for ambient air quality were presented in Table 2. Only the percentage of urban green within a 500m radius buffer around the residential address (OR 0.20; 95%-CI 0.03-1.27) and residential proximity to the nearest highway (OR 0.93; 95%-CI 0.87-1.00) were statistically different between cases and controls on a p<0.10 level. No statistical differences were observed between cases and controls regarding the percentage of industrial, residential, agricultural, natural or urban green area, total road length around the residential address, population density, address density, or major air pollution compounds (Table 2).

Multivariable analysis

Next to the percentage of urban green within a 500m radius buffer and residential proximity to the nearest highway; gender, age and smoking status at index date were included in the multivariable model. Based on this model, a higher age at diagnosis (OR 1.02, 95%-CI 1.01-1.04) and current smoking at index date (OR 4.30; 95%-CI 3.01-6.14) were significantly associated with a higher risk of MC (Table 3).

Sensitivity analysis

All analyses were repeated after exclusion of CCi/LCi cases and cases with unrevised biopsies. In total, 284 cases and 481 matched controls were included. The general outcomes of the univariate analyses remained unchanged, except for the fact that urban green within a 500m radius buffer was not statistically different anymore in the univariate analysis. The results of the multivariable analyses, including age, gender, smoking status and residential proximity to the nearest highway, remained unchanged, with a significant association for a higher age (OR 1.02; 95%-CI 1.01-1.04) and current smoking (OR 4.20; 95%-CI 2.83-6.23).

Discussion

This is the first study to explore the role of ambient air quality on the risk of MC. Although various direct and indirect markers for ambient air quality were studied, none of them were significantly associated with an increased risk of MC on a multivariable level. Though, the previously reported risk factors age and current smoking were confirmed.

Ambient air is a heterogeneous composition of gases, particles and volatile organic compounds (VOCs) (*e.g.* benzene). Especially PM_{10} and NO_2, emitted by both natural and anthropogenic sources (*e.g.* industry, traffic, agriculture), have a negative impact on general health by increasing the risk of mortality, hospital admissions and pulmonary, cardiovascular or gastrointestinal disorders (21, 29). However, the results of the present study showed that the primary components and proxy markers for air pollution (*e.g.* PM_{10}, high industrial area, residential proximity to roads) were not associated with MC on the univariate and multivariable level, which makes a major role for ambient air quality in MC pathophysiology unlikely. However, a possible contributory effect should not be discarded completely. Although the level of exposure to ambient air pollution was not different between MC cases and controls, the effect of this exposure might still be different between the two populations, for instance due to (genetic) susceptibility. As an example, in inflammatory bowel disease the *PTPN2*-gene is only associated with Crohn's disease in a smoking

population (30), which supports the hypothesis that specific genetic variants are required for specific environmental factors to contribute to disease development.

In contrast to most (proxy) markers for ambient air quality, current smoking was found to be an incontestable risk factor for MC, which is in line with various recent studies (2, 5, 6, 14, 31). Considering the fact that there is overlap in the composition of cigarette smoke and polluted air, the results of this study might be an argument that other compounds of cigarette smoke, generally not present in polluted air (*e.g.* nicotine) do account for the strong associations. However, it should be noted that the level of exposure to toxic gases and particles via cigarette smoke is considerably higher and more frequent in comparison to ambient air pollution.

The strength of this study resides in the ability to link the subject's residential address at index date to outcome variables from the same area and time period, which increased the validity of the results. Although no eminent role for ambient air quality was observed in this study, similar approaches linking ambient air quality data to health outcomes were able to detect significant associations by appliyng GIS (32-36), also in the same area (31). In addition, the case population in the current study was population-based, well-defined, relatively large, and with a revised histological diagnosis in 92% of the cases. Furthermore, controls were derived from the same area, were adequately distributed over the study area and were solidly matched to the MC cases. Although the control population was two years younger on average, we do not think this had major impact on the study outcome. Last, analyses have been corrected for a major MC risk factor, *i.e.* smoking status at index date. Despite 4-13% of data was missing, residual confounding was reduced by imputation of these missing data.

Legal limits for average annual concentrations of PM_{10} and NO_2 in the Netherlands are 40 µg/m^3 and WHO guideline values are 20 µg/m^3 for PM_{10} and 40 µg/m^3 for NO_2 (37). The concentrations in our study area were generally below these values. This means that the results of this study are conclusive

for low exposed populations only. Therefore, the conclusions need to be confirmed in different populations, preferably with higher exposure to the assessed risk factors.

Some limitations should be noted. First, the size of the study area may have been too small to have sufficient variation in the distribution of air pollution determinants. Second, the sample size may have been too small to detect small variations in the exposure variables. Third, the residential address is often not the location were people spend most of their day (work, traveling, time spend in traffic). Therefore, exposure to environmental factors on the primary residential address may not be most representative for an individual's level of exposure to air pollution. Fourth, the source data applied in this study were not available for each index year. Although most recent data relative to the index date were applied, and three-year average concentrations for air pollution compounds were calculated, small annual variations in the exposure variables might have influenced the outcomes. Finally, it should be noted that data on drug exposure at index date (*e.g.* NSAIDs or PPIs) were not available.

In conclusion, this was the first study to explore an association between ambient air quality and the risk of MC. Based on the results of this study, ambient air quality is not a major contributing factor to the risk of MC.

References

1.	Pisani LF, Tontini GE, Vecchi M, Pastorelli L. Microscopic Colitis: What Do We Know About Pathogenesis? Inflamm Bowel Dis. 2016;22(2):450-8.

2.	Yen EF, Pokhrel B, Du H, Nwe S, Bianchi L, Witt B, et al. Current and past cigarette smoking significantly increase risk for microscopic colitis. Inflamm Bowel Dis. 2012;18(10):1835-41.

3.	Verhaegh BP, de Vries F, Masclee AA, Keshavarzian A, de Boer A, Souverein PC, et al. High risk of drug-induced microscopic colitis with concomitant use of NSAIDs and proton pump inhibitors. Aliment Pharmacol Ther. 2016;43(9):1004-13.

4.	Masclee GM, Coloma PM, Kuipers EJ, Sturkenboom MC. Increased risk of microscopic colitis with use of proton pump inhibitors and non-steroidal anti-inflammatory drugs. Am J Gastroenterol. 2015;110(5):749-59.

5.	Jaruvongvanich V, Poonsombudlert K, Ungprasert P. Smoking and Risk of Microscopic Colitis: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2019;25(4):672-8.

6.	Burke KE, Ananthakrishnan AN, Lochhead P, Olen O, Ludvigsson JF, Richter JM, et al. Smoking is Associated with an Increased Risk of Microscopic Colitis: Results From Two Large Prospective Cohort Studies of US Women. J Crohns Colitis. 2018;12(5):559-67.

7.	Wickbom A, Nyhlin N, Montgomery SM, Bohr J, Tysk C. Family history, comorbidity, smoking and other risk factors in microscopic colitis: a case-control study. Eur J Gastroenterol Hepatol. 2017;29(5):587-94.

8.	Roth B, Gustafsson RJ, Jeppsson B, Manjer J, Ohlsson B. Smoking- and alcohol habits in relation to the clinical picture of women with microscopic colitis compared to controls. BMC Womens Health. 2014;14:16.

9.	Roth B, Manjer J, Ohlsson B. Microscopic colitis and reproductive factors related to exposure to estrogens and progesterone. Drug target insights. 2013;7:53-62.

10.	Sonnenberg A, Turner KO, Genta RM. Differences in the socio-economic distribution of inflammatory bowel disease and microscopic colitis. Colorectal Dis. 2017;19(1):38-44.

11.	Pabla B, Ness RM. Do Sex Hormones Cause, or Are They Only Associated With, Microscopic Colitis? Gastroenterology. 2018;155(6):1679-81.

12.	Fischer H, Holst E, Karlsson F, Benoni C, Toth E, Olesen M, et al. Altered microbiota in microscopic colitis. Gut. 2015;64(7):1185-6.

13.	Rindom Krogsgaard L, Kristian Munck L, Bytzer P, Wildt S. An altered composition of the microbiome in microscopic colitis is driven towards the composition in healthy controls by treatment with budesonide. Scand J Gastroenterol. 2019;54(4):446-52.

14.	Fernandez-Banares F, de Sousa MR, Salas A, Beltran B, Piqueras M, Iglesias E, et al. Impact of current smoking on the clinical course of microscopic colitis. Inflamm Bowel Dis. 2013;19(7):1470-6.

15. Garcia-Perez J, Lopez-Cima MF, Perez-Gomez B, Aragones N, Pollan M, Vidal E, et al. Mortality due to tumours of the digestive system in towns lying in the vicinity of metal production and processing installations. The Science of the total environment. 2010;408(16):3102-12.

16. Kaplan GG, Dixon E, Panaccione R, Fong A, Chen L, Szyszkowicz M, et al. Effect of ambient air pollution on the incidence of appendicitis. Cmaj. 2009;181(9):591-7.

17. Kaplan GG, Hubbard J, Korzenik J, Sands BE, Panaccione R, Ghosh S, et al. The inflammatory bowel diseases and ambient air pollution: a novel association. Am J Gastroenterol. 2010;105(11):2412-9.

18. Orazzo F, Nespoli L, Ito K, Tassinari D, Giardina D, Funis M, et al. Air pollution, aeroallergens, and emergency room visits for acute respiratory diseases and gastroenteric disorders among young children in six Italian cities. Environmental health perspectives. 2009;117(11):1780-5.

19. Opstelten JL, Beelen RM, Leenders M, Hoek G, Brunekreef B, van Schaik FD, et al. Exposure to Ambient Air Pollution and the Risk of Inflammatory Bowel Disease: A European Nested Case-Control Study. Dig Dis Sci. 2016;61(10):2963-71.

20. Moller W, Haussinger K, Winkler-Heil R, Stahlhofen W, Meyer T, Hofmann W, et al. Mucociliary and long-term particle clearance in the airways of healthy nonsmoker subjects. Journal of applied physiology. 2004;97(6):2200-6.

21. Beamish LA, Osornio-Vargas AR, Wine E. Air pollution: An environmental factor contributing to intestinal disease. J Crohns Colitis. 2011;5(4):279-86.

22. Manzo ND, Slade R, Richards JH, McGee JK, Martin LD, Dye JA. Susceptibility of inflamed alveolar and airway epithelial cells to injury induced by diesel exhaust particles of varying organic carbon content. J Toxicol Environ Health A. 2010;73(8):565-80.

23. Salim SY, Kaplan GG, Madsen KL. Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. Gut microbes. 2014;5(2):215-9.

24. Rogler G, Vavricka S. Exposome in IBD: recent insights in environmental factors that influence the onset and course of IBD. Inflamm Bowel Dis. 2015;21(2):400-8.

25. Langner C, Aust D, Ensari A, Villanacci V, Becheanu G, Miehlke S, et al. Histology of microscopic colitis-review with a practical approach for pathologists. Histopathology. 2015;66(5):613-26.

26. RIVM. Grootschalige Concentratie en Depositiekaarten Nederland. 2015.

27. EEA. European Environment Agency - CORINE Land Cover Database [Available from: http://www.eea.europa.eu/publications/COR0-landcover

28. Verhaegh BP, Jonkers DM, Driessen A, Zeegers MP, Keszthelyi D, Masclee AA, et al. Incidence of microscopic colitis in the Netherlands. A nationwide population-based study from 2000 to 2012. Dig Liver Dis. 2015;47(1):30-6.

29.   Heroux ME, Anderson HR, Atkinson R, Brunekreef B, Cohen A, Forastiere F, et al. Quantifying the health impacts of ambient air pollutants: recommendations of a WHO/Europe project. International journal of public health. 2015;60(5):619-27.

30.   van der Heide F, Nolte IM, Kleibeuker JH, Wijmenga C, Dijkstra G, Weersma RK. Differences in genetic background between active smokers, passive smokers, and non-smokers with Crohn's disease. Am J Gastroenterol. 2010;105(5):1165-72.

31.   Munch A, Tysk C, Bohr J, Madisch A, Bonderup OK, Mohrbacher R, et al. Smoking Status Influences Clinical Outcome in Collagenous Colitis. J Crohns Colitis. 2016;10(4):449-54.

32.   Ruttens D, Verleden SE, Bijnens EM, Winckelmans E, Gottlieb J, Warnecke G, et al. An association of particulate air pollution and traffic exposure with mortality after lung transplantation in Europe. The European respiratory journal. 2017;49(1).

33.   Nawrot TS, Vos R, Jacobs L, Verleden SE, Wauters S, Mertens V, et al. The impact of traffic air pollution on bronchiolitis obliterans syndrome and mortality after lung transplantation. Thorax. 2011;66(9):748-54.

34.   Bijnens EM, Derom C, Gielen M, Winckelmans E, Fierens F, Vlietinck R, et al. Small for gestational age and exposure to particulate air pollution in the early-life environment of twins. Environmental research. 2016;148:39-45.

35.   Pinichka C, Makka N, Sukkumnoed D, Chariyalertsak S, Inchai P, Bundhamcharoen K. Burden of disease attributed to ambient air pollution in Thailand: A GIS-based approach. PLoS One. 2017;12(12):e0189909.

36.   Atabi F, Mirzahosseini SA. GIS-based assessment of cancer risk due to benzene in Tehran ambient air. Int J Occup Med Environ Health. 2013;26(5):770-9.

37.   WHO. Fact sheet: Ambient (outdoor) air quality and health 2016 [Available from: http://www.who.int/mediacentre/factsheets/fs313/en/.

Figure Legends

Figure 1. Panel A and B show the distribution of the included cases and controls in South Limburg. Panels C-F visualize the spatial distribution of particulate matter (PM) (C), land use (D), major roads (E) and population density (F) in South Limburg, for the year 2006. These panels give an impression of the source data and do not represent the complete data, as multiannual data were used for the analyses.

Tables

Table 1. Baseline characteristics

	Cases (n=345)	Controls (n=583)	p-value
Female, n (%)	271 (78.6%)	450 (77.2%)	0.66
Age at index date, mean years ± SD	63.3 ± 13.0	61.2 ± 12.4	0.01
Duration of stable address before index date, mean years ± SD	21.3 ± 12.8	21.3 ± 12.1	0.96
Type of MC – PA revision			
- CC, n (%)	108 (31.3%)		
- LC, n (%)	176 (51.0%)		
- CCi, n (%)	6 (1.7%)		
- LCi, n (%)	28 (8.1%)		
- Unrevised, n (%)*			
- CC, n (%)	15 (4.3%)		
- LC, n (%)	12 (3.5%)		
Smoking status at index date			
- Current, n (%)	151 (43.8%)	89 (15.3%)	<0.01
- Former, n (%)	81 (23.5%)	236 (40.5%)	<0.01
- Never, n (%)	113 (32.8%)	258 (44.3%)	<0.01

CC: Collagenous colitis; LC: lymphocytic colitis; CCi: incomplete collagenous colitis; LCi: incomplete lymphocytic colitis

* Diagnosis was based on the conclusion provided in the pathology report

Table 2. Univariate analyses of direct and indirect markers for ambient air pollution

	Cases (n=345)	Controls (n=583)	Crude Odds Ratio (95%-CI)	Adjusted Odds Ratio (95%-CI)*	p-value
Air pollution components (µg/m³)					
PM_{10}, mean ± SD	27.36 ± 3.02	27.17 ± 2.94	1.02 (0.98-1.06)	1.02 (0.98-1.07)	0.35
O_3, mean ± SD	36.96 ± 3.28	37.04 ± 3.23	0.96 (0.92-1.00)	0.97 (0.93-1.01)	
NO_2, mean ± SD	25.15 ± 3.71	24.77 ± 3.55	1.03 (0.99-1.01)	1.03 (0.99-1.07)	0.17
Land use					
Industrial area, mean %					
- 100m buffer	1.31%	1.29%	1.02 (0.25-4.13)	1.58 (0.36-6.90)	0.55
- 500m buffer	2.89%	3.59%	0.48 (0.12-1.94)	0.74 (0.16-3.36)	0.74
- 2500m buffer	8.37%	7.88%	2.88 (0.42-19.86)	2.19 (0.28-17.14)	0.46
Residential area, mean %					
- 100m buffer	83.73%	82.01%	1.81 (0.78-1.80)	1.13 (0.72-1.76)	0.60
- 500m buffer	66.92%	63.87%	1.50 (0.92-2.44)	1.38 (0.82-2.33)	0.22
- 2500m buffer	33.83%	32.72%	1.47 (0.67-3.22)	1.20 (0.52-2.77)	0.67
Urban green, mean %					
- 100m buffer	0.79%	1.65%	0.31 (0.06-1.78)	0.32 (0.05-1.99)	0.22
- 500m buffer	2.46%	3.37%	0.24 (0.04-1.37)	0.20 (0.03-1.27)	0.09
- 2500m buffer	3.59%	3.66%	0.56 (0.01-25.79)	0.25 (0.00-15.17)	0.51
Nature, mean %					
- 100m buffer	0.98%	0.99%	0.99 (0.18-5.38)	1.53 (0.25-9.26)	0.65
- 500m buffer	2.59%	2.04%	2.54 (0.46-14.12)	2.40 (0.39-14.95)	0.35
- 2500m buffer	5.82%	6.11%	0.45 (0.05-4.10)	0.72 (0.07-7.50)	0.78

Agricultural area, mean %					
- 100m buffer	13.11%	13.77%	0.92 (0.59-1.46)	0.91 (0.56-1.48)	0.69
- 500m buffer	23.98%	25.81%	0.79 (0.49-1.28)	0.84 (0.51-1.41)	0.52
- 2500m buffer	44.75%	46.31%	0.73 (0.40-1.33)	0.84 (0.44-1.58)	0.58
Roads					
Total road length (km), mean ± SD					
- 100m buffer	0.93 ± 0.37	0.89 ± 0.36	1.30 (0.91-1.88)	1.06 (0.71-1.56)	0.78
- 200m buffer	3.55 ± 1.23	3.38 ± 1.16	1.13 (1.01-1.26)	1.06 (0.94-1.19)	0.35
- 500m buffer	18.76 ±6.29	18.08 ± 6.05	1.02 (1.00-1.04)	1.01 (0.99-1.03)	0.42
Residential proximity to the nearest major road (km), mean ± SD	0.81 ± 0.71	0.83 ± 0.70	0.94 (0.78-1.14)	0.94 (0.77-1.16)	0.57
Residential proximity to the nearest highway (km), mean ± SD	2.52 ± 1.97	2.83 ± 2.09	0.93 (0.87-0.99)	0.93 (0.87-1.00)	0.06
Demography					
Number of inhabitants*1,000 per km^2, mean ± SD	2.87 ± 1.92	2.79 ± 1.86	1.02 (0.95-1.10)	1.01 (0.94-1.09)	0.80
Number of addresses*100 per km^2, mean ± SD	1.28 ± 0.81	1.18 ± 0.69	1.02 (1.00-1.04)	1.02 (1.00-1.04)	0.11

PM_{10}: Particulate matter <10μm, 95%-CI: 95% Confidence Interval;

* Adjusted for gender, year of birth and smoking status

Table 3. Results of the multivariable analysis

	Odds Ratio (95%-CI)
Female Gender	1.03 (0.73-1.47)
Age at index date (years)	1.02 (1.01-1.04)
Smoking status at index date	
- Never smoker	1.00
- Former smoker	0.78 (0.55-1.10)
- Current smoker	4.30 (3.01-6.14)
Percentage of urban green (500m buffer)	0.19 (0.03-1.20)
Residential proximity to the nearest highway (km) (logarithm)	0.78 (0.58-1.06)

95%-CI: 95% Confidence Interval