REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Radon exposure and inflammatory bowel disease in a radon prone area

Authors:
Violeta Mauriz-Barreiro, Manuel Barreiro-de Acosta, Iria Bastón-Rey, Rocío Ferreiro-Iglesias, Cristina Calviño-Suárez, Juan Miguel Barros-Dios, J. Enrique Domínguez-Munoz, Alberto Ruano-Raviña

DOI: 10.17235/reed.2021.8239/2021
Link: PubMed (Epub ahead of print)

Please cite this article as:
Mauriz-Barreiro Violeta , Barreiro-de Acosta Manuel, Bastón-Rey Iria, Ferreiro-Iglesias Rocío, Calviño-Suárez Cristina, Barros-Dios Juan Miguel, Domínguez-Munoz J. Enrique, Ruano-Raviña Alberto. Radon exposure and inflammatory bowel disease in a radon prone area. Rev Esp Enferm Dig 2021. doi: 10.17235/reed.2021.8239/2021.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

OR 8239

Radon exposure and inflammatory bowel disease in a radon prone area

Violeta Mauriz-Barreiro[1], Manuel Barreiro-de Acosta[1], Iria Bastón-Rey[1], Rocío Ferreiro-Iglesias[1], Cristina Calviño-Suárez[1], Juan Miguel Barros-Dios[1,2,3], J. Enrique Domínguez-Munoz[1] and Alberto Ruano-Raviña[2,3]

[1]Gastroenterology Department. Hospital Clínico Universitario de Santiago. Santiago de Compostela, Spain. [2]Department of Preventive Medicine and Public Health. University of Santiago de Compostela. Santiago de Compostela, Spain. [3]CIBER Epidemiology and Public Health. CIBERESP. Spain

Received: 03/08/2021

Accepted: 15/11/2021

Correspondence: Manuel Barreiro-de Acosta. IBD Unit. Gastroenterology Department. Hospital Clínico Universitario de Santiago. Choupana, s/n. 15701 Santiago de Compostela, A Coruña. Spain

email: manubarreiro@hotmail.com

AUTHOR CONTRIBUTIONS

Study concept and design: VMB, MBA, ARR.

Acquisition of data: VMB, MBA, IBR, RFI, CCS.

Analysis and interpretation of data: VMB, MBA, ARR.

Drafting of the manuscript: VMB, MBA, ARR.

Critical revision of the manuscript for important intellectual content: VMB, MBA, IBR, RFI, CCS, JMBD, JEDM, ARR.

Approval of the final manuscript: VMB, MBA, IBR, RFI, CCS, JMBD, JEDM, ARR.

Guarantor of the article: MBA, ARR.

CONFLICT OF INTEREST

MBA has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Janssen, Celltrion and Takeda.

RFI has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Janssen, Pfizer and Takeda.

IBR has served as a speaker for MSD, Janssen, Pfizer and Takeda.

VMB has served as speaker for Janssen.

The others authors declare no conflict of interest.

ABSTRACT

Introduction: inflammatory bowel disease (IBD) is a multifactorial pathology with an increasing incidence. There is no study that has assessed a possible relationship with very high residential radon exposure in the study area. The aim of the study was to analyze if residential radon concentration is associated with a higher incidence of IBD.

Material and methods: an ecological study was performed. All incident cases of inflammatory bowel disease in the area of Santiago de Compostela were included between January and December 2017. Radon levels at a municipal level were correlated with demographic factors and type of IBD.

Results: ninety-six patients were included, 63 (65.6 %) with ulcerative colitis, 29 (30.25) with Crohn's disease and four (4.2 %) with indeterminate colitis. The incidence rate per 100,000 inhabitants-year was 21.6 cases. There were no statistically significant differences in the type of disease developed regarding radon levels ($p > 0.05$). No correlation between radon levels and the cumulative incidence of inflammatory bowel disease at the municipal level was observed (Spearman's rho = 0.13, p-value 0.5).

Conclusion: in the area of Santiago de Compostela, there is a higher incidence of IBD in comparison with previous studies using western countries as reference. However, there was no correlation with the municipal average radon concentration and incidence of IBD or any of its types in this study.

Keywords: Inflammatory bowel diseases. Incidence. Radon.

INTRODUCTION

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Inflammatory bowel diseases (IBD) are a group of pathologies of unknown etiology, with a sustained and self-perpetuating expression of an abnormal synthesis of inflammation mediators, affecting genetically predisposed people and initiated by partially identified environmental factors. There is a genetic influence, with more than 80 genes involved in the development of Crohn's disease (CD) (1), participation of immunological factors with an imbalance of pro and anti-inflammatory cytokines and influence of environmental factors.

Many risk factors have been associated with the development of IBD, such as tobacco in CD, stress, depression and anxiety, dietary habits, changes in intestinal microbiota and dysbiosis, the "hygiene theory", gastrointestinal infections, vaccination, use of antibiotics, non-steroidal anti-inflammatory drugs and the use of contraceptives, among others. There are also some protective factors, such as tobacco and appendectomy for ulcerative colitis (UC) and breastfeeding (2-6).

The incidence of these diseases varies depending on the geographical area, with a north-south (7,8) and west-east gradient. The incidence is higher in industrialized and developed countries (9,10) as well as in urban compared to rural areas and at higher latitudes (which may be related to less sun exposure and lower levels of vitamin D, with the consequent decrease in its anti-inflammatory effects) (10). Living in coastal or inland areas also influences the development of the disease (11), with a higher prevalence of CD on the coast and of UC inland. The healthcare area of Santiago de Compostela has one of the highest incidence rates of IBD throughout all the national Spanish territory (12).

In Galicia, a region located in the northwest of Spain, there is a higher incidence of inflammatory diseases in relation to other regions. Thus, this could be related to environmental risk factors. Among them, high indoor radon concentrations might play some role, as Galicia is a radon-prone area due to the geological composition of the Galician subsoil (13). Radon is a colorless, odorless and tasteless radioactive gas that is released from radium-226 contained in subsoil rocks after a radioactive decomposition process. This gas is a human carcinogen, causing lung cancer, but its association with inflammatory diseases has not been formally studied. A recent paper has suggested a synergic effect between radon and smoking and the onset of chronic obstructive

pulmonary disease (COPD), an inflammatory lung disease (14).

The aim of this study was to assess if there was a correlation between average municipal radon concentrations and an incident diagnosis of IBD. Furthermore, its association with the clinical and demographics characteristics of the disease at a municipal level in the study area were also assessed.

MATERIALS AND METHODS

Design and settings

The study area has a population of 442,950 inhabitants, distributed in rural and urban areas, with 100,000 inhabitants where the main hospital is located. This healthcare area comprises 46 municipalities, which were the units of study.

An ecological study was performed that aimed to correlate IBD (UC, CD or indeterminate colitis) incidence with the average indoor radon concentration in the municipalities of the healthcare area. The annual incidence of IBD and its types was calculated after recruiting all consecutive cases diagnosed in our unit between January and December 2017. For each municipality, the population aged over 18 (overall, and broken down by sex) obtained from the Galician Institute of Statistics (IGE) January 1st 2017 was used as the denominator.

All cases complied with the following inclusion criteria: age over 18, diagnosis of IBD and resident in the Health Area of Santiago de Compostela. For the diagnosis of IBD and according to the European Crohn's and Colitis Organization (ECCO) guidelines, clinical, biochemical, endoscopic and histologic criteria must be used as there is no single test that provides a definitive confirmation. For diagnostic confidence, it is mandatory to perform an ileocolonoscopy with biopsies for histological analysis, which is performed in all patients with suspicion of the disease (15). Patients with a non-definitive diagnosis of the disease or patients with a residence outside the Health Area of Santiago de Compostela were excluded.

The following information was obtained from each case: demographic variables such as residence location and type of dwelling (flat or house) and clinical variables (sex, age, smoking habit, type and characteristics of IBD). Indoor radon exposure by each municipality was obtained from the Galician Radon Map (www.radon.gal), developed

by the Galician Radon Laboratory, located at the University of Santiago de Compostela. This map contains more than 4,300 indoor radon measurements in Galicia. This laboratory is certified by the National Entity of Accreditation (it is one of the three Spanish certified labs) and has international recognition to study the effect of radon in health (16,17).

The study protocol was approved by the Ethics Research Committee. All patients signed the informed consent.

Statistical analysis

The relationship between radon levels by municipality (geometric mean and percentage of houses above 300 Bq/m^3) and type of IBD was studied. The difference between radon levels and location of the residence (rural *vs* urban) and the difference in levels and the type of residence (house *vs* flat) were analyzed. Medians were compared via non parametric Mann-Whitney and Kruskal-Wallis tests. Correlation studies were calculated with the Spearman's test. Stata® 15 (StataCorp LP, Texas) was used for statistical analysis.

RESULTS

Ninety-six patients were included, with a median age of 41 years and an interquartile range between 33 and 56. Half (50.0 %) were female and 50.0 % were nonsmokers. Sixty-nine individuals (71.9 %) were resident in a rural area and 56 patients (58.3 %) lived in a detached house.

Regarding the classification of IBD, 63 (65.6 %) patients had UC, 29 (30.2 %) had CD and four (4.2 %), indeterminate colitis. Among patients with CD, 93.1 % (27 patients) did not present perianal disease, which was present in 6.9 % (two patients). With regard to patients with UC, 30 (47.6 %) had proctitis, 18 (28.6 %) had left sided colitis and 15 (23.8 %), pancolitis. In the group of patients with CD, 14 (48.3 %) had exclusively ileal involvement, four (13.8 %) colonic involvement only and eleven (37.9 %) ileocolonic involvement. The upper intestinal tract was not affected in any patient. When dividing the patients with CD according to their behavior, 69 % were inflammatory (non-stricturing, non-penetrating), 24 % stricturing and 7 % penetrating.

Table 1 shows clinical and demographic characteristics.

The incidence rate of IBD per 100,000 inhabitants and year was 21.6 cases and ranged between municipalities from 11.2 cases/100,000 inhabitants in A Estrada to 33.8 cases/100,000 inhabitants in Lousame. The median incidence was 29.8 cases per 100,000 inhabitants. The incidence of IBD was similar in rural municipalities (thinly populated) *versus* urban municipalities (densely populated), and on the coast (near the sea) *versus* inland (situated in the interior of the territory). The annual incidence rates per 100,000 habitants were 6.5 for CD, 14.2 for UC and 0.9 for indeterminate colitis.

The number of radon measurements available for each municipality ranged from 3 to 284. Indoor radon exposure was highly variable, and the geometric mean ranged from 65.0 Bq/m^3 to 257.6 Bq/m^3.

There was no correlation between municipalities with more or less than 10 % of the dwellings with values > 300 Bq/m^3 and annual incidence of UC or CD (high or low, taking the national incidence as a reference) ($p > 0.05$). The results are shown in figures 1 and 2. When stratifying the population by sex, there was no correlation ($p > 0.05$). There was no correlation between cumulative incidence per municipalities and radon concentration (Spearman's rho = 0.13, p-value 0.5), nor when stratifying by sex, with Spearman's rho = -0.13 in females (p-value 0.5) and Spearman's rho = 0.06 in males (p-value 0.7). A correlation between cumulative incidence per municipalities and percentage of radon measurements above 300 Bq/m^3 was not observed (Spearman's rho = 0.16, p-value 0.4).

The average geometric mean radon concentration was 122.7 Bq/m^3, with a maximum value of 257.64 Bq/m^3. No correlation between indoor radon and subtypes of IBD was observed (Spearman's rho = 0.06, p-value 0.5). The median radon concentration in rural areas was 123.97 Bq/m^3 and 119.67 Bq/m^3 in urban areas. There was no correlation between radon levels and residence location (rural *vs* urban), with Spearman's rho = 0.02, p-value 0.9, or house *vs* flat, with Spearman's rho = 0.12, p-value 0.3. There were no statistically significant differences between radon levels and location (rural *vs* urban) and the characteristics (flat *vs* house) of the residence ($p > 0.05$). There were no statistically significant differences between radon levels and sex and no correlation between radon levels and age of the study participants, with a

Spearman's rho of -0.13 (p-value 0.2). When dividing the population in age groups (≤ 65 or > 65 years), there was no significant variation in radon levels ($p > 0.05$).

There were no statistically significant differences between radon concentration according to the classification of IBD (UC, CD or indeterminate colitis) ($p > 0.05$). Analyzing patients with UC separately, the median radon concentration was 104.9 Bq/m^3, 118.38 Bq/m^3 in CD and 168.13 Bq/m^3 in indeterminate colitis.

DISCUSSION

In this study, there was no association between IBD and indoor radon concentration in the study area. There was no association with gender, IBD type or age at diagnosis. Nevertheless, we must highlight that these are preliminary results from an ecologic study with many limitations (discussed below). Furthermore, to our knowledge, this is the first study of the association between indoor radon exposure and IBD.

In Galicia (North-West of Spain), there is a higher incidence of IBD, especially UC, compared to other regions. Thus, there may be some environmental risk factors involved. Among them, high radon concentrations may play some role. These concentrations are high in this territory compared to surrounding areas because of the geological composition of Galician subsoil. Granite rocks are very rich in uranium and hence, there is a higher concentration of radon in Galicia. This gas has been related to the appearance of lung cancer (18), and radon exposure was classified as a human carcinogen many years ago (19).

The study area (Santiago de Compostela Health Area) has a high incidence of IBD, both CD and UC (21.6 cases per year per 100,000 habitants, 6.5 for CD and 14.2 for UC, respectively) compared to previous studies performed in western countries. Our study shows a higher incidence, when taking the study performed by ECCO as a reference, which found a global incidence of IBD in western European countries of 18.5 cases per 100,000 habitants per year (9.8 for UC and 6.3 per CD). Compared with the EpidemIBD study by Chaparro et al. (12), where an incidence of 16 cases of IBD per 100,000 habitants/year (eight cases of UC and 7.5 cases of CD) was observed in the Spanish population, the Health Area of Santiago de Compostela also has a higher incidence. Therefore, the incidence in the area of Santiago de Compostela found in this study is

higher than the overall incidence observed in Spain.

There could be some biological mechanisms suggesting that radon might have some effect on IBD onset. One has been suggested for other diseases outside the respiratory system. In this case, solid descendants of radon gas (i.e., polonium) could be phagocytosed by macrophages from the cell lining of the lungs and disseminated to the digestive system or other areas of the body. It has also been suggested that alpha radiation might be involved in inflammatory diseases, with some effect on interleukine-8 (14). These mechanisms could be the basis of the biological pathway of indoor radon causing some effect on IBD. A further explanation could come from radon diluted in drinking water, although other studies did not find an association with kidney diseases. We have to highlight that most participants live in areas with treated water and do not usually drink water from private wells.

Since this study has an ecological design, some limitations must be highlighted. The most important is that individual radon measurements have not been used in the participants' dwellings and this has been substituted by the municipal average. Therefore, individual radon assignment does not necessarily represent the real radon concentration of participants. A second limitation is the limited number of cases used to estimate annual incidence by municipality. Although we have included all consecutive cases diagnosed within a year from each municipality of the healthcare district, a longer time series would have been more reliable for these estimations. Nevertheless, as the patients originated from the only Gastroenterology Department of the healthcare area and the full health coverage of all the population, this makes our estimations representative. The short recruitment time means that some municipalities have a low number of cases (or even none), since their population may be lower than 3,000-4,000 inhabitants. Another limitation is that it was not possible to know how much time the participants resided in their current home at the time of the debut of the disease. Thus, it is difficult to know if the calculated radon concentration was actually due to exposure during previous years. A final limitation is that this is a single-center study, and only includes participants from the healthcare area of Santiago de Compostela.

This study has also some advantages. Firstly, it was performed in a radon-prone area, and should an association exist between radon and IBD, it is easier to be found in a place such as Galicia. A further advantage is that this study includes incident cases, with a consecutive sampling during one year. With regard to incident disease, all cases have a correct diagnosis and a correct classification of each IBD type, as well as other clinical parameters not analyzed in this study.

In summary, radon levels in the area of Santiago de Compostela are higher in comparison with other territories, and this gas could be associated with some other diseases apart from respiratory diseases. There is a higher incidence of IBD in the Health Area of Santiago de Compostela in comparison with previous studies taking western countries as a reference. It is still possible that some environmental risk factors, such as radon concentration (very high in this region), might be responsible for this difference. In the present study, it was not possible to demonstrate such an association, maybe because of the sample size and its design. Future studies to answer this research question should measure individual radon exposure to definitively ascertain if such an association exists, preferably performed in radon prone-areas.

REFERENCES

1. Barreiro-de-Acosta M, Mendoza JL, Lana R, et al. NOD2/CARD15: geographic differences in the Spanish population and clinical applications in Crohn's disease. Rev Esp Enferm Dig 2010;102:321-6. DOI: 10.4321/S1130-01082010000500006

2. Malik TA. Inflammatory bowel disease: historical perspective, epidemiology, and risk factors. Surg Clin North Am 2015;95:1105-22. DOI: 10.1016/j.suc.2015.07.006

3. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. Gastroenterol Hepatol (NY) 2010;6:339-46.

4. Friedman S, Nørgård BM. Confirming complexity: assessing environmental and genetic risk factors for inflammatory bowel disease. Gastroenterology 2019;156(8):2124-5. DOI: 10.1053/j.gastro.2019.04.030

5. Ng SC, Bernstein CN, Vatn MH, et al.; Epidemiology and Natural History Task Force of the International Organization of Inflammatory Bowel Disease (IOIBD). Geographical variability and environmental risk factors in inflammatory bowel disease.

Gut 2013;62:630-49. DOI: 10.1136/gutjnl-2012-303661

6. Amarapurkar AD, Amarapurkar DN, Rathi P, et al. Risk factors for inflammatory bowel disease: a prospective multi-center study. Indian J Gastroenterol 2018;37:189-95. DOI: 10.1007/s12664-018-0850-0

7. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). Gut 1996;39:690-7. DOI: 10.1136/gut.39.5.690

8. Barreiro-de-Acosta M, Magro F, Carpio D, et al. Ulcerative colitis in northern Portugal and Galicia in Spain. Inflamm Bowel Dis 2010;16:1227-38. DOI: 10.1002/ibd.21170

9. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46-54.e42. DOI: 10.1053/j.gastro.2011.10.001

10. Barreiro-de-Acosta M, Álvarez Castro A, Souto R, et al. Emigration to western industrialized countries: a risk factor for developing inflammatory bowel disease. J Crohns Colitis 2011;5:566-9. DOI: 10.1016/j.crohns.2011.05.009

11. Carpio D, Barreiro-de-Acosta M, Echarri A, et al. Influence of urban/rural and coastal/inland environment on the prevalence, phenotype, and clinical course of inflammatory bowel disease patients from northwest of Spain: a cross-sectional study. Eur J Gastroenterol Hepatol 2015;27:1030-7. DOI: 10.1097/MEG.0000000000000395

12. Chaparro M, Garre A, Núñez Ortiz A, et al. Incidence, clinical characteristics and management of inflammatory bowel disease in Spain: large-scale epidemiological study. J Clin Med 2021;10:2885. DOI: 10.3390/jcm10132885

13. Barros-Dios JM, Ruano-Ravina A, Gastelu-Iturri J, et al. Factors underlying residential radon concentration: results from Galicia, Spain. Environ Res 2007;103:185-90. DOI: 10.1016/j.envres.2006.04.008

14. Ruano-Ravina A, Cameselle-Lago C, Torres-Durán M, et al. Indoor radon exposure and COPD, synergic association? A multicentric, hospital-based case-control study in a radon-prone area. Arch Bronconeumol (Engl Ed) 2020;S0300-2896(20)30539-1. DOI: 10.1016/j.arbres.2020.11.015

15. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis 2019;13:144-64. DOI: 10.1093/ecco-jcc/jjy113

16. Lorenzo-González M, Ruano-Ravina A, Torres-Durán M, et al. Lung cancer risk and residential radon exposure: a pooling of case-control studies in northwestern Spain. Environ Res 2020;189:109968. DOI: 10.1016/j.envres.2020.109968

17. Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2005;330(7485):223. DOI: 10.1136/bmj.38308.477650.63

18. Ruano-Ravina A, Rodríguez MC, Cerdeira-Caramés S, et al. Residential radon and lung cancer. Epidemiology 2009;20:155-6. DOI: 10.1097/EDE.0b013e31818ef498

19. Radon. IARC Monogr Eval Carcinog Risks Hum 1988;43:173-259.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Table 1. Clinical and demographic characteristics of cases diagnosed with IBD

Characteristics	*Values*
Median age (IQR)	41 (33.5 to 56)
Sex	
Females	48 (50 %)
Males	48 (50 %)
Residence	
Rural	69 (71.9 %)
Urban	27 (28.1 %)
House	56 (58.3 %)
Flat	40 (41.7 %)
Smoker	
Yes	8 (8.3 %)
No	48 (50 %)
Ex-smokers	40 (41.7 %)
Inflammatory bowel disease	
Ulcerative colitis	63 (65.6 %)
Proctitis	30 (47.6 %)
Left sided colitis	18 (28.6 %)
Pancolitis	15 (23.8 %)
Crohn's disease	29 (30.2 %)
Ileal	14 (48.3 %)
Colonic	4 (13.8 %)
Ileocolonic	11 (37.9 %)
Upper intestinal involvement	0 (0 %)
Non structuring/non penetrating	20 (69 %)
Stricturing	7 (24 %)
Penetrating	2 (7 %)
Indeterminate colitis	4 (4.2 %)
Perianal disease	

Yes	3 (3.1 %)
No	93 (96.9 %)
Comorbidities	
Yes	23 (24.0 %)
Tumors	5 (5.2 %)
Pulmonary disease	6 (6.3 %)
Cardiac disease	2 (2.1 %)
Autoimmune disease	6 (6.3 %)
Neurologic disease	2 (2.1 %)
Gynecologic disease	1 (1.0 %)
Renal disease	1 (1.0 %)
No	73 (76.0 %)

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

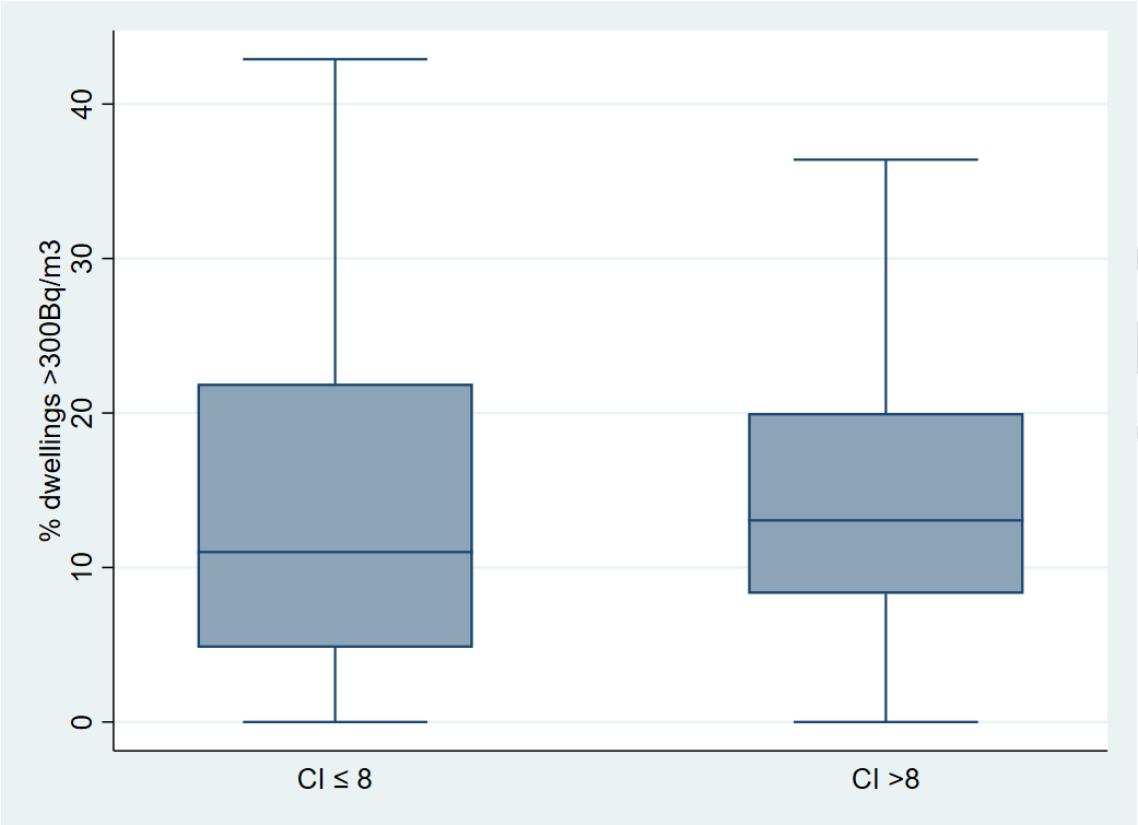

Fig. 1. Relationship between municipalities with more than 10 % of the dwellings with values > 300 Bq/m^3 and a cumulative incidence of UC (high or low).

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

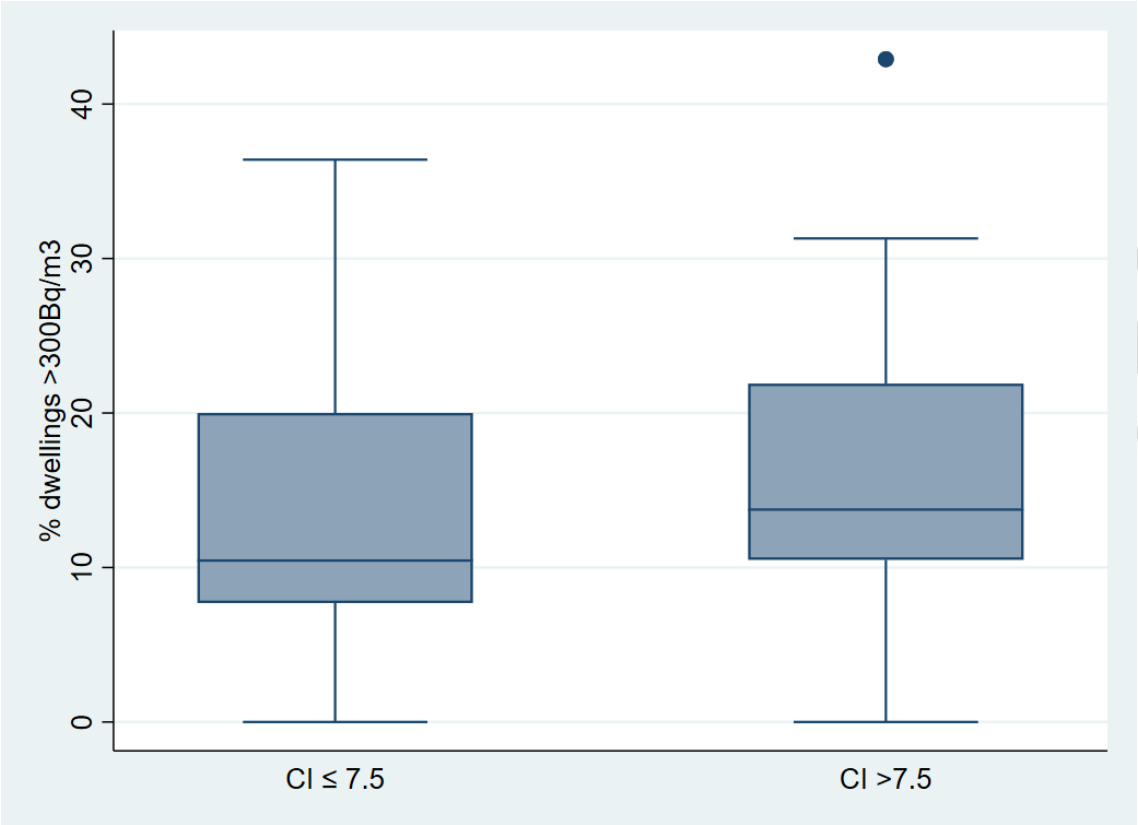

Fig. 2. Relationship between municipalities with more than 10 % of the dwellings with values > 300 Bq/m^3 and a cumulative incidence of CD (high or low).