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## **LOW EXPOSURE TO SUNLIGHT IS A RISK FACTOR FOR CROHN'S DISEASE**

Virginie Nerich, Prevost Jantchou, Marie-Christine Boutron-Ruault, Elisabeth Monnet, Alain Weill, Vincent Vanbockstael, Guy Robert Auleley, Corinne Balaire, Patrick Dubost, Stéphane Rican, et al.

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**LOW EXPOSURE TO SUNLIGHT IS A RISK FACTOR FOR  
CROHN'S DISEASE**

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For Peer Review

## **Abstract**

**Background:** Low sunshine exposure might contribute to IBD pathogenesis.

**Aim:** To assess the geographic distribution of IBD incidence in relation to sunshine exposure in France, in order to test the hypothesis that higher sun exposure is associated with lower IBD risk.

**Methods:** Using the national health insurance databases, incidence rates of CD and UC were estimated for each of 94 French administrative areas (“départements”), in 2000-2002. The surface UV radiation intensity was obtained by combining modeling and satellite data from Meteosat<sup>®</sup>, the European meteorological satellite. Relationships between incidence rates and sun exposure were tested for significance by using a Poisson regression. We mapped smoothed relative risks (sRR) for CD and UC, using a Bayesian approach and adjusting for sun exposure, in order to search for geographical variations.

**Results:** Areas with a smoothed RR of CD incidence significantly above 1 corresponded to areas with low sunshine exposure, whereas those with high or medium sunlight exposure had smoothed RRs either lower than 1 or not significantly different from 1. There was no association between sun exposure and UC incidence.

**Conclusions:** This geographic study suggests that low sunlight exposure is associated with an increased incidence of CD. Further studies are needed to determine if this association is causal.

**Key words:** Crohn’s disease; ulcerative colitis; geographical variation; France; sun exposure.

## **INTRODUCTION**

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract. Genetic predisposition of inflammatory bowel disease (IBD) is established, particularly in CD, in which several susceptibility genes that affect bacterial clearance (including autophagy), the IL23 pathway, and T cell homeostasis have been identified<sup>1</sup>. Environmental factors also contribute to IBD pathogenesis<sup>2</sup>. Smoking, appendectomy and intestinal infections have been reproducibly linked with susceptibility to IBD<sup>2</sup>. It is likely that other environmental factors increase IBD risk<sup>2</sup>. These environmental factors could possibly be found through the association between IBD and other diseases for which environmental factors are already known.

An association between multiple sclerosis (MS) and IBD has been reproducibly reported and could occur more often than by chance alone<sup>3-4</sup>. Geographical, case-control and prospective studies have suggested that sun exposure may protect from MS<sup>5-8</sup>. Therefore, we hypothesized that the association between MS and IBD is due to shared environmental factors, especially sun exposure, and thus we assessed the geographic distribution of CD and UC in relation to sunshine exposure.

## **MATERIALS AND METHODS**

### **Setting**

This study was conducted in metropolitan France (excluding Corsica and the overseas French territories) totalling 59,368,981 inhabitants on January 1, 2003. Its surface area is 535 280 km<sup>2</sup>, with an average of 111 people per square kilometre. There are considerable variations, however, as half the population lives on just over 10% of the territory, and large areas remain sparsely populated.

### **Geographical units**

This study was performed at the scale of "départements", i.e. the 94 administrative areas (subsequently called departments), as described previously<sup>9</sup>.

## **IBD Data**

In France, patients with IBD, whatever their place of residence, are fully reimbursed for their health care expenses by the national health insurance (NHI) system. The IBD data used for this study were obtained from the French statutory NHI system, which is based on professional status. Three main subsystems included in the NHI, cover 96% of the French population. The general fund insures salaried workers and their families in private secondary and tertiary industries and in the public sector (i.e. 84% of the population). The agricultural fund insures farmers and agricultural employees and their families (i.e. 7% of the population). The third fund provides medical coverage to self-employed professionals and their families (i.e. 5% of the population). **Unemployed and retired people remain affiliated to the last subsystem they were affiliated to when employed.**

CD and UC are two of the 30 specified long-term illnesses which provide patients with a 100% reimbursement rate, thus covering the total cost of requested health care. **Thus, all French IBD patients have equal access to free medical care.** This full coverage by statutory health insurance is subject to prior NHI approval, after examination of an official form that certifies that the patient has CD or UC and that has been signed by the patient's physicians (general practitioner and/or gastroenterologist). Each health insurance fund records individual data on an annual basis for all patients who have obtained 100 percent coverage for each of the 30 specified long-term illnesses. We contacted doctors in charge of national patient data files in the three insurance funds to request anonymous information concerning all new beneficiaries of 100 percent coverage for IBD granted between January 1, 2000 and December 31, 2002. We obtained centralized files covering the whole French territory. They contained the following individual information: age, sex, postcode of the place of residence, diagnosis that conferred the 100 percent coverage, coded either CD (ICD code K50) or UC (ICD code K51) with the tenth revision of the International Classification of Diseases (ICD). This study was approved by the "Commission Nationale de l'Informatique et **des Libertés**" (CNIL, Paris, France), a national commission which provides legal protection of computerized personal data.

## **Sun exposure data**

Ground radiometers are the most accurate method to measure sun exposure, but they are too few in number to offer a comprehensive geographical coverage. The surface UV radiation intensity can be obtained by combining modeling and satellite data from Meteosat<sup>®</sup>, the European meteorological satellite. This method provides a comprehensive map of sunlight exposure with a precision of 5 km. Correlation between measured and modelled erythemal daily doses was found to be highly significant<sup>10</sup>.

## **Statistical analysis**

### **Incidence rates**

The analysis was conducted separately for CD and UC. IBD patients were tabulated by sex, 5-year age classes and administrative area. The number of insured people in each area on January 1, 2003 was obtained from the health insurance funds and totalled to obtain the overall number of people affiliated with these funds within each area. For the population as a whole, incidence rates were calculated by sex for CD and UC, based on the number of all new beneficiaries of 100 percent coverage for CD or UC granted during the study period, with the person-years denominator being the sum of the insured population estimates for the 3 years in the three subsystems described above.

### **Influence of sun exposure on incidence rates**

Ground UV dose from sunshine was expressed in kJ/m<sup>2</sup> and was provided by month and by administrative area for the years 1984 to 2002. We calculated a mean annual UV dose for the studied period, which was classified into quintiles, and linked with incidence data tabulated by area. Age- and sex- adjusted incidence rate ratios (IRR), with their 95% confidence intervals (CI), were estimated using the Poisson regression, for CD and UC. We used the likelihood ratio statistics to calculate P-values for each variable.

### **Spatial analysis and disease mapping**

A spatial analysis with a Bayesian approach was then performed, as described previously<sup>9</sup>. Sun exposure was introduced as a covariate into this model and tested for improvement of the model fit,

1  
2 which was adjusted for age and sex. The model provides smoothed Relative Ratios (RR) which are  
3  
4 more accurate and steady than the traditional standardized incidence ratios.  
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6  
7 We mapped the 94 administrative areas grouped into 3 classes according to the value and  
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9 significance of smoothed RR: administrative areas with smoothed RRs significantly lower than 1,  
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11 administrative areas with smoothed RRs not significantly different from 1, and administrative areas  
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13 with smoothed RRs significantly higher than 1.  
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## 16 17 18 **RESULTS**

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20 From January 1, 2000 to December 31, 2002, 14,113 new patients with CD (including 8,138  
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22 women and 5,975 men) and 12,339 new patients with UC (including 5,959 women and 6,380 men)  
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24 were registered by the three health insurance funds, among the overall French insured population of  
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26 57,098,525.  
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30 The map of France showing the average annual erythemal daily dose (kJ/m<sup>2</sup>) by administrative area  
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32 is displayed in figure 1.  
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### 35 **Crohn's disease**

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37 In the population as a whole, the incidence rate was 8.2 for 100,000 inhabitants (95% CI: 8.1-8.4)  
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39 for the whole population, 7.1 (95% CI: 6.9-7.2) for men, and 9.4 (95% CI: 9.2-9.6) for women with  
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41 no important variation between the three studied years. Table 1 shows the age and sex adjusted  
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43 incidence rate ratios and 95% confidence intervals derived from the Poisson regression analysis for  
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45 CD, according to quintiles of sun exposure, and taking as the reference the quintile of highest sun  
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47 exposure. The two quintiles with the lowest sun exposure were associated with an increased IRR of  
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49 CD. The intermediate quintile had an IRR not significantly different from 1. The second quintile  
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51 with the highest sun exposure was associated with a decreased IRR of CD.  
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55 Local UV dose improved the Bayesian model of geographic distribution of CD, and the effect of  
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57 local UV dose was stronger than the effect of local spatial autocorrelation. Variations of smoothed  
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59 RR of CD in both sexes according to sunlight exposure are displayed in Figure 2. Areas with a  
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2 smoothed RR significantly higher than 1 corresponded to areas with low sunlight exposure (North  
3 of France), whereas those with high or medium sunlight exposure had smoothed RRs either lower  
4 than 1 (centre of France) or not significantly different from 1 (figure 2).  
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### 8 Ulcerative colitis

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10 In the population as a whole, the incidence rate was 7.2 for 100,000 inhabitants (95% CI: 7.1-7.3), it  
11 was 7.7 (95% CI: 7.5-7.9) in men and 6.8 (95% CI: 6.6-7.0) in women. Table 2 shows the age and  
12 sex adjusted incidence rate ratios and 95% confidence intervals derived from the Poisson regression  
13 analysis for UC, according to quintiles of sun exposure. There was no statistically significant  
14 association between sun exposure and UC incidence (cf. Support Information).  
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### 26 DISCUSSION

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28 The present study assessed the geographic distribution of IBD in relation to sun exposure. It appears  
29 that CD incidence is higher in geographical areas with a low sunshine exposure than in areas with  
30 high or medium sunshine exposure, where CD incidence is either lower than or not significantly  
31 different from the mean national incidence rate. Thus, there seems to be a threshold of sun exposure  
32 under which CD incidence increases. By contrast, no association between UC incidence and sun  
33 exposure was found.  
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42 Our study is based on data derived from administrative health care records and relies on ecological  
43 data. These limitations have already been discussed in our previous papers<sup>9, 11</sup>. Moreover, in a  
44 recent paper concerning geographic mapping of IBD, Green and Bernstein suggest to use small  
45 geographic areas in order to minimize the misclassification of populations by risk categories<sup>12</sup>.  
46 However, the sun exposure data are available at the scale of “departments” and not at a smaller  
47 scale. Additionally, the association between sun exposure and CD is not necessarily causal. It can  
48 be due to an underlying genetic or environmental factor which has a geographical distribution  
49 similar to that of sun exposure, such as chemicals, water or soil microbial ecology and diet. In a  
50 recent prospective study, high total protein intake, specifically animal protein, was associated with a  
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1 significantly increased risk of IBD in middle-aged French women<sup>13</sup>. It could be questioned whether  
2 this could confound the geographical variation of CD. However, the findings for protein intake  
3 were similar for CD and UC, unlike the present association between CD and sun exposure. If a role  
4 of vitamin D is suspected, the role of dietary vitamin D could also be questioned. It must be  
5 emphasized that in France, very few dairy products are fortified with vitamin D and about 90% of  
6 vitamin D is related to sun exposure. Thus a potential opposite effect of specific foods such as  
7 dairies through proteins on one hand and vitamin D on the other is most likely very limited.  
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18 On the other hand, the association between CD and sun exposure could also be causal, as suggested  
19 by several epidemiological and biological data. Firstly, there is a reproducible North-South gradient  
20 of CD incidence which has been found in the USA, Scotland and France<sup>9, 14, 15</sup>. Sun exposure might  
21 well explain the North-South gradient found in these countries. Secondly, the geographic  
22 distribution of multiple sclerosis (MS) appears to be similar to that of CD in France and several  
23 lines of evidence suggest that sun exposure protects from MS<sup>16</sup>. A strong inverse correlation  
24 between UV radiation and MS prevalence has been found in a geographical study performed in  
25 Australia<sup>5</sup>. A case-control study has shown that exposure to the sun in infancy may protect against  
26 multiple sclerosis<sup>6</sup>. It has also been shown that people with the highest blood levels of vitamin D  
27 had the lowest risks of MS<sup>7</sup>. Furthermore, results from a cohort study of 187,500 nurses showed  
28 that women who consumed at least the current daily recommended dose of vitamin D have a lower  
29 risk of developing MS<sup>8</sup>. Exposure to the sun may explain the French North-South gradient of MS  
30 and CD. Thirdly, there is a biological plausibility for our findings<sup>17</sup>. Sun and vitamin D have been  
31 found to act as immune regulators. UV radiation and vitamin D have been shown to induce  
32 regulatory T cell function<sup>18</sup>. UV radiation induces immune suppression via induction of IL-4 and  
33 IL-10 and suppression of IL-12 production<sup>19</sup>. 1,25-dihydroxyvitamin D inhibits dendritic cell  
34 differentiation and maturation, which induces a shift in T cell differentiation from Th1 and Th17 to  
35 a Th2 phenotype<sup>20</sup>. Recent studies have found that vitamin D is also a key regulatory factor of  
36 innate immunity. Vitamin D, produced in response to UV radiation, stimulates the production of  
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2 cathelicidin, which can kill various viruses and bacteria, including the mycobacteria<sup>21</sup>. More  
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4 recently, a study performed in primary cultures and lines of human monocytic and epithelial  
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6 intestinal cells has found that 1,25-dihydroxyvitamin D stimulates the expression of NOD2 in the  
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8 presence of its agonist muramyl dipeptide<sup>22</sup>. Taken together, these results suggest that low sunshine  
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10 exposure and vitamin D deficiency impair innate immunity and induce a shift in T cell  
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12 differentiation towards TH1/TH17 phenotype, which are both characteristic of CD.  
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16 Our study suggests that low sunlight exposure is associated with higher CD risk. This potential  
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18 association should be further investigated within case-control and cohort studies. If a protective role  
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20 of sun exposure on CD risk is confirmed, prevention of CD through vitamin D supplementation  
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22 should be tested in high-risk subjects. Vitamin D supplementation may also reduce the risk of  
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24 relapse in patients with CD, as shown by a recent randomized trial<sup>23</sup>.  
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**TABLES**

Table 1: Age- and sex-adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) derived from Poisson regression analysis for Crohn's Disease according to the average annually erythemal daily dose

	Crohn's disease		
	IRR	95% CI	<i>p</i> -value
Sex			<10 <sup>-4</sup>
<i>Female</i>	Reference		
<i>Male</i>	0.76	0.70 – 0.81	
Age (years)			<10 <sup>-4</sup>
15 – 29	Reference		
0 – 14	0.09	0.07 – 0.11	
30 – 44	0.70	0.64 – 0.76	
45 – 59	0.41	0.37 – 0.45	
≥ 60	0.26	0.23 – 0.29	
Average annually erythemal daily dose (kJ/m <sup>2</sup> )			<10 <sup>-4</sup>
1.729 – 1.928	Reference		
1.606 – 1.725	0.85	0.74 – 0.98	
1.488 – 1.585	0.90	0.78 – 1.04	
1.397 – 1.484	1.12	1.00 – 1.26	
1.272 – 1.396	1.42	1.27 – 1.58	

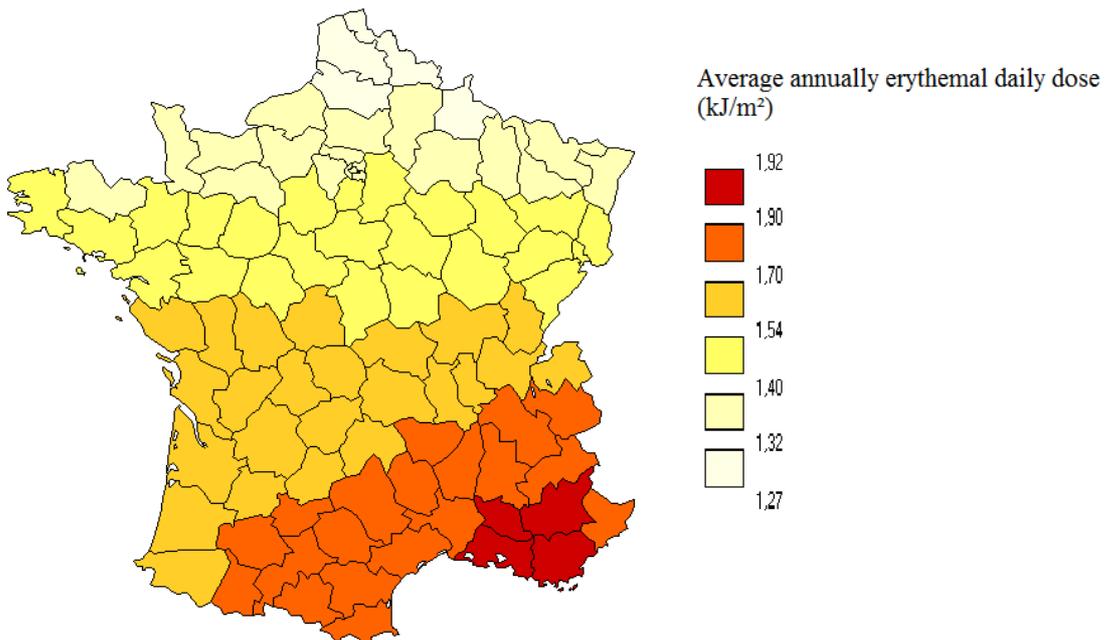
Table 2: Age- and sex-adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) derived from Poisson regression analysis for Ulcerative Colitis according to the average annually erythemal daily dose

	Ulcerative colitis		
	IRR	95% CI	<i>p</i> -value
Sex			0.01
<i>Female</i>	Reference		
<i>Male</i>	1.13	1.03 – 1.25	
Age (years)			< 10 <sup>-4</sup>
25 – 49	Reference		
0 – 24	0.26	0.22 – 0.30	
50 – 74	0.69	0.62 – 0.77	
≥ 75	0.46	0.37 – 0.57	
Average erythemal daily dose (kJ/m <sup>2</sup> )			0.25
1.729 – 1.928	Reference		
1.606 – 1.725	0.86	0.73 – 1.01	
1.488 – 1.585	0.85	0.71 – 1.01	
1.397 – 1.484	0.87	0.75 – 1.01	
1.272 – 1.396	0.93	0.81 – 1.07	

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**FIGURES**

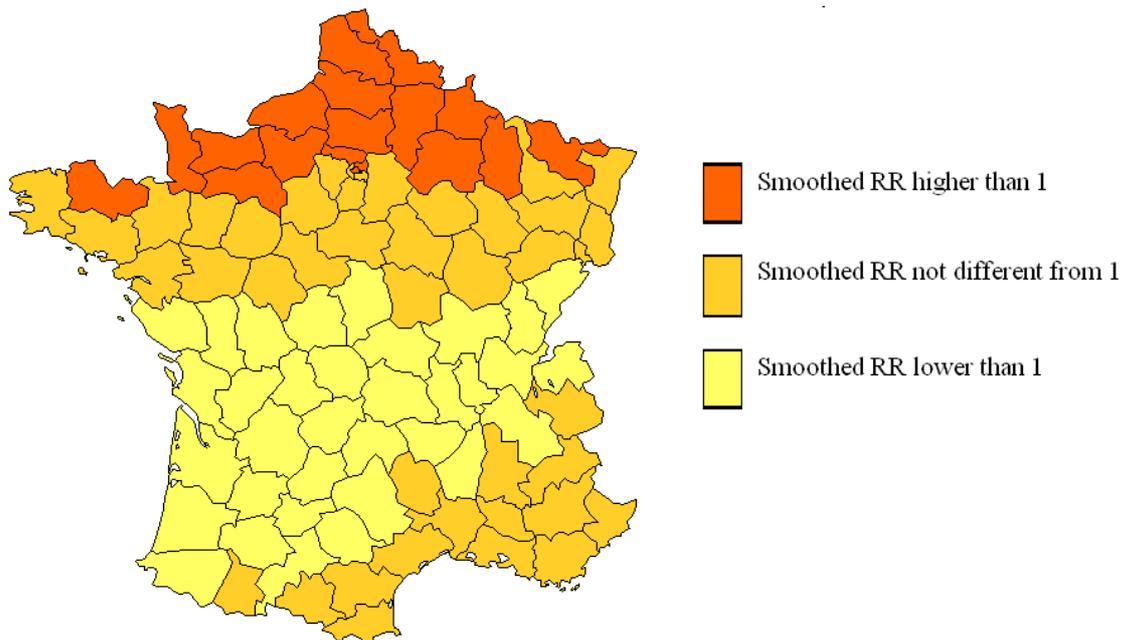
Figure 1: Map of France showing the average annually erythemal daily dose (kJ/m<sup>2</sup>) according to “departments”.



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Figure 2: Map of France showing age and sex adjusted CD smoothed Relative Risk (RR) obtained with the Bayesian model, taking into account the average annually erythemal daily dose



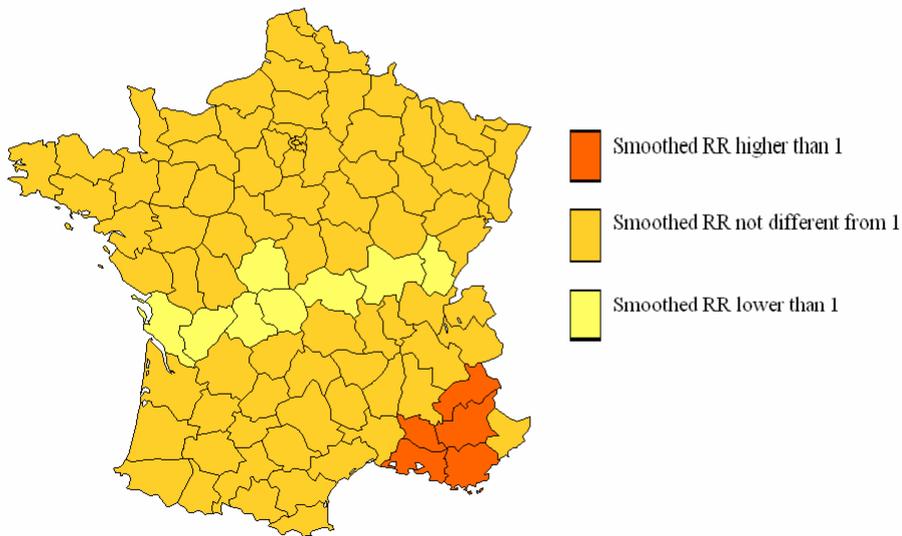
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For Peer Review

Supporting information: Map of France showing age and sex adjusted UC smoothed Relative Risk (RR) obtained with the Bayesian model, taking into account the average annually erythemal daily dose



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Review