RESEARCH ARTICLE

Impact of global warming on Raynaud's phenomenon: a modelling study [version 1; peer review: 2 approved]

Charles Khouri1-3, Matthieu Roustit1,3, Jean-Luc Cracowski1-3

1Clinical pharmacology, Grenoble Alpes University Hospital, Grenoble, France
2Centre Regional de pharmacovigilance, Grenoble Alpes University Hospital, Grenoble, France
3HP2, U1042, University Grenoble Alpes, Grenoble, France

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Abstract

**Background:** Raynaud's phenomenon is induced by excessive vasoconstriction of the peripheral microcirculation in response to environmental factors, essentially cold, but also stress or emotions. The objective of the present study is to evaluate the impact of global warming on the worldwide prevalence and severity of Raynaud's phenomenon over the 21st century.

**Method:** We first estimated the correlation between average temperature and prevalence and severity of Raynaud's phenomenon. Then, we mapped the prevalence and the severity of Raynaud's phenomenon worldwide at Christmas 1999 using historical data and, using climate projections from the Inter-Sectoral Impact Model Intercomparison Project, we predicted the prevalence and severity of Raynaud's phenomenon at Christmas 2099 according to four greenhouse-gas emission scenarios.

**Results:** The prevalence of Raynaud's phenomenon in the general population is expected to decrease by 0.5% per degree Celsius increase. Furthermore, patients are expected to suffer from one less attack per week for each increase of 2.5 degrees Celsius.

**Conclusions:** Our study shows that global warming may have a significant impact on the prevalence and the severity of Raynaud's phenomenon over the 21st century. However, as expected, this will greatly depend on the level of greenhouse-gas emissions.

**Keywords**
Raynaud's phenomenon, global warming

This article is included in the Climate Action gateway.
Raynaud’s phenomenon is induced by excessive vasoconstriction of the peripheral microcirculation in response to environmental factors, essentially cold, but also stress or emotions\(^1\). Primary, or idiopathic, Raynaud’s phenomenon is the most frequent form (80–90\%), while in some cases Raynaud’s phenomenon can be secondary to various auto-immune diseases (such as systemic sclerosis or systemic lupus erythematosus) or drugs\(^1\). The prevalence of Raynaud’s phenomenon is estimated to be approximately 3 to 5\% in the general population, with substantial variability according to climate and sex\(^2\). Exposure to cold increase sympathetic adrenergic outflow inducing cutaneous vasoconstriction by constricting skin toes and fingers arteriovenous anastomoses\(^3\). In individual with Raynaud’s phenomenon, the already-heightened sympathetic vasoconstriction is further amplified in intensity and will precipitate vasospasm of this vascular network\(^2,3\). Therefore sudden temperature change but also mean environmental temperature are determinant of Raynaud’s phenomenon burden and strong seasonal variation are described\(^4\)–\(^6\). Most vasodilators currently used in Raynaud’s, such as nifedipine or sildenafil, only have limited efficacy, below the minimal clinically important difference\(^7\). Moreover, most recent trials have produced negative results, due to high heterogeneity and a significant placebo effect\(^8\).

We hypothesize that global warming should not leave Raynaud’s phenomenon as an unmet clinical need for too long. The objective of the present study is to evaluate the impact of global warming on the worldwide prevalence and severity of Raynaud’s phenomenon over the 21\textsuperscript{st} century.

**Method**

We first estimated the correlation between average temperature and the prevalence of Raynaud’s phenomenon. The prevalence data were extracted from a systematic review of observational studies (Table 1)\(^9\). For each study we calculated the mean temperature during the winter preceding the publication of the study (from 1\textsuperscript{st} November to 31 March) using historical climate data from the database developed by the Inter-Sectoral Impact Model Intercomparison Project (ISIMIP). The results were then extrapolated to other countries using latitudes coordinates.

We further predicted the impact of global warming on the severity of Raynaud’s phenomenon, expressed as the average daily frequency of attacks, by using a model based on a Poisson regression including temperature (and other covariates), recently published by our team\(^10\) (this model is available online from DRYAD). This model is derived from a series of n-of-1 trials containing more than 2000 days of study.

### Table 1. Extracted data from the systematic review of Garner et al.\(^9\). Data is reproduced under the terms of the Creative Commons Attribution Non Commercial (CC BY-NC 4.0).

| Study | Year | Country | City | Latitude | Sample size | Mean age | Mean RP frequency |
|-------|------|---------|------|----------|-------------|----------|------------------|
| Brand | 1997 | USA     | Boston | 42.36    | 4182        | 51.8     | 7.20             |
| Fraenkel | 1999 | USA     | Boston | 42.36    | 1525        | 53.9     | 7.80             |
| Harada | 1991 | Japan   | Ehime  | 33.84    | 3873        | 20–70    | 1.60              |
| Ivorra | 2001 | Spain   | Valencia | 39.47   | 276         | 54.4     | 3.30              |
| Maricq | 1997 | USA     | South Carolina | 33.84 | 2518        | >18      | 2.10             |
| Maricq | 1997 | France  | Toulon  | 43.12    | 2187        | >18      | 7.10              |
| Maricq | 1997 | France  | Nyons   | 44.36    | 2341        | >18      | 6.00              |
| Maricq | 1997 | France  | Grenoble | 45.19   | 2341        | >18      | 9.25              |
| Maricq | 1997 | France  | Tarentaise | 45.37  | 2296        | >18      | 11.05             |
| Onbasi | 2005 | Turkey  | Van     | 38.50    | 768         | 29.2     | 5.90              |
| Heslop | 1983 | UK      | Southampton | 50.91 | 450         | 20–59    | 12.70             |
| Purdie | 2009 | New Zealand | Wellington | 41.25 | 234         | >18      | 11.50             |
| Sahin | 2003 | Turkey  | Van     | 38.50    | 251         | 28.9     | 3.98              |
| Leppert | 1987 | Sweden  | Vasteras | 59.61   | 2705        | 18–59    | 11.00             |
| Olsen | 1978 | Denmark | Copenhagen | 55.68 | 67          | 21–50    | 15.51             |
| Tzialalis | 2011 | Greece  | Athens  | 37.98    | 3912        | 18–28    | 0.31              |
| Cakir | 2008 | Turkey  | Edirne  | 41.15    | 1414        | 27.2     | 3.60              |
| Gallo | 1994 | Italy   | Milan   | 45.46    | 1920        | 15–84    | 4.20              |
| Vouligari | 2000 | Greece  | Ioannina | 39.77   | 500         | 33.7     | 5.20              |
| Jones | 2003 | UK      | Manchester | 53.48 | 716         | 12–15    | 14.90             |
exposition, with daily temperature measurements collected at the nearest weather station to the patient’s home.

Finally, we mapped the prevalence and the severity of Raynaud’s phenomenon worldwide at Christmas 1999 and, using climate projections from the ISIMIP, we predicted the prevalence and severity of Raynaud’s phenomenon at Christmas 2099, according to four greenhouse-gas emission scenarios (Representative Concentration Pathway (RCP) 2.6, RCP4.5, RCP6.0, and RCP8.5) described in the Fifth Assessment Report of the United Nations Intergovernmental Panel on Climate Change. The HadGEM2-ES model was used for the modelling scenario.

The RCPs represent the range of greenhouse-gas emission scenarios consistent with projections described in the literature; they include a mitigation scenario (RCP2.6), two intermediate scenarios (RCP4.5 and RCP6.0), and one scenario with high greenhouse-gas emissions (RCP8.5).

Data analysis were performed with R version 3.3.0 and map visualization with Panoply version 4.10.4 software.

A patient, Mrs Laurence Schuller, member of the board of the French Scleroderma Patient Association, was invited to comment on the study design and to interpret the results.

Results
We found a high correlation between average temperature and the prevalence and severity of Raynaud’s phenomenon (p<0.001). According to these data, no Raynaud’s phenomenon attack is expected to occur above an average temperature of 13°C, which is consistent with individual data collected in our series of N-of-1 trials. Consequently, the prevalence of Raynaud’s phenomenon in the general population is expected to decrease by 0.5% per degree Celsius increase. Furthermore, patients are expected to suffer from one less attack per week for each increase of 2.5 degrees Celsius.

The worldwide prevalence and severity of Raynaud’s phenomenon at Christmas 1999 and the range of predictions based on four greenhouse-gas emission scenarios at Christmas 2099 are shown in Figure 1.

Discussion
Our study shows that global warming may have a significant impact on the prevalence and the severity of Raynaud’s phenomenon over the 21st century. However, as expected, this will greatly depend on the level of greenhouse-gas emissions. The most optimistic greenhouse gas scenario (RCP 2.6), which aims at keeping global warming below 2°C above pre-industrial temperatures, only has a limited impact on the global prevalence and severity of Raynaud’s phenomenon. On the other hand, scenarios without greenhouse-gas emission reductions (predictions ranging between RCP6.0 and RCP8.5) may largely improve the condition of patients suffering from Raynaud’s phenomenon. For example, people in western European countries could expect to be totally free of this painful and disabling condition in the event of the two higher gas-emission scenarios. Finally, patients in North America, Western Europe and Asia still suffering from Raynaud’s phenomenon are not expected to suffer more than one or two crises over the Christmas period in 2099.

A limitation to our model is that we did not consider the potential increase in the use of air-conditioning and the stress caused by global warming, which may enhance RP. Climate change is also likely to result in temperature anomalies, including rapid temperature fluctuations which are known to be triggering factors of Raynaud’s phenomenon attacks. Nevertheless, mean temperatures are correlated to RP prevalence. In this study we only used one modelling scenario, the HadGEM2-ES model, which is widely used for climate research, therefore uncertainty of our projections has not been evaluated but exist undoubtedly. The findings should thus be interpreted as potential impacts of climate change on Raynaud’s phenomenon according to one hypothetical scenario and not as projections.

Conclusion
In conclusion, this study shows that global warming is likely to have a significant impact on the prevalence and the severity of Raynaud’s phenomenon. Yet, whether the advantages of global warming will outweigh its drawbacks, even for Raynaud’s phenomenon patients, remains to be carefully scrutinized.

Data availability
Source data
The data from the N-of-1 trial PROFIL are freely available on datadryad.org

DRYAD: Data from: On-demand sildenafil as a treatment for Raynaud phenomenon: a series of n-of-1 trials. https://doi.org/10.5061/dryad.c670tq2

The files required are:
- PROFIL_DATA (The dataset of the study in plain text format with variables names as header 2306 observations on 50 variables)
- model_1 (Final model)

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Historical and climate projections are available from the ISIMIP Earth System Grid Federation (ESGF) server in
Figure 1. Prevalence and daily frequency of Raynaud’s phenomenon during Christmas 1999 and Christmas 2099 according to four greenhouse gas emission scenarios (Representative Concentration Pathway (RCP) 2.6, RCP4.5, RCP6.0, and RCP8.5).
searching the climate forcing “HadGEM2-ES” and the variable “tasAdjust”:
- tas_day_HadGEM2-ES_historical_r1i1p1_EWEMBI_landon-19910101–20001231.nc (historical data)
- tas_day_HadGEM2-ES_rcp26_r1i1p1_EWEMBI_landon-20910101–21001231 (climate projection for RCP 2.6)
- tas_day_HadGEM2-ES_rcp26_r1i1p1_EWEMBI_landon-20910101–21001231 (climate projection for RCP 4.5)
- tas_day_HadGEM2-ES_rcp26_r1i1p1_EWEMBI_landon-20910101–21001231 (climate projection for RCP 6.0)
- tas_day_HadGEM2-ES_rcp26_r1i1p1_EWEMBI_landon-20910101–21001231 (climate projection for RCP 8.5)

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Rebecca S. Overbury
Department of Internal Medicine, Division of Rheumatology, University of Utah, Salt Lake City, UT, USA

This is a research article that attempts to hypothetically model how rising temperatures, assumed due to increased levels of greenhouse gas emissions, would affect the prevalence and severity (as defined by frequency of "crises") of Raynaud's phenomenon. Overall, this is a truly fascinating, if disturbing, question to consider and one that is likely to be relevant for worldwide clinicians moving forward. The authors present previous research supporting a sound hypothesis from which to ask this question. I find this a novel and interesting research question.

I do not have expertise to speak to the methods of modelling in particular. However, the authors are transparent, if succinct, in explaining their methods and all necessary materials for reproducibility appear to be available. Someone well-versed in this may desire more detail.

As a Rheumatologist, I recognize that the affect of this climate change phenomenon in patients with primary versus secondary Raynaud's is likely to differ; and I would be interested to hear more about this. This is not addressed here, but is arguably outside the scope of this methodology.

Is the work clearly and accurately presented and does it cite the current literature?  
Yes

Is the study design appropriate and is the work technically sound?  
Yes

Are sufficient details of methods and analysis provided to allow replication by others?  
Yes

If applicable, is the statistical analysis and its interpretation appropriate?  
Yes
Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Rheumatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 09 November 2020

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**Rossella De Angelis**  
Department of Clinical and Molecular Sciences, Rheumatology Unit, Carlo Urbani Hospital, Polytechnic University of Marche, Ancona, Italy

The predicted prevalence and the severity of Raynaud's phenomenon at Christmas 2099, according to four greenhouse gas emission scenarios as described in the 5th Assessment Report of United Nations.

So:

1. If possible, a slightly detailed explanation of reference item 11 would be particularly welcome, also to make the data more understandable to doctors.

2. A rather more refined description of the statistical model HadGe2_ES (not only with a simple bibliographic citation), in order to make the reading of the work more fluent. On the other hand, a doctor who is interested in the study should go into the bibliographic item no. 12, which is not easily understandable at a first reading.

The work is, however, very interesting and describes a likely scenario. Those clinicians who deal with Raynaud's phenomenon should take this hypothesis into account. In any case, a welcome reading.

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and is the work technically sound?**
Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**
Partly

If applicable, is the statistical analysis and its interpretation appropriate? 
Yes

Are all the source data underlying the results available to ensure full reproducibility? 
Partly

Are the conclusions drawn adequately supported by the results? 
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Rheumatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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