Derivation and validation of BOREAS, a risk score identifying candidates to develop cold-induced hypertension

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1. Introduction

Environmental temperature plays a role in the seasonal variation of blood pressure: colder temperatures increase blood pressure levels (Rose, 1961; Brennan et al., 1982; Hintsala et al., 2013; Alpérovitch et al., 2009; Sinha et al., 2010a). Since high levels of blood pressure induce hypertension, seasonal variation in blood pressure may lead to an increase in the prevalence of hypertension in cold months (Sinha et al., 2010a; Brook et al., 2011). Indeed hypertension is a major risk factor for vascular disease, so the seasonal phenomenon of blood pressure may increase the cardio-vascular hospitalizations or deaths in cold months (Vasan et al., 2002; Ulmer et al., 2004; Dilaveris et al., 2006; Matsumoto et al., 2010).

It is plausible that blood pressure seasonality might differ between individuals. Those suffering stronger increase of blood pressure in cold months might even develop hypertension – and
thus increase their vascular risk – only in cold months. However, general practitioners can hardly assess such seasonality when diagnosing hypertension: screening the entire population during the cold months would be unrealistic. Thus, a tool to identify individuals more prone to suffer hypertension only in cold months becomes compelling. In this scenario, primary care databases containing massive electronic health records become a powerful tool to improve hypertension diagnosis. These databases include the clinical practice and provide multiple blood pressure measurements per individual at a low cost.

This study aims to (i) to describe blood pressure seasonal variation; (ii) to describe the prevalence of cold-induced hypertension, i.e., nonhypertensive blood pressure values in the warm months and hypertensive values in the cold months; (iii) to assess the possible effect of blood pressure patterns in promoting vascular events and also the effect size per mmHg increase; and (iv) to develop and validate a prescreening test to identify the nonhypertensive subjects more likely to develop cold-induced hypertension.

2. Methods

2.1. Study population

Data was obtained from the Information System for the Development of Research in Primary Care (SIDIAP), which was designed to provide an anonymized, valid, reliable database for biomedical research drawn from clinical records of patients registered in the primary care centers of the Catalan Public Health Service (SIDIAP Database, 2012; Ramos et al., 2012). We included subjects older than 18 years from the Girona region (Catalonia, Spain), with ≥3 blood pressure measures recorded between October 1, 2003 and March 31, 2009 with results in both cold (October–March) and warm (April–September) periods. These periods were defined according to environmental temperature of Girona’s Mediterranean climate (Fig. 1).

2.2. Blood pressure patterns

We used the mean of all blood pressure values of each patient in a given period. We defined an elevated blood pressure (EBP) reading as systolic blood pressure (SBP) ≥140 or diastolic blood pressure (DBP) ≥90 mmHg (Mancia et al., 2013). We assigned to each subject one of these patterns depending on blood pressure levels and diagnosis or treatment of hypertension (Fig. 2):

1. Nonhypertensive (noHTN), if < 2 EBP readings and no hypertension diagnosis or antihypertensive treatment.
2. Known hypertensive, if previously diagnosed by a physician under the International Classification of Diseases, 10th Revision (ICD/10), codes 10–15, or under antihypertensive treatment.
3. Unknown hypertensive, if ≥2 EBP readings recorded with no hypertension diagnosis or antihypertensive treatment; we further defined two subgroups according to the period when EBP readings were achieved:
   a. Cold-Induced Hypertensive: unknown hypertensive individuals with ≥2 EBP readings exclusively in cold periods (i.e., all measures in the warm period were normal).
   b. Non-Seasonal Hypertensive: unknown hypertensive individuals with ≥2 EBP readings regardless of temporal period (warm or cold).

2.3. Risk factors

Demographic and clinical characteristics of each participant were collected prior to study inclusion, considering: sex, age, body mass index (BMI) (categorized into: Normal, ≤25 kg/m²; Overweight, > 25 and ≤ 30 kg/m²; Obese, > 30 kg/m²), and prevalent diagnosis (ICD 10 codes) of diabetes (E11, E12, E14), tobacco consumption (F17: for smokers or Z72.0 for former smokers), renal failure (N17, N18), myocardial infarction (E21-E22), angina (I20), stroke (I63), and transient ischemic attack (G45-G46). The sources of information for monitoring the incidence of cardiovascular events were also discharges from hospital, review of medical records in primary care and population registry of myocardial infarction. Prehypertension in warm months was defined as mean SBP or mean DBP measures between 120 and 139 mmHg or 80 and 89 mmHg, respectively.

2.4. Statistical analysis

Results are expressed as percentages for categorical variables and as mean ± standard deviation for the continuous variables. We used a General Mixed Model with repeated measures and random intercept per subject to examine the
relationship between SBP and period (warm/cold). The same procedure was conducted using DBP as dependent variable.

Then, a Cox proportional-hazards model was used to determine the risk to develop cardiovascular events associated with the blood pressure patterns. We included the time to the first event occurrence of vascular disease (angina, myocardial infarction, stroke, or transient ischemic attack) subsequent to the latest blood pressure measure as outcome variable; and age, gender, renal failure, diabetes, BMI, tobacco consumption, prehypertension in warm months and blood pressure – pattern as adjusting variables. Patients were censored when death, a vascular event occurred or at the end of the follow-up.

Finally, we built a model to identify nonhypertensive individuals prone to suffer temporal hypertension induced by cold outdoor temperature (which we named the BOREAS score). The dataset (N = 23,979) included those participants with normotensive blood pressure in summer (classified as cold-induced hypertensives or NoHTN) without missing data on any covariable. The derivation model included a random sample of 60% of the total database (Fig. 3). It was performed using a logistic regression including variables that showed significant differences in univariate analysis and important clinical variables as potential confounders. Due to a significant interaction between sex and age, we constructed two BOREAS models, one for men and the other for women (Fig. 3). The validation of the model was based on the remaining 40% of the total database and we assessed accuracy and reliability as follows: (i) comparing 95% confidence intervals (CI) between coefficients estimated by the regression model that best fitted the validation data and those of the derivation function; (ii) estimating the Brier score, which computes the sum of squared differences between the observed outcome and fitted probabilities on the data set (scores range from 0 [perfect] to 0.25 [worthless]); (iii) comparing the area under the receiver operating characteristics (ROC) curve obtained by the BOREAS score and by the regression model best fitted to the study data, to evaluate the model’s discrimination capacity. The ROC curve analysis also provided cut-off values for both men and women, derived from calculating the maximum of the sum of the sensibility and specificity. All analyses were performed using R statistical package (R Foundation for Statistical Computing, Vienna, Austria; Version 2.13).

3. Results

3.1. Seasonality of blood pressure

From the 95,277 subjects included in the study we obtained 553,786 blood pressure measurements (5.8 ± 3.6 measurements per subject). The average of lag time between individual blood pressure measurements was 150 days ± 216 days. A U-shaped relationship was observed between blood pressure and months. The mean SBP increased by 5.5 ± 0.1 mmHg, from 135.4 ± 18.7 mmHg in July to 140.9 ± 18.9 mmHg in December (Fig. 1a). The mean DBP increased 1.8 ± 0.1 mmHg, from 77.6 ± 10.8 mmHg in July to 79.4 ± 10.9 mmHg in February (Fig. 1b). When considered by 6-month periods, mean SBP increased by 3.3 ± 0.1 mmHg, from 136.7 ± 18.8 mmHg in the warm period to 140.0 ± 19.0 mmHg in the cold period and mean DBP from 78.1 ± 10.8 mmHg in the warm period to 79.1 ± 10.8 mmHg in the cold period. Mixed models showed a significant effect of 6-months periods in both SBP (P < 0.001) and DBP (P < 0.001). The proportion of subjects with ≥ 2 EBP measures increased from 24.5% in the warm period to 32.7% in the cold period (P < 0.001).

3.2. Prevalence of cold-induced hypertension

Among the 95,277 study subjects, 27.3% were nonhypertensive, 61.6% were known hypertensive, and 11.6% were unknown hypertensive subjects (Table 1, Fig. 2). Subjects classified as cold-induced hypertensives represented 2.1% of the study population, 5.3% of the nondiagnosed or nontreated subjects, and 17.8% of the unknown hypertensive individuals. Baseline patient characteristics according to blood pressure patterns are shown in Table 1.

3.3. Effect of blood pressure patterns on the risk of vascular disease

Vascular disease was observed in 5299 individuals (6.0% of the total population) during the follow-up. The median follow-up time was 1416 ± 551 days. Cold-induced hypertensive patients were at higher vascular event risk than nonhypertensive or even nonseasonal hypertensive individuals (Table 2). Known hypertensive

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**Table 1.** Baseline characteristics of the study sample according to blood pressure patterns.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Nonhypertensive</th>
<th>Unknown hypertensive</th>
<th>Known Hypertensive</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Cold-induced</td>
<td>Not seasonal</td>
<td></td>
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<tr>
<td>N</td>
<td></td>
<td></td>
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<tr>
<td>Warm months SBP (mmHg)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>134.7 (16.0)</td>
<td>121.4 (11.5)</td>
<td>1382 (7.7)</td>
<td>142.4 (9.9)</td>
</tr>
<tr>
<td>ΔSBP between periods (mmHg)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.7 (12.8)</td>
<td>2.1 (11.3)</td>
<td>13.9 (9.7)</td>
<td>0.4 (12.1)</td>
</tr>
<tr>
<td>Warm months DBP (mmHg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>77.6 (9.2)</td>
<td>73.3 (7.9)</td>
<td>75.9 (7.3)</td>
<td>81.3 (8.0)</td>
</tr>
<tr>
<td>ΔDBP between periods (mmHg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.9 (7.7)</td>
<td>0.79 (7.81)</td>
<td>5.62 (7.23)</td>
<td>-0.11 (7.46)</td>
</tr>
<tr>
<td>Men&lt;sup&gt;c&lt;/sup&gt;</td>
<td>40,671 (42.7)</td>
<td>8852 (34.0)</td>
<td>899 (45.7)</td>
<td>4329 (47.6)</td>
</tr>
<tr>
<td>Age&lt;sup&gt;d&lt;/sup&gt;</td>
<td>61.5 (15.6)</td>
<td>51 (17)</td>
<td>62 (15)</td>
<td>63 (14)</td>
</tr>
<tr>
<td>Vascular disease&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7362 (7.7)</td>
<td>599 (2.3)</td>
<td>74 (3.8)</td>
<td>351 (3.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14,877 (15.6)</td>
<td>2510 (5.6)</td>
<td>388 (19.7)</td>
<td>1749 (19.2)</td>
</tr>
<tr>
<td>Renal disease&lt;sup&gt;b&lt;/sup&gt;</td>
<td>501 (0.5)</td>
<td>44 (0.2)</td>
<td>3 (0.2)</td>
<td>19 (0.2)</td>
</tr>
<tr>
<td>BMI (Kg/m²)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28.4 (5.1)</td>
<td>26.4 (4.8)</td>
<td>28.6 (5.7)</td>
<td>28.6 (4.9)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

<sup>a</sup> Mean (SD).

<sup>b</sup> Number (%).

<sup>c</sup> Mean (SD).

<sup>d</sup> Percent.

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**Fig. 3.** Diagram of processes for derivation and validation of BOREAS score.
patients had the highest risk compared with nonhypertensive individuals (Table 2).

### 3.4. Boreas score

The best logistic regression model to predict cold-induced hypertension in men included diabetes, BMI > 25 kg/m², age, and prehypertension in the warm period (Fig. 4a). No interactions were found. In women, factors associated with cold-induced hypertension were diabetes, BMI > 25 kg/m², and the interaction of age and prehypertensive blood pressure values during the warm period (Fig. 4b).

Validation model coefficients significantly differed from those of the derivation model (Figs. 4a and b). We obtained a Brier Score of 0.01500 for men and 0.01699 for women. The area under the ROC curve (AUC) obtained with the validation model was similar to that of the derivation model in both men (AUC: 0.689; 95%CI: 0.666–0.712 vs 0.685; 95%CI: 0.657–0.714) and women (AUC: 0.773; 95%CI: 0.756–0.791 vs 0.775; 95%CI: 0.753–0.797). In the validation dataset, the probability cut-off values in the BOREAS score that yielded the maximum sensitivity and specificity were 9.3% in men and 6.0% women. In men, this cut-off defined 44.0% (95%CI: 42.2–45.8) of the participants as high risk and presented a sensitivity of 68.9% (95%CI: 67.3–70.5), a specificity of 58.9% (95%CI: 57.2–60.6). In women, this cut-off defined 33.9% (95%CI: 32.7–35.1) of the participants as high risk and had a sensitivity of 78.0% (95%CI: 77.0–79.0), a specificity of 63.5% (95%CI: 62.3–64.7).

### 4. Discussion

Although screening programs have been attempted over recent decades, detection of hypertension can still be improved (Mancia et al., 2013; de la Sierra et al., 2008; Banegas et al., 2009). In this study we observed a seasonal effect on blood pressure that has consequences for the diagnosis of hypertension. The blood pressure response to the seasons follows an individual pattern, so that hypertension can only be detected in the cold season in some cases. These patients have an increased risk of vascular disease compared with nonhypertensive individuals and a risk that is similar to any other undiagnosed hypertensive person.

The BOREAS score may help to detect those individuals who should preferably be screened during the cold season. Using the BOREAS score at cut-off values of maximum sensitivity and specificity, we can detect nearly 75% of cold-induced hypertensives without incurring a significant burden in the primary care setting. Furthermore, the predictive capacity of BOREAS can be modulated by changing the cut-off value for intervention.

Our data highlighted the strong relationship between blood pressure and the seasons. We detected a SBP increase of 3.3 mmHg between temporal periods, higher than that reported by previous studies using 6-month periods (0.3 mmHg) (Halonen et al., 2011) and in the lower range of most publications using shorter periods (4–10 mmHg). Variation between studies in climate and population characteristics may partially explain such differences.

Although seasonal variations in blood pressure have been mainly attributed to outdoor temperature (Rose, 1961; Brennan et al., 1982; Hintsala et al., 2013; Alpérovitch et al., 2009; Sinha et al., 2010a; Halonen et al., 2011), the exact mechanisms explaining the association between blood pressure and temperature remain unknown. It has been suggested that activation of the sympathetic nervous system and secretion of catecholamine are increased in response to cold temperatures. This could increase heart rate and peripheral vascular resistance, resulting in an increase in blood pressure (Hanna, 1999). Endothelium-dependent mechanisms could also be involved in the relationship between temperature and vasodilation (Widlansky et al., 2007; Sun, 2010). Additional meteorological factors including humidity, rainfall, or barometric pressure have not been consistently associated with blood pressure (Brennan et al., 1982; Alpérovitch et al., 2009; Sinha et al., 2010a; Modesti et al., 2006). Other parameters such as reduced vitamin D levels, weight gain, lower activity, or dietary changes could play further roles in the context of seasonal effects (Brook et al., 2011).

Although seasonal blood pressure variation has been largely investigated, few studies dealt with the impact on hypertension prevalence (Sinha et al., 2010b; Corsonello et al., 2003). In our population-based study, seasonal blood pressure variation leads to a 8.2% increase in hypertension prevalence during the cold period. These results are similar to those published by Sinha et al. (2010b) who estimated a 9% increase, and a higher rate than the 4.5% reported by Corsonello et al. (2003). Furthermore, our study contributes to better understand the seasonal blood pressure variation at an individual level. In our results, the difference in SBP between seasonal periods was several times higher in patients classified as cold-induced hypertensive than in other individuals (Table 1). The definition of the cold-induced hypertensive group may force an increment of blood pressure in cold-months. However, we observed the unexpectedly high seasonal variation of blood pressure in cold-induced hypertensives might indicate that some kind of individual susceptibility towards hypertension in colder periods.

In cold periods the increment of hypertension prevalence may trigger the occurrence of vascular diseases (Matsumoto et al., 2010; Barnett et al., 2005). Our findings highlighted that although cold-induced hypertensive individuals may show nonhypertensive blood pressure values during half of the year, they were at higher risk of suffering cardio or cerebrovascular diseases than the nonhypertensive subjects. These findings may support the hypothesis that screening for hypertension should include the diagnosis or treatment of individuals prone to cold-induced hypertension.

BOREAS identified age, diabetes, BMI, and prehypertension blood pressure values as the major contributing factors to cold-induced hypertension onset. Most of these have also been reported as contributing factors to seasonal variation of blood pressure in other studies. Age has been associated with increased sensitivity of blood pressure to environmental factors (Alpérovitch et al., 2009; Corsonello et al., 2003; Woodhouse et al., 1993; Goodwin et al., 2001; Lipsitz et al., 2006). It has been hypothesized that disorders of baroreflex control and enhanced vasoactivity could contribute to the aging-associated increase in blood pressure variation and cardiovascular morbidity (Lipsitz et al., 2006; Kenney and Armstrong, 1996).

Seasonal variation of blood pressure might also be driven by high BMI. Our findings agree with Halonen et al. (2011) who reported stronger seasonal variation among obese subjects than leaner individuals. In contrast, other authors found an inverse
association between seasonal variations in blood pressure and BMI (Kristal-Boneh et al., 1996; Miquel et al., 2001; Zheng et al., 2010), supporting the hypothesis that more body fat provides better insulation and therefore leads to smaller changes in blood pressure with exposure to low temperatures (Halonen et al., 2011).

Our study has several limitations. First, data were not obtained for research purposes, although the data used to build the dataset used in this study had been examined and found to be of high quality (Ramos et al., 2012). In this line, our study was based on casual blood pressure measures conducted at the office rather than more accurate methods like ambulatory blood pressure monitoring, which has greater sensibility in detecting seasonal differences in blood pressure (Parikh et al., 2008). Second, we were not able to demonstrate a casual link between blood pressure and outdoor temperature. However, assuming that climate in general may contribute to blood pressure seasonal variability, our results may not apply to other parts of the world, especially if the climate is different from our geographical region (Hopstock et al., 2013).

Fig. 4. Adjusted odds ratio and 95% confidence interval of occurrence of cold-induced hypertensive pattern, for the BOREAS model obtained by the derivation (black square) and validation (white square) models for (a) men and (b) women.
Third, we used only one BMI measurement per individual and did not account for the likely contribution of any change in body weight to hypertension status (Parikh et al., 2008). Fourth, we controlled for the administration of antihypertensive drugs but did not take into consideration the effects of other drugs, possibly leading to confounding results. Moreover, we did not consider lifestyle factors associated with incident hypertension such as diet (Alpérovitch et al., 2009; Corsonello et al., 2003), alcohol consumption (Corsonello et al., 2003), or physical activity (Woodhouse et al., 1993; Jansen et al., 2001; Mundal et al., 1997), even when changes were prescribed to delay hypertension occurrence. Fifth, we did not consider possible confounding variables which could affect the seasonality of blood pressure, such as housing conditions (Saeki et al., 2013), other environmental factors (Brook et al., 2011), changes of diet (León-Muñoz et al., 2012; Núñez-Córdoba et al., 2009; Shahar et al., 1999), time spent outdoors (Saeki et al., 2014), or physical activity (Goodwin et al., 2001). Besides, the study population was based on individuals having several blood pressure measurements, which is more representative of a somewhat screened population rather than of an entire general population, what could have consequences when estimating hypertension prevalence. Finally, considering a cut-off of 9.3% in men and 6.0% in women, sensitivity and specificity obtained with the BOREAS score are modest, although sensitivity is even higher than in some cardiovascular risk functions studies (Comín et al., 2007). Nevertheless, these moderate sensitivity and specificity in BOREAS entail harmless clinical implications: those cold-induced hypertensives that BOREAS failed to identify (false negatives) would follow the current hypertension screening; while those normotensive that BOREAS identified as possible cold-induced hypertensive (false positives) would receive an additional blood pressure measurement in the winter. Thus, BOREAS complements the current hypertension screening, by helping practitioners to better organize blood pressure readings through the year.

Key strengths of our study include the large sample size, quality of the database, representativeness of the population sample, and a longitudinal assessment of the disease. Furthermore, we used multiple blood pressure measurements taken over the course of at least 18 months for each individual, which enables us to account for the wide, spontaneous variation typical of blood pressure (Mancia et al., 2013). Using clinical data routinely collected in general practice improves the feasibility of applying BOREAS in initial hypertension screening, using classical risk factors already entered in computerized clinical calculators. Finally, we defined 6-month and warm periods to facilitate the implementation of our findings in clinical practice. Therefore, physicians could carry out these measurements at any point from October to March, rather than being forced to concentrate blood pressure measurements within a few winter months for those individuals who are more likely to be susceptible to temporal hypertension.

5. Conclusions

Seasonal changes in blood pressure may play a role in the progression of hypertension, and individual susceptibility to seasonal blood pressure variability should be taken into account in the diagnosis of hypertension. Therefore, physicians should be aware that blood pressure is typically higher during winter and play closer attention to hypertension control during colder periods. In the clinical practice it could be difficult to target all individuals with hypertension in winter due to huge medical and economic costs. An individualized approach to risk stratification of hypertension occurrence among nonhypertensive individuals could be a more desirable strategy. We recommend screening for hypertension during the cold months, at least in those individuals identified by the BOREAS score to be at greatest risk of progression of hypertension.

Founding sources

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Conflict of interests

None.

Ethical approval

It is not needed as data was obtained from a large database.

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References


Woodhouse, P.R., Khaw, K.T., Plummer, M., 1993. Seasonal variation of blood pressure and its relationship to ambient temperature in an elderly population. J. Hypertens. 11, 1267–1274.