The Association of Anorexia Nervosa and Climate Revisited: A Bibliometric Perspective

Emilio Gutierrez1,2,3*
Facultad de Psicología, Universidad de Santiago de Compostela
Unidad Venres Clinicos, Facultad de Psicología, Universidad de Santiago de Compostela, Campus Vida, 15768, Santiago de Compostela
Departamento de Psicología Clínica y Psicobiología, Facultad de Psicología, Universidad de Santiago de Compostela, Campus Vida, 15768, Santiago de Compostela

Andrea Puime1
Facultad de Psicología, Universidad de Santiago de Compostela

Olaia Carrera2
Unidad Venres Clinicos, Facultad de Psicología, Universidad de Santiago de Compostela, Campus Vida, 15768, Santiago de Compostela

Angela Fraga3
Departamento de Psicología Clínica y Psicobiología, Facultad de Psicología, Universidad de Santiago de Compostela, Campus Vida, 15768, Santiago de Compostela

Reyes Vazquez2
Unidad Venres Clinicos, Facultad de Psicología, Universidad de Santiago de Compostela, Campus Vida, 15768, Santiago de Compostela

Esther Claver4
Departamento de Psicología y Sociología, Facultad de Ciencias Humanas y de la Educación, Campus Huesca, Universidad de Zaragoza

ABSTRACT: Objective: A decade ago a first bibliometric study considered the worldwide distribution of scientific publications of anorexia nervosa to be an indirect indicator of its prevalence at different latitudes. This bibliometric approach was grounded on the hypothesis that the prevalence for a particular disorder in a geographical area could be associated to an increase in the allocation of funds and health care resources supporting clinical and research programs, which in turn would be associated with an increase in the production of related scientific literature. Method: References to anorexia nervosa, anxiety disorders and seasonal affective disorders were retrieved from PubMed and PsycINFO databases and collected for the period 2000-2014. The distributions of the bibliographic references were mapped according to the institutional affiliation of their first author. Furthermore, according to their geographical coordinates each reference was catalogued in accordance with the Köppen classification system. Results: A remarkable similarity in the distribution of references to anorexia nervosa for the two periods was observed as well as a differential association of anorexia nervosa to mid-latitudes climates in comparison to references to anxiety disorders and seasonal affective disorders. Discussion: The distribution of references for anorexia nervosa have remained considerably stable over the last 25 years associated to higher but not extreme latitudes and to climates with regular seasons with no severe temperature variations across seasons. The replication of the data for these two time periods implies that ambient temperature should be included in the list of environmental risk factors for anorexia nervosa. Keywords: Anorexia nervosa; Culture; Bibliometrics; Epidemiology; Latitude; Ambient temperature; Climate

*Correspondence regarding this article should be directed to: emilio.gutierrez@usc.es
A decade ago the first study on the relationship between ambient temperature and anorexia nervosa (AN) was approached in a pioneering bibliometric survey where the worldwide distribution of scientific publications was deemed to be an indirect indicator of the incidence and prevalence of the disorder at different latitudes (Vazquez et al., 2006). It should be noted that any discussion on global trends in AN is hampered by limited epidemiological data available on a worldwide scale. This was the main reason motivating a bibliometric approach to the distribution of references to AN (Vazquez et al., 2006). Interestingly, our finding that references to AN abridge into the 40-55° latitude range in the Northern Hemisphere loosely parallel the vast majority of epidemiological studies undertaken on populations living in this latitude range in the Northern Hemisphere (Hoek & Van Hoeken, 2003). Currently, the circumstances have not changed with respect to the lack of epidemiological studies worldwide (Smink et al., 2012). In spite of a few preliminary studies, a leading author on this topic has stated in a recent review that: “epidemiological data in Asia and Pacific Island countries remain sparse; the same holds true for Latin America and epidemiological data in Africa are even more scarce” (Hoek, 2016).

That bibliometric approach was grounded on the hypothesis that the prevalence for a particular disorder in a geographical area could be associated to an increase in the allocation of funds and health care resources supporting clinical and research programs, which in turn would be associated with an increase in the production of related scientific literature. Latitude was selected as a marker of ambient temperature as latitude is one of the key factors determining regional climate. After testing the hypothesis on two medical disorders differentially associated with latitude, psoriasis and cataracts, Vazquez et al., reported that the distribution of references to AN diverged from references to the two other mental disorders. Thus, with respect to references to schizophrenia, seasonal affective disorders (SAD), and anxiety disorders (ANX), the distribution of references to AN were significantly and differently associated to latitudes in the Northern Hemisphere, but references to AN were closely related to references of psoriasis (Gutierrez et al., 2013). Psoriasis is a chronic skin condition associated to reduced sunlight at higher latitudes, and there is a wealth of epidemiological data confirming the association of psoriasis prevalence with higher latitudes in the Northern Hemisphere (Gutierrez et al., 2017). Thus, the association detected in the study of Vazquez et al. (2006) between higher latitudes in the Northern Hemisphere and references to psoriasis, further reinforced the usefulness of a bibliometric approach as an adequate substitute in disorders characterized by absence of epidemiological studies, as it happens in AN.

The aims of this study were twofold: first of all, to replicate the results of Vazquez et al., covering the period 1990-1999, for the period 2000-2014. However, a main shortcoming of the Vazquez et al. study was the reliance on latitude as indicator of ambient temperature. Although latitude is a relevant factor determining a region’s climate, altitude, the proximity to the coastline, and the influence of oceanic streams are also key climatic factors within a given latitude. The second aim will entail an advance over previous study which relied on latitude as a marker of ambient temperature. Thus, a second aim in the present study will be to map references with respect to specific climate types where seasonal changes in ambient temperature was a distinguishing factor.

The association of references to AN with latitude and climate were contrasted with two other mental disorders, seasonal affective disorders (SAD), and anxiety (ANX) disorders also studied in Vazquez et al. With respect to SAD, a type of depression usually accompanied by fatigue, hypersonomolence, hyperphagia, carbohydrate craving, weight gain, and loss of libido (Miller, 2005), there is a wealth of evidence for a “latitude theory” due to the enhanced incidence of SAD closely related to seasonal differences at higher latitudes. Anxiety disorders are the most prevalent mental disorders associated to huge health care costs. ANX encompasses a range of disorders characterized by feelings of anxiety and fear, such as generalized anxiety disorder, panic disorder with or without agoraphobia, social anxiety disorder, separation anxiety disorders and specific phobias. In contrast to SAD, there are adequate cross-national epidemiological data on ANX worldwide with no indication it lacks an association with specific latitudes (Bandelow & Michaelis, 2015; Michael et al., 2007).

METHOD

References from PubMed and PsycINFO, were retrieved using the terms “anorexia nervosa”, “anxiety disorders” and “seasonal affective disorder”. Search dates were restricted to the period 01/01/2000 to 31/12/2014 and language was restricted to English. As in Vazquez et al., the retrieved references met three requirements; a) to include only empirical studies to avoid the selection of references of theoretical papers, b) involving human subjects to exclude animal research, and c) only journal articles were selected to avoid books, book chapters, dissertations and conference papers. Only references lacking information about authorship and institutional affiliation were excluded. To avoid overlapping publications being tallied in the different categories covered, searches with two of the above mentioned index terms with the operator AND were carried out (i.e., “anorexia nervosa” AND “anxiety disorders”) and duplication were resolved according to abstract content. A Drupal web based application was developed to manage and organize the search output for the different literature searches. Using the title field from the references, the application checked search outputs for each category to ensure that no duplicate references were included.

The application provided a detachable with an autocomplete function to enter the name of the city matching the first author’s institutional affiliation of each reference. The autocomplete menu used to select the city was linked to allcountries.zip (http://www.geonames.org), a free of charge geographical database from GeoNames which covers all countries and contains over eleven million georeferenced place names (latitude, longitude, country, hemisphere and West-East axis). The geographical coordinates were used to automatically generate a code based on the Koppen-Geiger classification system according to Koppen-Geiger-ASCII. zip file (http://koeppen-geiger.vu-wien.ac.at/present.htm) which includes the Köppen codes on a 0.5 degree latitude and longitude grid (Kottek et al., 2006).

Wladimir Koppen’s classification of climate that was originally formulated over 100 years ago is still in widespread use. Each
Koppen-Geiger code consists of three letters, the first identifies five vegetation groups; the equatorial zone (A), the arid zone (B), the warm temperate zone (C), the snow zone (D), and the polar zone (E). A second letter in the classification stands for the precipitation level (e.g., Cs for warm temperate climate with dry summer), and a third letter reflecting the air temperature (e.g., Csc for warm temperate climate with dry and cool summer). At a worldwide level, the most common climate type by land area is BW (14.2%, Hot desert) followed by Aw (11.5%, Tropical savannah), (Peel et al., 2007).

Moreover, similar to the period 1990-1999, the vast majority of the references for the three disorders for the period 2000-2014 continued to be located in the Northern Hemisphere, although the percentage for ANX had significantly decreased in the Northern Hemisphere but increased in the Southern Hemisphere; χ²(1)=30.66, p<0.0001. The distribution of references from both tropical zones i.e., Northern Hemisphere (0°-23° N), and the Southern Hemisphere (0°-23° S) were merged together into a common category i.e., the Tropics, which encompassed the references from Tropic of Cancer to the Tropic of Capricorn. The remaining references to Northern Hemisphere above parallel 24° (Northern Hemisphere ≥ 24°N), and Southern Hemisphere below parallel 23° (Southern Hemisphere ≤ 24°S) are also shown in Table 1. In short, in the two time periods, only the distribution of ANX references for both Hemispheres and the Tropics had changed from 1990-1999, χ²(2)=40.2099, p<0.00001.

The distribution of references for the three mental disorders in the Northern Hemisphere from the Equator to latitude 64° N are shown in Table 2. Percentage of references to ANX were significantly greater than AN references in all latitude bands (Z scores of 7.319, 6.007 and 11.001, respectively for differences in the ranges 0°-24°, 25°-44°, and 55°-64°; p<0.002 in all cases), except for the latitude range 45° to 54°, where AN references were significantly higher than references for ANX (Z=3.84, p<0.002) and SAD (Z=16.793, p<0.0002). In turn, percentage of references to SAD were preponderant in higher latitude bands of 55° to 64° (Z scores of 9.171 and 11.001 respectively for comparisons with ANX and AN, p<0.0002 in both cases).

Table 1. References for three disorders at two different time intervals

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AN</td>
<td>SAD</td>
</tr>
<tr>
<td>World</td>
<td>1316</td>
<td>367</td>
</tr>
<tr>
<td>North H.</td>
<td>1227 (93.2%)</td>
<td>357 (97.3%)</td>
</tr>
<tr>
<td>South H.</td>
<td>89 (6.8%)</td>
<td>10 (2.7%)</td>
</tr>
<tr>
<td>Tropics (24°S – 24°N)</td>
<td>20 (1.5%)</td>
<td>6 (1.6%)</td>
</tr>
<tr>
<td>North H. (≥ 24°N)</td>
<td>1210 (91.9%)</td>
<td>354 (96.5%)</td>
</tr>
<tr>
<td>South H (≥ 24°S)</td>
<td>86 (6.5%)</td>
<td>7 (1.9%)</td>
</tr>
<tr>
<td>North America* Latitude: 25°-53°N Longitude: 123°-70°W</td>
<td>1799 (34.2%)</td>
<td>331 (49.7%)</td>
</tr>
<tr>
<td>Europe* Latitude: 35°-69°N Longitude: 21°W-37°E</td>
<td>3049 (57.9%)</td>
<td>2794 (42%)</td>
</tr>
</tbody>
</table>

Abbreviations: H = Hemisphere, AN = Anorexia nervosa, SAD = Seasonal affective disorders, ANX = Anxiety disorders. *Not included 1 reference from Anchorage, (longitude 150°W). *The 13 references of two Russian locations, Syktyvkar and Novosibirsk, were not included (longitudes 50E, and 82E, respectively). *Percentages of references from Europe and North America with respect to references for the North H ≥ 24°N.
As illustrated in Figure 1, references to SAD associated to higher latitudes showed the same displacement to the right as the distribution of AN references in comparison to the previous study (Vazquez et al., 2006). In spite of the fact that AN references had tripled during the period 2000-2014 with respect to the period 1990-1999, the distribution of AN references in the Northern Hemisphere remained almost the same for the two periods, as shown in the bottom panel of Figure 1.

For the period 1990-1999, 67% of the world’s references to AN, according to the first author’s institutional affiliation, were located between parallel 40°-55° in the Northern Hemisphere, that is, 72% of the Northern Hemisphere references to AN were concentrated in this 15° latitude bandwidth (Vazquez et al., 2006). Interestingly, for the period 2000-2014, 67.7% of world references to AN were found in the same latitude bandwidth (40°-55° N), indicating that 71% of the references to AN in the HN were concentrated in a 15° latitude bandwidth. Strikingly, these results were almost identical to those reported by Vazquez et al. Furthermore, the concentration of AN references in this 15° latitude bandwidth was significantly higher than the percentage of world references for ANX (56.7%; Z = 14.772, p < 0.0002) and marginally with SAD (62.8%; Z = 1.988, p = 0.0495). However, when the interval of the 40°-55° latitude band were compared solely in terms of the total for Northern Hemisphere references, the percentage of AN references was only significantly higher than for ANX (71% vs. 62.6%, Z = 11.223, p < 0.0002) and there were no differences between ANX and SAD.

References in the North Hemisphere included references from locations spread across the entire Northern Hemisphere, ranging from North America, a portion of upper South America, Europe, and the upper half of Africa and Asia. However, as shown in the last two lines of Table 1, most of the references in the Northern Hemisphere were derived from latitude and longitude coordinates corresponding to USA, Canada and Europe (EUR-US/CAN). Taken together, references located in EUR-US/CAN represented more than 80% of the world references for the three disorders, or almost nine out of ten references for the whole Northern Hemisphere, with no significant differences between the cumulative percentages for the three disorders. However, an asymmetric distribution in references for the three disorders was observed as references to AN were more frequent in Europe than in US and Canada, with a converse relationship for ANX, whereas SAD references were comparable.

Climate

As latitudes for Europe, US and Canada did not fully overlap and there was a skewed distribution of AN and ANX references for both continents, the distribution of references was mapped according to different climate zones. The percentage of references for each of the six climate groups for the three disorders are shown in Figure 2. Data are presented for the worldwide references, (top panels in Figure 2), references from the Northern Hemisphere (middle panel), and references located in EUR-US/CAN zone (bottom panel).

The six climate types provide an exhaustive account the references for each of the three geographical zones, that is, Worldwide, Northern Hemisphere and EUR-US/CAN.

As for the references to Tropical climate, ANX significantly exceeded the number of AN references in the three geographical zones (Z scores of 8.257, 3.576 and 3.097, respectively for world, Northern Hemisphere and EUR-US/CAN; p < 0.0002 in all cases). With respect to Humid Subtropical climate, the number of ANX references was significantly higher than references for both AN and SAD (ANX vs. AN, Z scores of 8.095, 8.739 and 13.290; ANX

<table>
<thead>
<tr>
<th>Climate Zone</th>
<th>AN</th>
<th>SAD</th>
<th>ANX</th>
<th>Significant contrast¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>5259</td>
<td>673</td>
<td>14864</td>
<td></td>
</tr>
<tr>
<td>EU-US/CAN</td>
<td>393</td>
<td>1904</td>
<td>6840</td>
<td>ANX=ANX &gt;SAD=ANX</td>
</tr>
<tr>
<td>North America</td>
<td>255</td>
<td>105</td>
<td>961</td>
<td>ANX=ANX &gt;SAD=ANX</td>
</tr>
<tr>
<td>South America</td>
<td>252</td>
<td>101</td>
<td>939</td>
<td>ANX=ANX &gt;SAD=ANX</td>
</tr>
<tr>
<td>Europe</td>
<td>243</td>
<td>97</td>
<td>854</td>
<td>ANX=ANX &gt;SAD=ANX</td>
</tr>
<tr>
<td>Asia</td>
<td>207</td>
<td>61</td>
<td>693</td>
<td>ANX=ANX &gt;SAD=ANX</td>
</tr>
</tbody>
</table>

* Totals differ from those shown in the row ‘North H’ in Table 1 since no references counted above 64°N. *Z values yielding significance levels of p < 0.001 except in the comparison SAD vs. AN, (latitudes 45°-54°), p = .008

As for the references to SAD vs. AN, (latitudes 45°-54°), p = .008

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The three geographically selected zones (Mediterranean: ANX and SAD in the temperate climates in the Semi-arid Hemisphere and EUR-US/CAN zone, p <0.0002 in all cases) vs. SAD, 5.104, 4.724 and 4.236; respectively for world, Northern Hemisphere and EUR-US/CAN zone, p<0.005 in all cases). Furthermore, references to ANX were also significantly greater than SAD references in the Semi-arid (Z=3.302, p<0.001; Z=8.041, p=0.002, and Z =6.803, p<0.0002, respectively for world, Northern Hemisphere and EUR-US/CAN zone) but only significantly exceeded those of SAD for EUR-US/CAN (Z=2.711, p=0.007). Moreover, references to ANX were also significantly greater than SAD references at Worldwide and Northern Hemisphere levels in case of Mediterranean climate (Z=2.612, p=0.009, and Z=3.1232, p=0.002 respectively). Finally, SAD references were significantly more frequent than references to AN and ANX in Continental Climate regions in the three geographical zones (SAD vs. AN, Z scores of 9.340, 8.983 and 10.212; SAD vs. ANX, Z scores of 8.937, 8.067 and 7.575, respectively for World, Northern Hemisphere and EUR-US/CAN zone; p<0.0002 in all cases).

**DISCUSSION**

The results of this study exhibit a remarkable coherence in a double sense. First, with regard to the distribution of AN references, as shown in Figure 1, a striking correspondence was observed between AN references for the period 2000-2014 and data published for the period 1990-1999 (Vazquez et al., 2006). Moreover, as described in the first report, there was a greater preponderance of AN references relative to ANX and SAD at specific latitudes in the Northern Hemisphere (40°-55°N), corroborating the hypothesis advanced in the first report, which would imply an underlying association between AT and the incidence of the disorder.

Second, the analysis of references from a climate perspective confirmed the association of references to latitude. References to AN were significantly more numerous than references to ANX or SAD in temperate climates, where more than half the world’s population resides (Cohen & Small, 1998). Temperate zones are typical of mid-latitudes, especially in the Northern Hemisphere owing to greater landmass. According to latitude, the temperate zone is further sub-classified into climate types, namely, Humid Subtropical, Mediterranean, and Oceanic climates. Of these three temperate climates, Humid Subtropical climate is associated with lower latitudes. Thus, Humid Subtropical climate predominates inland and on the east coast of continents, between 20° and 30° latitude (up to 48° in Europe), whereas Mediterranean climate prevails on the west coast of continents, between latitudes 30° and 40° to 45° in Mediterranean Europe, central coast and inland areas of California, and parts of southern Australia. Lastly, Oceanic climate (also known as “marine”, “west coast” and “marine”) occurs on the west coast of continents between 45° and 55° latitudes, and is the climate of Europe’s Atlantic coast from southern Norway to northern Portugal, and the northwest coast of the United States and Canada. On the other hand, most of the references located in Semi-arid climate tended to be located in temperate zones or elevated regions in (sub)-subtropical zones. According to references retrieved this climate is typically found in continental interiors of North America.

More than 50% of AN references were located in two of these temperate climates, Oceanic and Mediterranean (52%, 53%, and 56%, for World, Northern Hemisphere, and EUR-US/CAN, respectively), which were significantly higher (p<0.0002) with respect to references to the other two disorders (42%, 41%, and 43% for SAD, and 43%, 44%, and 45% for ANX). Moreover, AN references were significantly higher than ANX and SAD references in Semi-arid climate. In contrast, ANX references were significantly higher for the Humid Subtropical climates as a third of ANX references were located in this climate zone whereas this happened in fewer than a quarter of references to AN and SAD. Finally, ANX references were significantly more numerous for the Tropical climate that extends northward and southward from the equator to about 15° to 25° latitude.

Undoubtedly, the main limitation of this study resides in the assumptions that underlie the strategy employed to substantiate a putative link between AN and AT, i.e. bibliometrics. The first assumption is that the publication rate for a disorder in a geographical region is associated to the occurrence of the disorder in that region because of the presumed greater research facilities and health care services devoted to that disorder.

This hypothesis has been already tested for Psoriasis
and Cataracts, two medical diseases with an abundance of epidemiological studies that have established the global prevalence of both disorders. For these diseases, both the world and Northern Hemisphere distribution of references are differentially associated with high latitudes (Psoriasis) or low latitudes (cataracts), in accordance with existing epidemiological data (Vazquez et al., 2006). In short, it is reasonable to assume there is a match between care facilities and human research, between research and funding requirements inherent to a greater frequency of a disorder in a specific geographical area. To assume the opposite i.e., that resources and needs repel each other, or the independence of both factors (that the resources and needs associated with a higher rate of a disorder are not linked) defy logic.

A second assumption is that the institutional affiliation of the first author is an adequate measure of the location of the study. However, the increasing mobility and frequent collaboration between researchers from different countries and continents could be a confounding factor that would seriously jeopardize the reference to the first author’s institutional affiliation as an appropriate index of a disorder’s relevance in the area surrounding the institutional affiliation. However, as these aspects—co-authorship and mobility—would run counter to the hypothesis that the first author’s affiliation retains any geographical distribution underlying a disorder, they would make the test more robust, (increasing the possibility of a Type II error) as both would introduce noise to the hypothesized signal; i.e., the incidence of a disorder linked to latitude is reflected in the distribution of references.

**CONCLUSION**

The distribution of AN references have remained remarkably stable over the last 25 years, and this trend was associated to high but not extreme latitudes. The analysis for the period 2000-2014 corroborated the association detected in the previous report (Vazquez et al., 2006) though the underlying causes behind this association are yet to be elucidated. This raises an intriguing question as to why world ANX references tripled AN references that were only significantly higher in climates associated to lower latitudes (Tropical and Humid subtropical). In comparison, AN references predominated in mid-latitude climates (Oceanic and Mediterranean), and SAD references were exceedingly more frequent in Continental climate. These climate types are characterized according to the presence and difference among seasons for the different climates. Hence, Tropical climates have no winter, with average monthly temperatures throughout the year above 18ºC. In comparison, temperate climates (Humid subtropical, Mediterranean and Oceanic) located between 30º-60º north or south of the equator have the greatest weather variability with true seasons (long hot summers & short mild winters)

In contrast to the temperate climate typical of mid-latitudes, SAD references prevailed in the Continental climate, a harsh climate with extreme temperature fluctuations between hot summers and extremely cold winters. These conditions are present in continents or regions isolated by mountain ranges that buffer oceanic influences. Continental climates tend to be found in the upper band of the mid-latitude range (between latitudes 37ºN and 60ºN) bordering the polar latitude band, within central and northeastern zones of North America, Europe, and Asia.

The association of AN references to specific latitudes and climates as described in this study does not provide strong evidence that ambient temperature was a risk factor in AN. However, there is growing evidence pointing to the fact that ambient temperature makes a difference in core constitutive features of AN, such as menses resumption, weight and activity fluctuations across seasons, and aspects of AN treatment. Nevertheless, this raises the follow up question as to what ambient temperature mechanism affect AN. As we have experimentally shown in the animal lab, at variance with the protective function of a warmer environment, restricted feeding in a cold environment could endanger thermoregulatory homeostasis via loss of body insulation caused by weight loss, which in turn would trigger an increase in physical activity to produce heat as a remedy for hypothermia (Gutierrez et al., 2002).

It is worth noting that the link between AT, reduced food intake, weight loss and activity seems to transcend the limits of animal experimentation, and is also relevant to human patients affected by AN. In AN patients reduced fat mass not only curtailed body energy reserves and body temperature regulation but also posed a threat to the body’s insulation (Crisp, 2002). Thus, a significant relationship between ambient temperature and physical activity in adolescent AN patients has been described in a study carried out in the Netherlands (Carrera et al., 2012). Interestingly, this study was the first in the literature monitoring both variables in a sample of AN patients. In a sample of untreated adolescent AN patients physical activity levels tended to rise during the cold season (November–April, mean ambient temperature 4.5ºC). Furthermore, the BMIs of patients on referral during the cold season were significantly lower than for patients on referral during the warm season (May–October, mean ambient temperature 16ºC). Second, differences in body weight at the time of hospital admission were closely associated with ambient temperature in a retrospective study carried out in Spain with adolescent AN patients (Fraga et al., 2015). Moreover, this study evidenced that the recurrently higher BMI reported in the binge-purging AN subtype, with respect to AN subtype, was mainly due to differences between AN subtypes during the colder months of the year (November to April). Furthermore, length of treatment was significantly longer for AN patients during the colder months of the year (Fraga et al., 2015), a result that has recently been reproduced in a German sample (Born et al., 2015). Finally, further evidence of the benefits of warm ambient temperature has been reported in a study carried out in Italy (Favaro & Santonastaso, 2009) where menses resumption in AN patients were twice as high during spring and summer as those occurring during autumn or winter, despite the fact that during the warm season AN patients weighed 2 kg less than in the colder months. This influence of ambient temperature on key parameters of AN has been largely ignored for decades, the same as the unreported active sauna use by AN patients (Gutierrez et al., 2002; Vilhãoiini et al., 2004). Undoubtedly, we will see in near future the promising role this new evidence is going to play in the development of new routes for treatment of AN (Gutierrez & Carrera, 2013; Gutierrez & Carrera, 2014; Zandian et al., 2017; Gutierrez & Carrera, 2016).

Meanwhile, it is worth noting that the locations of these studies, Utrecht, (55ºN) Madrid, (40ºN), Munich (48ºN), and Padua (42º) were all within the latitude band 40º-55º where the greatest frequency of AN references was observed, which was perhaps more than mere coincidence.
CONFLICT OF INTEREST STATEMENT
The authors declare that they have no conflict of interest.

REFERENCES


