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Abstract: N/A

Athens, November 17, 2008

To: Editor-in-Chief, *European Journal of Clinical Microbiology and Infectious Diseases*

Re: Submission of a revision

Dear Editor,

We are pleased to submit a revised version of our original article entitled “Effect of meteorological variables on the incidence of lower urinary tract infections” for your consideration for publication in the *European Journal of Clinical Microbiology and Infectious Diseases*.

We revised our manuscript according to your suggestions. Specifically, we formatted the article to fit to the “Brief Report” type of article (deleted the abstract, decreased the length of the text, deleted the headings within the text, decreased the number of references to 10, and unified Figures 1 and 2 to one Figure).

The manuscript has not been published or considered for publication elsewhere. There are not any financial or other relationships that might lead to a conflict of interest. The manuscript has been read and approved by all authors.

Sincerely,

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4 **Effect of meteorological variables on the incidence of lower urinary**

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41 **Short title:** Weather and urinary tract infections

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4 The influence of environmental factors on human health has long been an intriguing
5 issue. In fact, scientific data support the notion that certain diseases are related to
6 environmental conditions. A seasonal variation has been observed for diverse clinical
7 entities such as myocardial infarction and cervical cancer, and particularly so for
8 several infectious diseases, typically for those with a respiratory mode of transmission
9 (1). The seasonal variation in the incidence of infectious diseases could generally be
10 attributed to factors like the epidemiology of the culprit pathogens, changes in
11 environmental and meteorological parameters, alterations in human behavior, and
12 even seasonal changes in host physiology.
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21 Urinary tract infections (UTIs) represent a major category of community-acquired
22 infections. Most aspects of the epidemiology of these infections have been clarified,
23 including the fact that they are encountered more frequently in women, due to
24 anatomical reasons, and adolescents, due to the increased sexual activity in this age
25 group (2). Still, whether environmental parameters are associated with the occurrence
26 of these infections has not been adequately studied.
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33 In this context, we aimed to assess the effect of meteorological variables, such as
34 environmental temperature and relative humidity, on the incidence of lower urinary
35 tract infections. Specifically, we performed a retrospective study that analyzes the
36 association between meteorological variables and the relative frequency of lower
37 UTIs in a primary care setting. Both meteorological and clinical data were recorded in
38 a systematic prospective manner.
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45 Analyzed meteorological data consisted of average weekly temperature (measured in
46 degrees Celsius) and average weekly humidity (expressed as percentage), regarding
47 the metropolitan area of Athens, Attica, Greece, in the time period between 1st
48 November 2000 to 18th January 2005 (a total of 1540 days or 220 weeks). These data
49 were recorded at the meteorological station of the National Technical University of
50 Athens, which is at the municipality of Zografos. The university grants public access
51 to these data (<http://www.meteo.ntua.gr/e/histdata/>).
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58 Analyzed clinical data referred to the types of diagnoses recorded by specialized
59 physicians after house call visits. Patients' demographic characteristics, such as age
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4 and sex, were also assessed. The study population included all patients examined after
5 house calls in the region of Attica, Greece, during the time period between 1st
6 November 2000 and 18th January 2005. All of the above mentioned clinical data were
7 provided by “SOS Doctors,” which is a private health-care organization that offers
8 urgent medical services. The study was approved by the Ethics Committee of “SOS
9 Doctors,” Greece.
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16 The detailed process from the triage of house calls to the subsequent physician’s visit
17 at the patient’s residence, for the provision of medical services, has been previously
18 reported (3). Findings regarding the clinical evaluation of the patients were
19 systematically recorded by the physicians performing the house call visits
20 immediately in a specially designed case report form. Variables included in these
21 forms referred to the presenting symptoms, past and preset medical history, primary
22 clinical findings, most probable diagnosis selected among specific coded diagnostic
23 categories, and suggested treatment. Diagnoses were reached on the basis of clinical
24 criteria, with the additional use of simple bedside tests, at the physicians’ discretion.
25 Lower UTIs were primarily diagnosed on the basis of characteristic clinical
26 manifestations. A urine dipstick test was used at the physician’s discretion.
27 Pyelonephritis, prostatitis, or epididymitis were recorded as separate diagnostic
28 categories.
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40 The primary focus of this study was the temporal association between average weekly
41 temperature as well as average weekly humidity with the weekly percentage of house
42 call visits resulting in a diagnosis of lower urinary tract infection, relatively to all
43 house call visits with the exclusion of those performed for respiratory tract infections.
44 Weekly values were elected over daily values to adjust for high frequency variability
45 in the measured variables. A time lag of 3 days between meteorological
46 measurements and the house call visits was arbitrarily elected to adjust for the
47 estimated time interval between the occurrence of a facilitating event and the
48 subsequent development of clinical symptoms/signs of a lower urinary tract infection
49 to the degree that an urgent house call visit by a physician would be performed. The
50 percentage of house call visits for lower urinary tract infections, rather than the
51 absolute number of these infections, was included in the analysis to adjust for the
52 temporal variation in the number of house calls for “SOS Doctors”, potentially
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1 attributed to factors such as vacation periods, environmental conditions facilitating or
2 precluding the use of other types of primary care services, or the availability of other
3 primary care services. House calls visits for upper and lower respiratory tract
4 infections were not taken into account for the calculation of the percentage of house
5 call visits performed for urinary tract infections, to correct for the recognized
6 association between the occurrence of the former type of infections and
7 meteorological parameters. In secondary analyses we evaluated the same as above
8 associations without excluding house call visits for respiratory tract infections from
9 the calculation of the percentage of house call visits performed for UTIs as well as
10 with the use of a 2-day instead of a 3-day time lag between meteorological and
11 clinical measurements.
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24 Variables included in the analysis were examined for normality of data with the one
25 sample Kolmogorov-Smirnov test. Bivariate correlations between meteorological
26 variables and the percentage of house call visits for UTIs were obtained using the
27 Spearman's rho, in the case of variables without a normal distribution, or using the
28 Pearson's correlation coefficient, in the case of variables with a normal distribution.
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34 In the time period of the study 3221 house calls visits of "SOS Doctors" performed
35 for lower UTIs were recorded. The mean age ($\pm$ standard deviation) of affected
36 patients was 62.9 ($\pm$ 21.0) years. Female patients constituted the majority (53.77%).
37 The outcomes of the analyses are reported in Table 1. In the primary analysis, the
38 weekly percentage of house call visits performed for lower urinary tract infections,
39 relatively to all house call visits excluding those performed for respiratory tract
40 infections, recorded 3 days after meteorological measurements, was found to have a
41 significant positive correlation with average weekly temperature (Spearman's rho =
42 +0.468, $p < 0.001$), and a significant negative correlation with average weekly
43 humidity (Spearman's rho = -0.394, $p < 0.001$) (Figure 1).
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53 In the secondary analysis of the correlation of the weekly percentage of house call
54 visits performed for lower urinary tract infections, relatively to all house call visits
55 including those performed for respiratory tract infections, recorded 3 days after
56 meteorological measurements, and the meteorological variables of average weekly
57 temperature and average weekly humidity, similar significant associations
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(Spearman's rho for temperature= 0.491, Spearman's rho for humidity= -0.406, p values <0.001) were found as in the primary analysis (Table 1).

In the secondary analysis of the correlation between the weekly percentage of house call performed for lower urinary tract infections, relatively to all house call visits excluding those performed for respiratory tract infections, recorded 2 days after meteorological measurements, and the meteorological variables of the average weekly temperature and the average weekly humidity, similar significant associations (Spearman's rho for temperature= 0.468, Spearman's rho for humidity= -0.386, p values <0.001) were found as in the above analyses (Table 1).

The findings of our study suggest that, in a wide metropolitan area with a temperate climate, higher environmental temperature and decreased humidity are associated with an increase in house call visits for lower urinary tract infections. Due to the large number of observations included in the analysis, statistical correlations are of high significance. It should be mentioned, however, that the strengths of the observed associations are not of a great degree. Nonetheless, strong correlations between the examined parameters would be rather unexpected, considering the multifactorial nature of the pathogenesis of lower urinary tract infections.

The association of temperature and humidity with the development of urinary tract infections could be explained considering that these meteorological parameters affect mood in humans (4), and therefore they may affect social behavior including sexual activity, which is a factor strongly linked to the development of lower urinary tract infections, particularly in women. It should be mentioned, though, that the great majority of patients included in our analysis belonged to sexually less active age groups, so the above presumptive associations could only partly account for the findings of our study. This consideration may explain why women only marginally outweighed men in our study population, whereas in a younger age group it would be expected that considerably more lower urinary tract infections would be observed in female patients.

Another potential relation between increased environmental temperature and the development of lower urinary tract infections could be attributed to the fact that

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4 higher temperature may relate to decreased diuresis, which in turn is one of the
5 principal factors associated with the development of urinary tract infections. In detail,
6 increased temperature enhances perspiration and consequently total body water loss
7 (5). Furthermore, peripheral vasodilation and pooling of blood in the skin that ensue
8 upon exposure to heat can cause a decrease in effective blood volume. All of these
9 factors may lead, especially in individuals with compromised physiologic responses,
10 to diminished urine output (5). On the other hand, the physiologic thermoregulatory
11 response to cold includes adrenergic stimulation, which induces peripheral
12 vasoconstriction, along with a rise in cardiac output and blood pressure. These factors
13 in concert with a rise in the concentration of atrial natriuretic peptide may account for
14 the increased diuresis that is frequently observed upon cold exposure. Thus, exposure
15 to cold may facilitate the clearance of potential bacterial contaminants of the urinary
16 tract.
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19 Data in the literature regarding the subject of this study are not conclusive.
20 Specifically, a study performed in Canada has shown a seasonal variation in hospital
21 admissions due to urinary tract infections, although the specific characteristics of the
22 seasonal pattern of these infections were not reported (6). Another study in South
23 Korea has shown that acute pyelonephritis occurs more commonly during the summer
24 season (7). To the contrary, there are some reports in children that indicate a temporal
25 association between urinary tract infections and those of the respiratory tract. (8,9)
26 Whether this association can be translated into a seasonal variation in the incidence of
27 urinary tract infections in children, considering that respiratory tract infections are
28 known to occur more frequently in winter, is controversial (10).
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31 A number of potential limitations should be taken into account in the interpretation of
32 the findings of our study. First, the diagnosis of lower urinary tract infections was not
33 relied in strict diagnostic criteria, such as urine culture, and therefore some cases may
34 have been misclassified. Yet, in routine clinical practice obtaining urine culture for
35 the diagnosis of acute uncomplicated cystitis is not deemed necessary. The inherent
36 limitations regarding the methodological aspects of retrospective studies should also
37 be considered. Nevertheless, the data included in the analyses of our study were
38 recorded in a prospective manner and should be regarded as of a high quality.
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4 Although no selection criterion was applied, the majority of the population included
5 in our study consisted of patients belonging in advanced age groups. This may be
6 attributed to the fact that younger individuals may be more likely to seek primary
7 medical care in other types of services than house call visits. Accordingly, the
8 findings of our study may not be representative of the whole population in the
9 community and therefore should be extrapolated with caution in younger age groups.
10 In the same manner, it may not be appropriate to extrapolate the findings of our study
11 in populations residing in areas with substantially diverse climate.
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19 Another shortcoming of our study may be that data regarding the meteorological
20 variables were retrieved from a single meteorological station. It is expected that slight
21 differences in meteorological variables should have existed in other locations within
22 the study area. However, these differences could not have appreciably influenced the
23 findings of the analysis, since variations in the meteorological parameters in different
24 locations of relatively close proximity are expected to be highly correlated.
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31 Despite the afore mentioned limitations, the findings of our study may aid in the
32 design and institution of specific public health preventive measures, such as measures
33 to draw public attention on the need to consume more fluids and to avoid exposure to
34 heat during days of warm and dry weather. This may particularly important for elderly
35 patients, such as the population of our study, who often have underlying diseases, and
36 thus, a concomitant infection could cause clinical decompensation.
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43 In conclusion, our study indicates that the occurrence of lower urinary tract infections
44 in the community may be partly associated with meteorological parameters, such as
45 temperature and humidity. Irrespective of the potential interpretation regarding the
46 underlying factors that are responsible for this association, the findings of our study
47 clearly imply that elderly individuals, who constituted the majority of the included
48 patients, may run an increased risk, albeit not of a high degree, for lower urinary tract
49 infections at times of higher environmental temperature or lower humidity. From a
50 public health standpoint the awareness of this association may facilitate potential
51 preventive strategies.
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Table 1. Correlation between weekly percentage of house call visits for urinary tract infections and average weekly meteorological variables.

Correlation examined	Spearman's rho	p-value
Main analysis		
% of house calls for urinary tract infections excluding visits for respiratory tract infections vs. temperature 3 days earlier	0.468	<0.001
% of house calls for urinary tract infections excluding visits for respiratory tract infections vs. average relative humidity 3 days earlier	-0.394	<0.001
Secondary analysis		
% of house calls for urinary tract infections including visits for respiratory tract infections vs. average temperature 3 days earlier	0.491	<0.001
% of house calls for urinary tract infections including visits for respiratory tract infections vs. average relative humidity 3 days earlier	-0.406	<0.001
% of house calls for urinary tract infections excluding visits for respiratory tract infections vs. temperature 2 days earlier	0.468	<0.001
% of house calls for urinary tract infections excluding visits for respiratory tract infections vs. average relative humidity 2 days earlier	-0.386	<0.001

Figure. Scatter plots depicting the correlation of weekly percentage of house call visits (after exclusion of respiratory tract infections) for urinary tract infections (UTIs) (Y axis of the figures) versus the average weekly temperature (degrees Celsius) observed 3 days earlier (X axis - upper figure) and the average weekly relative humidity observed 3 days earlier (X axis - lower figure).