



ORIGINAL ARTICLE

The influence of socio-environmental determinants on hypertension. A spatial analysis in Athens metropolitan area, Greece

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Keywords

Hypertension • Socio-environmental factors • Geographic information systems

Summary

Introduction. While epidemiological and pathophysiological aspects of hypertension are still being investigated, there is an increased global interest between hypertension and social health determinants and environmental factors that this study aims to examine.

Methods. The sample size used in this work included 2,445 individuals, from Athens metropolitan area, who were randomly enrolled in ATTICA study, during 2001 to 2002. Principal component analysis (PCA), Poisson regression modeling and geographical analysis, based on Geographic Information Systems (GIS) technology, were applied.

Results. Geographical analysis and thematic mapping revealed

that the West municipalities of Athens had the lowest socio-environmental status. Three components were derived from PCA: high, low and mixed socio-environmental status. Poisson regression analysis showed that high socio-environmental status, educational and economic level were negatively correlated with hypertension in some sectors of Athens ($p < 0.05$, for all).

Conclusions. Through the use of geospatial surveillance the underlying epidemiology of hypertension, and those at greater risk, can be more precisely determined. This study underlines the need to account for environmental factors when developing public health policies and programs for effective hypertension prevention or reduction.

Introduction

Hypertension is a major global health challenge and is one of the principal risk factors for cardiovascular disease [1, 2]. Approximately 40% of adults over 25 years are diagnosed hypertensive, and at least 45% and 51% of deaths from heart disease and stroke, respectively, are associated with hypertensive status [3].

Although epidemiological and pathophysiological risk factors of hypertension are still being investigated [4], there is an increased global interest in social-health determinants that increase the prevalence of various diseases possibly via behavioral modification [5, 6]. Hypertension is one such disease, associated with highly modifiable behavioral risk factors (diet, excessive alcohol, tobacco use, and inactivity) influenced mainly by income, type of employment, education and housing conditions [1, 6-8]. The impact, however, of socioeconomic status (SES) on hypertension has been reported in several epidemiological studies with conflicting results [9-13], potentially due to spatial inequalities and differential socio-environmental characteristics among study areas. For instance, Sabri et al. [13] found that hypertension tended to be more prevalent in lower income population in United Arab Emirates. In contrast, a study carried out in Lebanon found that hypertension was sig-

nificantly associated with higher income levels [12]. On the other hand, Howitt et al. [10] did not observe variation in hypertension prevalence by socioeconomic position in Barbados, supporting this finding in the disparities of the social distribution of hypertension in the Caribbean [14, 15]. However, although it has been argued that residential socio-environmental status is associated with a variety of health outcomes, including cardiovascular diseases [16], research on environmental factors in association to blood pressure is limited [17].

The use of Geographic Information Systems (GIS), a geospatial technology with significant role in health research and spatial epidemiology [18-21], can help objectively identify health indicators, including socio-environmental conditions, social integration, physical aspects of places, and resources [22]. In addition, mapping socio-environmental factors and epidemiological data allows the recognition of spatial patterns [23] and the interpretation of statistical analysis results.

Therefore, the aim of the study was to examine the influence of socio-environmental conditions on hypertension prevalence, in the area of Athens, Greece by mapping spatial variation of hypertension among geographical and social heterogeneous areas, using GIS. To date, and to our knowledge, no such geospatial studies have been performed in Greece.

Methods

SAMPLE

The ATTICA study is a population-based health and nutrition survey [24], that was carried out in Athens metropolitan area (including 78% urban and 22% rural regions) during 2001-2002; the 10-year follow-up completed in 2012 [25], and it was held by the First Cardiology Clinic of Athens University Medical School and the Department of Nutrition and Dietetics of Harokopio University. In total 3,042 individuals voluntarily participated in the study; 1,514 men (18-87 y) and 1,528 women (18-89 y). The sampling was random and stratified by age, sex, distribution of the area municipalities, according to the latest census (2001). Individual information was interview based (at home or workplaces) by trained personnel (cardiologists, general practitioners, dieticians and nurses) upon signing an informed consent form. The ATTICA study was approved by the Hippokraton Hospital Scientific Committee (protocol reference number: 0017/2002). Written informed consent was obtained from all the study subjects.

During the survey, various sociodemographic, clinical and lifestyle characteristics of the participants were recorded, including educational status (years of school attended) and residential address (suburb). Arterial blood pressure was measured, according to the latest American Heart Association (AHA) recommendations [26]. In summary, individuals were measured using a calibrated sphygmomanometer (ELKA aneroid manometric sphygmometer, Von Schlieben Co, West Germany) at the end of the physical examination. Subjects were relaxed, in a comfortable sitting position, back and arm supported, with an angle of 45° from the trunk, and all clothing removed from the area of the upper right arm (where the cuff would be placed). The presence of hypertension was based on an average of three consecutive measurements (measured by a physician or nurse) of systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure $90 \geq$ mm Hg and/or use of special medication. Level of systolic and diastolic blood pressure were determined by the first perception of sound (tapping quality), and by phase V when the repetitive sounds become fully muffled (disappear), respectively. Changes in loudness were not considered.

SOCIO-ENVIRONMENTAL DATA

Environmental and socioeconomic parameters were used to outline the status of Athens' area sectors. Socioeconomic status was classified using the following proxy variables: (i) educational level, (ii) percentage of immigrants to the total population and population density (residents per km²) based on 2011 census' data of the Statistical Authority of Greece, (iii) average annual income and average real estate prices (year 2009) that were obtained from General Secretariat for Information Systems (GSIS) of the Greek Ministry of Economy and Finance, and (iv) average years of education (year 2001-2) from ATTICA study. The population was categorized

with higher education if they had completed upper secondary education and population with degree from university or technical institute - ISCED* level 3, 4, 5 and 6, and illiterate if the population had not completed primary school (ISCED level 0). The environmental variable used was the percentage of green urban areas to the total area of each municipality, based on land-use data for the reference year 2006, from Urban Atlas of European Environment Agency (EEA).

SPATIAL DATA

Athens is characterized by social segregation [28, 29] and geographical disparities in population composition and natural and built environment. In order to assess spatial distribution of hypertensive population in Athens, the parameter of spatial heterogeneity was accounted for and sectors were defined with social cohesion and common environmental characteristics, to avoid a potential effect of these inequalities on results obtained.

Athens metropolitan area was, therefore, divided into five main sectors as recommended [29, 30], consisted of municipalities with common socioeconomic characteristics. Geographical and statistical analyses were applied to the same sectors: East sector (Es) (7 units - 374,816 population, 391 sample size), South sector (Ss) (7 units - 437,171 population, 288 sample size), West sector (Ws) (11 units - 775,014 population, 548 sample size), North sector (Ns) (10 units - 496,025 population, 326 sample size) and Central sector (Cs) (5 units - 1,055,101 population, 892 sample size) (Fig. 1).

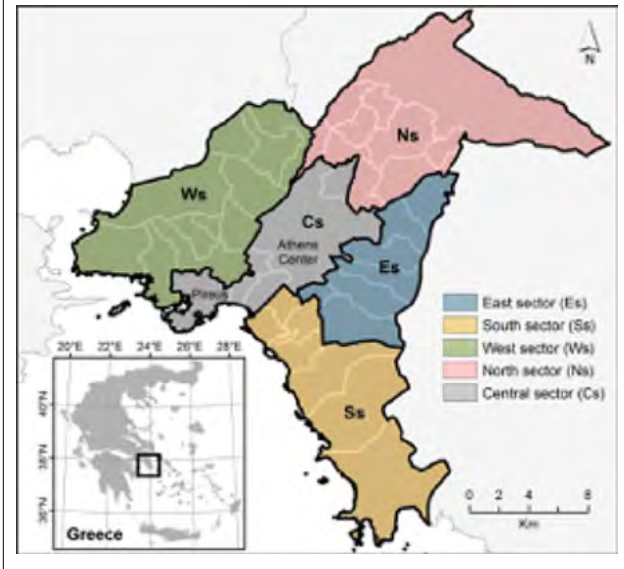
GEOGRAPHICAL ANALYSIS

GIS technology was used to manage geographic data. A spatial database was created, with GIS layers of administrative units (municipalities), socioeconomic and environmental data, and the ATTICA study observations. A series of GIS-supported procedures were implemented to geocode and aggregate all data in the corresponding municipalities. Geocoding of hypertension data was based on the address factor and the allocation of each observation was implemented. Aggregation was related to the summation of the observations (used to calculate total number of cases in each spatial unit). Hypertension prevalence was estimated by counts of hypertensive population, expressed as proportion to incidences per 1,000 observations, a typical action for spatial epidemiological analysis [31].

Furthermore, every socio-environmental variable was calculated for each administrative unit, enabling the production of a series of *choropleth* (thematic) maps that show spatial variation of socio-environmental variables and hypertension rate across the five sectors of Athens. Geodatabase, spatial analyses and mapping were performed using the ArcGIS version 10.4 (ESRI Inc., Redlands, California, USA).

* ISCED (International Standard Classification of Education) is UNESCO's classification standard for education level [27].

Fig. 1. Athens metropolitan area, sectors and municipalities (2015).



STATISTICAL ANALYSIS

Generalized linear models were used to investigate the relationship between hypertension prevalence and socio-environmental variables. To eliminate collinearity problems, three models with different socio-environmental variables were applied. Model 1 included immigrants and average years of education, Model 2 included population with higher education, average real estate prices and population density, and the last three variables of illiterate population, average annual income and green urban areas were inserted in Model 3. The three models were used for the whole study area and for each sector separately. Models were fitted using Poisson regression analysis to assess the association of hypertensive population per 1,000 observations (dependent variable) and socio-environmental variables (independent), and with patterns of socio-environmental status. To obtain socio-environmental status patterns, PCA was used. The data sets of the socio-environmental variables were subjected to multivariate data analysis using PCA in order to diminish the dimensionality of the initial information by reducing the number of variables to several groups of individuals (components) [32]. To decide the number of components to retain from the PCA, the eigenvalues that derived from the correlation matrix of the variables were examined and Kaiser criterion (eigenvalues > 1.0) was used. Socio-environmental patterns were defined in relation to the individual variable scores that correlated most with the factor. Scores ≥ 0.4 were used, since higher absolute values indicate variables contributing most to the formulation of a component. The results from the regression models are presented as b-coefficients and its standard errors. Normality was assessed using the Kolmogorov-Smirnov test. Statistical analysis were based on 5% significance level using SPSS version 23.0 (Armonk, NY: IBM Corp) software.

Results

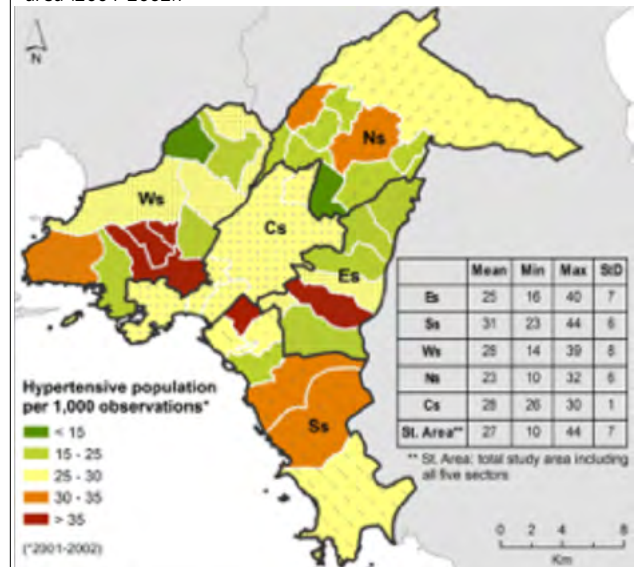
Figure 2 indicates that hypertension proportion varied among the municipalities, and within their sectors, except in Cs where uniform proportions were identified throughout the sector. The lowest proportions were found only in small municipalities, one in Ws and one in Ns, whereas the highest proportions were seen mostly in Ws, one in the Es, and a small proportion in Ss.

Figure 3 shows mean, minimum (Min), maximum (Max) and standard deviation (StD) values of the socio-environmental variables, both for the whole study area (St. Area) and for the five sectors separately, according to the values of the municipalities of each sector. Moreover, thematic maps indicated the spatial distribution of the variables' mean values, demonstrating the spatial and socioeconomic inequalities across the sectors.

Regarding the results of the socio-environmental variables mapping, Es had the lowest illiterate rate (Fig. 3b) and population density (Fig. 3g), and had high rate of higher educated population (Fig. 3c) and more years of education attendance than the mean value of the study area (Fig. 3a). The population of this sector had also high incomes (Fig. 3d), while real estate prices, as well as the immigrant rate, were almost on the same level as the mean value of the study area (Fig. 3e and 3f), whereas the % of green urban areas was lower than the study area's mean (Fig. 3h).

Ns was identified as sector with high socio-environmental status with the highest concentrations of higher-income population and real estate prices (Fig. 3d and 3e). Regarding the educational level, Ns' residents attended more years of education than the population of the rest sectors (Fig. 3a), however, a high rate of illiterate population (Fig. 3b) was also found along with an average rate of higher educated population (Fig. 3c) compared with the study area. Ns had the lowest mean immigrant

Fig. 2. Map of hypertension prevalence in Athens metropolitan area (2001-2002).



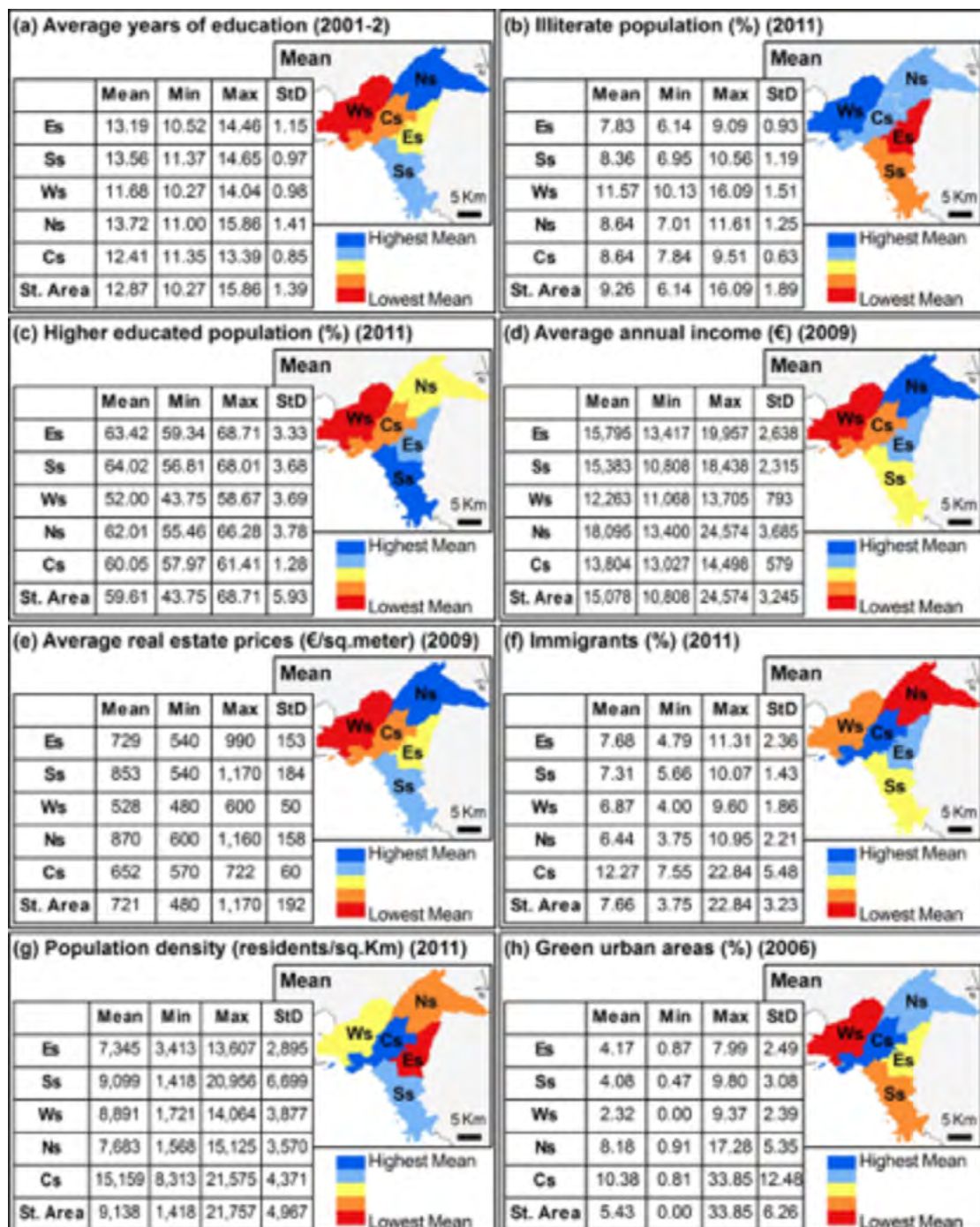
rates compared to the other sectors (Fig. 3f), it was not densely populated and was concentrated in green urban areas (Fig. 3g and 3h).

South sector (Ss) scored high rates in all variables related to educational level (Fig. 3a and 3c) with low rates of illiterate population (Fig. 3b). It had the second highest average real estate prices (Fig. 3e), whereas the annual income was slightly higher than the study area's mean value (Fig. 3d). However, Ss was the second most

densely populated sector (Fig. 3g) with very low rate of green urban areas (Fig. 3h), and with medium rates of immigrants (Fig. 3f).

Ws was identified as sector with very low socio-environmental status, as most mean values examined were much lower than the study area's mean values, especially regarding economy and education. Particularly, Ws population had (i) the lowest average years of education compared to residents of other sectors (Fig. 3a),

Fig. 3. Spatial distribution of socio-environmental factors in Athens metropolitan area.



(ii) the highest rate of illiterate population and, (iii) the lowest rate of higher educated population (Fig. 3b and 3c). Moreover, Ws had also the lowest average annual income and real estate prices (Fig. 3d and 3e). Green urban areas were also the least concentrated in this sector (Fig. 3h), although it was moderately densely populated (Fig. 3g). On the other hand, mean value of immigrants in Ws was the second lowest (after Ns) and below the mean of the study area's (Fig. 3f).

The last sector (Cs - sector 5) could be characterized as a low socio-environmental status sector, although it had slightly better rates than Ws in the educational and economic level (Fig. 3a to 3e). Furthermore, this sector was highly densely populated (Fig. 3g) with very high rate of immigrants (Fig. 3f). Concerning the physical environment, Cs had more green urban areas than all the other sectors, with mean value 10.38%, which was approximately twice the mean value of the whole study area's municipalities (Fig. 3h).

The Kolmogorov-Smirnov test for normality for average years of education, average annual income and average real estate prices reported $p = 0.038$, $p = 0.003$ and $p = 0.002$ respectively, revealing that the variables were not normally distributed. Table I shows the results of Poisson regression analysis that was performed between hypertension and the socio-environmental variables examined, in all mu-

nicipalities. Results revealed that economic level variables related (income and real estate prices) and average years of education, were negatively associated with the prevalence of hypertension ($p = 0.004$, $p = 0.049$ and $p < 0.001$ respectively). The same associations were confirmed in Es ($p = 0.017$, $p = 0.005$ and $p = 0.006$ respectively). Average years of education and real estate prices were also inversely correlated with hypertension in Ns ($p = 0.004$ and $p = 0.013$). Negative relationship with green urban areas was observed in Es ($p = 0.046$) and with population density in Ns ($p = 0.008$). In Ws, hypertension was inversely correlated with higher educated population ($p = 0.003$), while in two other sectors, Ss and Cs, no relationship between hypertension and any of the socio-environmental variables was found.

PCA extracted three components for Es, Ss and Cs, while two components were extracted for all municipalities' analysis, Ws and Ns. The loadings for the socio-environmental status components (patterns), which represent the correlation of each socio-environmental variable with the corresponding component, are presented in Table II (bold font indicates the coefficients with absolute loadings > 0.4). The first two extracted components are common for all sectors and they are characterized as high socio-environmental status (component 1) and low socio-environmental sta-

Tab. I. Results from Poisson regression analysis that evaluated the association of socio-environmental variables (independent) on hypertension (dependent).

	All municipalities		East sector		South sector	
Model 1	b ± SE	p value*	b ± SE	p value	b ± SE	p value
Immigrants, %	0.004 ± 0.0097	0.690	0.032 ± 0.0355	0.375	0.029 ± 0.0685	0.669
Average years of education	-0.082 ± 0.0226	< 0.001	-0.166 ± 0.0606	0.006	0.080 ± 0.1015	0.428
Model 2						
Population with higher education, %	0.002 ± 0.0085	0.771	0.053 ± 0.0426	0.217	0.044 ± 0.0467	0.349
Average real estate prices, €/m ²	-0.001 ± 0.0003	0.049	-0.003 ± 0.0009	0.005	-0.001 ± 0.0012	0.489
Population density, residents/km ²	2.64x10 ⁻⁶ ± 6.76x10 ⁻⁶	0.697	-1.98x10 ⁻⁵ ± 2.58x10 ⁻⁵	0.441	-2.78x10 ⁻⁶ ± 2.73x10 ⁻⁵	0.919
Model 3						
Illiterate population, %	-0.005 ± 0.0209	0.827	-0.171 ± 0.1613	0.290	-0.076 ± 0.0621	0.219
Average annual income, €	-3.74x10 ⁻⁵ ± 1.31x10 ⁻⁵	0.004	-1.16x10 ⁻⁴ ± 4.89x10 ⁻⁵	0.017	-1.05x10 ⁻⁶ ± 3.41x10 ⁻⁵	0.975
Green urban areas, %	-0.006 ± 0.0055	0.264	-0.087 ± 0.0436	0.046	-0.021 ± 0.0258	0.410
	West sector		North sector		Central sector	
Model 1	b ± SE	p value	b ± SE	p value	b ± SE	p value
Immigrants, %	0.015 ± 0.0434	0.725	-0.032 ± 0.0333	0.340	-0.004 ± 0.0171	0.814
Average years of education	-0.084 ± 0.0853	0.326	-0.146 ± 0.0512	0.004	-0.027 ± 0.1081	0.800
Model 2						
Population with higher education, %	-0.042 ± 0.0193	0.032	0.016 ± 0.0257	0.527	-0.066 ± 0.1678	0.693
Average real estate prices, €/m ²	9.84x10 ⁻⁵ ± 0.0014	0.945	-0.002 ± 0.0008	0.013	-3.69x10 ⁻⁴ ± 0.0018	0.836
Population density, residents/km ²	-3.02x10 ⁻⁶ ± 1.56x10 ⁻⁵	0.847	-6.63x10 ⁻⁵ ± 2.50x10 ⁻⁵	0.008	1.46x10 ⁻⁵ ± 0.0001	0.774
Model 3						
Illiterate population, %	0.017 ± 0.0452	0.714	0.031 ± 0.1140	0.784	0.052 ± 0.1455	0.723
Average annual income, €	-1.54x10 ⁻⁴ ± 0.0001	0.111	-2.53x10 ⁻⁵ ± 3.45x10 ⁻⁵	0.463	-7.63x10 ⁻⁵ ± 0.0002	0.757
Green urban areas, %	-0.028 ± 0.0263	0.283	-0.005 ± 0.179	0.765	0.002 ± 0.0120	0.894

*level of significance $\alpha = 0.05$

Tab. II. Score coefficients derived from principal components analysis regarding socio-environmental variables.

	All municipalities		East sector			South sector			West sector		North sector		Central sector		
	Component		Component			Component			Component		Component		Component		
	1	2	1	2	3	1	2	3	1	2	1	2	1	2	3
Average years of education	0.806	-0.027	0.568	0.228	0.059	-0.748	0.524	0.011	0.730	-0.580	0.910	0.151	0.920	0.197	-0.303
Population with higher education, %	0.917	0.162	0.894	0.157	0.172	0.773	0.528	-0.121	0.955	0.225	0.896	-0.039	0.995	-0.011	-0.086
Illiterate population, %	-0.866	-0.329	-0.774	-0.502	0.047	-0.666	-0.642	0.222	-0.751	-0.440	-0.873	-0.428	-0.949	-0.078	0.292
Average annual income, €	0.886	-0.130	0.925	-0.198	0.265	0.565	0.368	0.299	0.873	0.268	0.948	-0.053	0.260	0.782	0.565
Average real estate prices, €/m ²	0.887	-0.132	0.964	-0.036	0.023	0.891	-0.234	0.273	0.648	0.334	0.935	-0.107	0.576	-0.487	0.554
Immigrants, %	-0.173	0.812	-0.684	0.701	0.100	0.802	-0.290	-0.354	-0.390	0.752	-0.619	0.534	0.624	-0.184	0.675
Population density, residents/km ²	-0.253	0.763	-0.247	0.538	0.791	-0.272	0.642	-0.636	-0.540	0.424	-0.557	0.381	0.888	-0.351	-0.258
Green urban areas, %	0.347	0.445	0.239	0.713	-0.645	-0.064	0.570	0.808	-0.069	0.710	0.247	0.884	0.275	0.943	-0.060

* Score coefficients are similar to the correlation coefficients. Higher absolute values indicate that the body composition variable is correlated with the respective component. Numbers in bold indicate loadings greater than 0.4. ** Component 1: High socio-environmental status, Component 2: Low socio-environmental status, Component 3: Mixed socio-environmental status

tus (component 2), while the third component, extracted only for Es, Ss and Cs, is characterized as mixed socio-environmental status (component 3). Regression analysis that was performed between hypertension and the 3-PCA patterns, revealed that high socio-environ-

mental status was negatively associated with hypertension in Es and Ws, as well as in all municipalities analysis (Tab. III). In contrast, component 2 and component 3 were related with hypertension neither to all municipalities nor to sectors.

Tab. III. Results from Poisson regression analysis that evaluated the association of PCA component socio-environmental status (independent) on hypertension (dependent).

	All municipalities		East sector		South sector	
	b ± SE	p value	b ± SE	p value	b ± SE	p value
High socio-environmental status	-0.113 ± 0.0311	< 0.001	-0.245 ± 0.882	0.005	0.070 ± 0.0724	0.337
Low socio-environmental status	0.037 ± 0.0306	0.222	0.037 ± 0.0772	0.633	-0.109 ± 0.0746	0.145
Mixed socio-environmental status			-0.072 ± 0.0830	0.383	-0.057 ± 0.0774	0.461
	West sector		North sector		Central sector	
	b ± SE	p value	b ± SE	p value	b ± SE	p value
High socio-environmental status	-0.156 ± 0.0581	0.007	-0.078 ± 0.0700	0.267	-0.029 ± 0.0936	0.758
Low socio-environmental status	0.050 ± 0.0623	0.421	-0.124 ± 0.0667	0.062	-0.031 ± 0.0967	0.752
Mixed socio-environmental status					-0.031 ± 0.0955	0.749

* Component 1: High socio-environmental status, Component 2: Low socio-environmental status, Component 3: Mixed socio-environmental status

Discussion

In summary this study showed hypertension prevalence varies with social segregation and geographical inequalities in Athens, in particular with differing socio-environmental factors. Although it is well accepted that hypertension is a global health challenge, the present study is novel in using geographic approaches, to analyze spatial distribution of hypertension in adults and its relationship with socio-environmental status, in an urban characterized of geographical inequalities [29, 30]. This is critical to environmental public health surveillance, and formulating evidence based program development.

Strong negative associations with hypertension were found in sectors of higher educational and financial level (Ns and Es) in Athens, metropolitan area, in agreement with other studies, which have concluded that low socio-economic status, and especially low educational level is related with high blood pressure [7, 33-35]. However, a negative association was also found in sectors with low-educated and low-income population (Ws), underlying the evidence that multi-components need to be addressed.

Higher income and real estate prices were negatively associated to hypertension in accordance to study showing adverse influence of low economic status on hypertension [36]. In sectors, however, where higher economic status was concentrated (Ns and Es), prevalence of hypertension was high in some municipalities, in agreement with studies showing that hypertension is more prevalent among higher SES populations [19]. This may be due to the limited green urban space (Es) as per results from some studies, showing a negative association between higher-scoring green/recreational and prevalence of hypertension [37, 38]. The Ns, on the other hand, have a substantial amount of illiterate population. It seems, therefore that various socio-environmental factors may interact and need to be more thoroughly studied.

Low population density was also negatively correlated with hypertension (Ns). In agreement to studies suggesting that population density, as a result of urban growth, may generate numerous stressors [39] on blood pressure. On the other hand, in the most densely populated sector with the highest rate of green urban areas as well (Cs), these associations were not confirmed, suggesting an important effect of green space on hypertension prevalence, despite other risk factors present.

Pattern analysis used, to examine the association of socioeconomic and environmental characteristics on hypertension showed that high socio-environmental status, explained mostly by factors related to education and financial status (component 1), was negatively associated with hypertension in all municipalities, as well as in Es and Ws, although the latter had a large population of low SES. The latter further suggesting that area-environment-education and social state intertwine on their final effect on hypertension.

Many studies have already examined the influence of socioeconomic status on hypertension at individual level, though, to the best of our knowledge, this is one of the

first studies to document the relationship between hypertension and an area's socio-environmental conditions. Adding geographical dimension to consider spatial risk factor heterogeneity on hypertension prevalence is the main strength of this study, since, GIS-based analysis gives spatial epidemiology a big advantage over other methods, as it improves the understanding and prediction of health risk factors in a spatial context [40-42]. Moreover, reducing Athens metropolitan area into five sectors contributed to minimizing spatial inequality bias and using *choropleth* maps, increased visual understanding of results. However, this study has limitations with one related to potential socio-environmental remnant disparities within the limits of the municipalities. Another limitation is the time-difference among the variables (blood pressure data from 2001-2, annual income and real estate prices from 2009, and 2011 census data). Nevertheless, there were no significant proportionate socio-environmental differences among the municipalities, between 2001-2011, making socio-environmental variables from 2009 and 2011 reliable estimators, in time alignment with the epidemiological data. Finally, this study took place in an urban region and, therefore, results cannot be generalized to rural regions.

Conclusions

In conclusion, the present study revealed that as the socio-environmental status of a residential area increases, the hypertension rates decreases. Particularly, educational and economic level, as well as the amenities that are provided by non-densely populated areas with higher rates of green public spaces, are the main socio-environmental factors that should be given attention against hypertension. This can lead to more effective public health policies and intervention programs that target the reduction of hypertension prevalence.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

CC, AT and DBP conceived and designed the research. AF, CC, AT, CP and DBP contributed to acquisition of data. AF performed the spatial and statistical analysis. AF, CC, EM and ENG contributed to data interpretation. AF and EM participated in writing the manuscript. AF, CC, EM and DBP participated in the literature search.

All authors critically read and revised the manuscript and approved the final version.

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