Supplementary Materials

Carbamazepine levels related to the demographic indicators in groundwater of densely populated area

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1. Materials and methods

1.1 Analytical Standard, Material and Method for Carbamazepine

The reference standard was all analytical grade in powder form with purity higher than 98%. The labelled compound carbamazepine d10 (99% D) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Stock solution containing mixtures of the analytes were prepared at 10 ng/mL with methanol and stored at -20 ºC in the dark up to a maximum of two months. Working solutions (1, 0.1 and 0.01 ng/mL) were prepared before each analytical batch and stored at -20 ºC in the dark.

For determining the limits of quantification of CBZ, instrumental detection limits (IDL) and instrumental quantification limits (IQL) were determined by direct injection of picogram quantities of substance. The detection limits (LOD) and quantification limits (LOQ) for the whole method were calculated from real sample or by spiking wastewater sample with low amount of the substance, depending on the typical concentrations in sample. IDL and LOD were calculated as the concentrations giving peaks for which the signal-to-noise ratio was 3, and IQL and LOQ as the concentrations giving peaks for which the signal-to-noise ratio was 10. LOQs were used as cut- off values for quantification of the analytes. Finally, the LOQ measured for CBZ was 0.18 ng/L.

Specific analytical methods based on solid phase extraction (SPE) and liquid chromatography tandem mass spectrometry analysis (LC-MS/MS) were developed and validated for analyses. Generally, samples were double filtered on glass microfiber filters GF/A 1.6 mm (Whatman, Kent, U.K.) and on a mixed cellulose membrane filter 0.45 mm (Whatman, Kent, U.K.).

1.2 demographic variables

Table S1. Demographic variables of the ISTAT (2011) dataset

CODE	Demographic variables
P1	population-Total
P2	population-Males
P3	population-Females
P4	population-unmarried
P5	population-married
P6	population-separated
P7	population-widowers
P8	population-divorced
P9	population-unmarried males
P10	population-married or separated males
P11	population-legally separated males
P12	population-widowed males
P13	population-divorced males
P14	population-age < 5 years
P15	population-age 5-9 years
P16	population-age 10-14 years
P17	population-age 15-19 years
P18	population-age 20-24 years
P19	population-age 25-29 years
P20	population-age 30-34 years
P21	population-age 35-39 years
P22	population-age 40-44 years
P23	population-age 45-49 years
P24	population-age 50-54 years
P25	population-age 55-59 years
P26	population-age 60-64 years
P27	population-age 65-69 years
P28	population-age 70-74 years
P29	population-age > 74 years
P30	population-males-age < 5 years
P31	population-males-age 5-9 years
P32	population-males-age 10-14 years
P33	population-males-age 15-19 years
P34	population-males-age 20-24 years
P35	population-males-age 25-29 years
P36	population-males-age 30-34 years
P37	population-males-age 35-39 years
P38	population-males-age 40-44 years

P39	population-males-age 45-49 years
P40	population-males-age 50-54 years
P41	population-males-age 55-59 years
P42	population-males-age 60-64 years
P43	population-males-age 65-69 years
P44	population-males-age 70-74 years
P45	population-males-age > 74 years
P46	population-total of 6 years and more
P47	population with university degrees + tertiary diplomas
P48	population with higher Secondary school diploma
P49	Inferior population residence
P50	population with elementary license
P51	population-know Alphabets
P52	population-illiterate
P53	population-Males 6 years and older
P54	population-males with university degrees
P55	population-males with high school diploma
P56	population-males with lower average
P57	population-males with elementary licence
P58	population-males know alphabets
P59	population-illiterate males
P60	population-Total of 15 years and more belonging to the total manpower
P61	population-Total of 15 years and more occupied
P62	population-Total of 15 years and more unemployed looking for new employment
P63	population-males aged 15 years and more belonging to the labour force
P64	population-males aged 15 years and more occupied
P65	population-males aged 15 years and more unemployed looking for new employment
P66	population-Total of 15 years and more non-labour force
P67	population-males aged 15 years and more non-labour force
P68	population-Total of 15 years and more housewares/s
P69	population-Total of 15 years and more students
P70	population-Total males of 15 years and more students
P71	population-Total of 15 years and more in other state
P72	population-Total males of 15 years and more in other condition
P73	population moving Daily in the municipality of habitual dwelling
P74	population moving daily out of the municipality of habitual dwelling
P75	population-Total of 15 years and more earners of income from work or capital
P76	population-Total males of 15 years and more earners of income from work or capital

2. Results

2.1 Ground water monitoring stations

Table S2. Information of groundwater monitoring stations and population density in 1.5 km buffer

Monitoring station in aquifer B	name of monitoring stations in aquifer B	Monitoring station in aquifer A	name of monitoring stations in aquifer A	Avg. of Population in each buffer	Sum. Of population in each buffer
B1	LINATE	A1	FOG72	161.15	9508
B2	SALEMI	A2	2BIS	237.51	39189
B3	ANFOSSI	A3	MM55	208.03	111086
B4	VIALBA	A4	SAP1	205.21	32834
B5	ARMI	A5	MM75	199.2	96214
B6	GORLA	A6	SAP6	198.21	71950
B7	FELTRE	A7	FOG14	229.7	73046
B8	ABBIATEGRASSO	A8	MM163	228.98	53811
B9	PARCO	A9	ACQ2	159.74	77475
B10	SUZZANI	A10	SAP3	201.04	60313
B11	NOVARA	A11	SAP16	195.18	16981
B12	OVIDIO	A12	ACQ6	215.86	44683
B13	CANTORE	A13	INT2	162.85	93153
B14	ESTE	A14	MM71	151.93	84779
B15	PADOVA	A15	MM115	257.04	17479
B16	COMASINA	A16	MM7	213.01	88827
B17	LAMBRO	A17	FOG43	216.24	42600
B18	SAN SIRO	A18	MM177	197.34	70254
B19	ASSIANO	A19	FOG71	155.44	5285
B20	BAGGIO	A20	SAP26	240.64	38262
B21	CHIUSABELLA	A21	SAP18	189.39	40718

2.2 Result of PCA/FA analysis

Factor loadings matrix of the PCA/FA analysis is shown in table S3, P1-P76 show the demographic information of Milan area which presented in table S1.

Table S3. 76 demographic variables of the ISTAT (2011) dataset and factor loadings matrix of the PCA/FA analysis; The factor loadings higher than 0.5 and lower than –0.5 are shown in bold.

Num.	Demographic variables	F1= family index	F2= aging index	F3= adolescents and quinquagenarian Index	F4= divorce index	F5= illiterate index	F6= sexagenarian index	F7= child index	F8= education index
P1	population-Total	**0.63**	0.52	0.41	0.24	0.17	0.21	0.16	0.08
P2	population-Males	**0.67**	0.45	0.42	0.24	0.18	0.23	0.16	0.04
P3	population-Females	**0.59**	0.57	0.40	0.25	0.15	0.19	0.15	0.11
P4	population-unmarried	**0.71**	0.36	0.41	0.28	0.22	0.14	0.15	0.09
P5	population-married	**0.59**	0.53	0.43	0.11	0.07	0.33	0.18	0.06
P6	population-separated	0.40	0.35	0.27	**0.58**	0.17	0.18	0.16	0.05
P7	population-widowers	0.23	**0.84**	0.18	0.25	0.21	-0.06	0.03	0.03
P8	population-divorced	0.40	0.41	0.29	**0.58**	0.14	0.13	0.08	0.19
P9	population-unmarried males	**0.72**	0.32	0.42	0.27	0.26	0.15	0.15	0.03
P10	population-married or separated males	**0.61**	0.52	0.42	0.11	0.09	0.32	0.18	0.04
P11	population-legally separated males	0.39	0.24	0.20	**0.62**	0.11	0.14	0.12	0.07
P12	population-widowed males	0.29	**0.74**	0.17	0.19	0.15	-0.02	0.01	0.02
P13	population-divorced males	0.36	0.27	0.20	**0.64**	0.12	0.09	0.08	0.18
P14	population-age < 5 years	**0.81**	0.16	0.23	0.13	0.12	0.05	0.27	0.11
P15	population-age 5-9 years	0.40	0.20	0.38	0.15	0.11	0.10	**0.52**	0.12
P16	population-age 10-14 years	0.45	0.28	**0.57**	0.16	0.14	0.10	0.45	0.04
P17	population-age 15-19 years	0.37	0.29	**0.75**	0.16	0.19	0.10	0.21	0.00
P18	population-age 20-24 years	0.49	0.27	**0.63**	0.21	0.30	0.14	-0.02	-0.05
P19	population-age 25-29 years	**0.74**	0.24	0.32	0.21	0.26	0.15	-0.16	0.00
P20	population-age 30-34 years	**0.87**	0.20	0.13	0.18	0.21	0.12	-0.06	0.03

P21	population-age 35-39 years	**0.87**	0.23	0.16	0.19	0.12	0.10	0.13	0.05
P22	population-age 40-44 years	**0.76**	0.30	0.30	0.22	0.10	0.11	0.28	0.09
P23	population-age 45-49 years	**0.60**	0.37	0.48	0.26	0.12	0.09	0.25	0.07
P24	population-age 50-54 years	0.48	0.39	**0.60**	0.32	0.10	0.13	0.10	0.05
P25	population-age 55-59 years	0.41	0.40	**0.53**	0.33	0.14	0.32	-0.03	0.06
P26	population-age 60-64 years	0.34	0.46	0.36	0.29	0.10	**0.58**	0.02	0.07
P27	population-age 65-69 years	0.28	0.59	0.23	0.16	0.09	**0.62**	0.10	0.11
P28	population-age 70-74 years	0.23	**0.77**	0.17	0.09	0.08	0.41	0.17	0.07
P29	population-age > 74 years	0.19	**0.90**	0.19	0.16	0.13	-0.07	0.04	0.11
P30	population-males-age < 5 years	**0.78**	0.15	0.20	0.13	0.13	0.04	0.27	0.10
P31	population-males-age 5-9 years	0.50	0.18	0.34	0.14	0.10	0.11	**0.55**	0.10
P32	population-males-age 10-14 years	0.41	0.25	**0.54**	0.14	0.14	0.09	0.45	0.04
P33	population-males-age 15-19 years	0.34	0.25	**0.74**	0.12	0.20	0.09	0.17	-0.02
P34	population-males-age 20-24 years	0.44	0.23	**0.60**	0.18	0.33	0.12	-0.05	-0.08
P35	population-males-age 25-29 years	**0.68**	0.20	0.31	0.18	0.31	0.15	-0.19	-0.05
P36	population-males-age 30-34 years	**0.83**	0.18	0.12	0.15	0.27	0.12	-0.12	-0.04
P37	population-males-age 35-39 years	**0.87**	0.21	0.13	0.18	0.15	0.10	0.08	-0.01
P38	population-males-age 40-44 years	**0.77**	0.27	0.23	0.21	0.14	0.12	0.24	0.04
P39	population-males-age 45-49 years	**0.61**	0.33	0.41	0.27	0.13	0.08	0.28	0.05
P40	population-males-age 50-54 years	0.47	0.35	**0.57**	0.31	0.10	0.09	0.13	0.02
P41	population-males-age 55-59 years	0.40	0.35	**0.52**	0.35	0.14	0.25	-0.03	0.03
P42	population-males-age 60-64 years	0.33	0.38	0.39	0.33	0.10	**0.52**	-0.01	0.04
P43	population-males-age 65-69 years	0.29	0.49	0.24	0.18	0.07	**0.65**	0.08	0.08
P44	population-males-age 70-74 years	0.23	**0.67**	0.15	0.06	0.05	0.50	0.16	0.09
P45	population-males-age > 74 years	0.20	**0.88**	0.22	0.08	0.05	0.05	0.09	0.09
P46	population-total of 6 years and more	**0.61**	0.54	0.42	0.25	0.17	0.22	0.15	0.07
P47	population with university degrees + tertiary diplomas	0.48	0.20	0.38	0.14	-0.16	0.19	0.10	**0.67**
P48	population with higher Secondary school diploma	**0.66**	0.49	0.42	0.14	0.01	0.27	0.08	0.04
P49	Inferior population residence	0.47	**0.55**	0.33	0.28	0.35	0.18	0.10	-0.30
P50	population with elementary license	0.31	**0.66**	0.19	0.30	0.40	0.06	0.12	-0.31
P51	population-know Alphabets	**0.56**	0.32	0.36	0.25	0.31	0.07	0.45	-0.05
P52	population-illiterate	0.12	0.15	0.07	0.09	**0.88**	-0.01	0.09	-0.04
P53	population-Males 6 years and older	**0.65**	0.47	0.43	0.24	0.18	0.24	0.15	0.04
P54	population-males with university degrees	0.46	0.19	0.38	0.13	-0.15	0.19	0.11	**0.68**

P55	population-males with high school diploma	**0.69**	0.46	0.38	0.12	0.04	0.27	0.05	-0.04
P56	population-males with lower average	0.48	0.45	0.32	0.29	0.39	0.17	0.09	-0.37
P57	population-males with elementary licence	0.34	**0.54**	0.25	0.32	0.41	0.12	0.16	-0.33
P58	population-males know alphabets	0.50	0.21	0.35	0.19	0.26	0.10	**0.52**	-0.01
P59	population-illiterate males	0.19	0.06	0.06	-0.02	**0.86**	0.05	0.05	0.01
P60	population-Total of 15 years and more belonging to the total manpower	**0.77**	0.34	0.40	0.26	0.11	0.17	0.10	0.09
P61	population-Total of 15 years and more occupied	**0.78**	0.33	0.40	0.22	0.08	0.17	0.10	0.13
P62	population-Total of 15 years and more unemployed looking for new employment	0.42	0.27	0.25	**0.53**	0.36	0.16	0.09	-0.26
P63	population-males aged 15 years and more belonging to the labour force	**0.78**	0.31	0.39	0.26	0.15	0.17	0.10	0.07
P64	population-males aged 15 years and more occupied	**0.79**	0.30	0.40	0.21	0.11	0.17	0.10	0.11
P65	population-males aged 15 years and more unemployed looking for new employment	0.34	0.20	0.19	**0.55**	0.38	0.15	0.06	-0.30
P66	population-Total of 15 years and more non-labour force	0.34	**0.75**	0.37	0.22	0.21	0.26	0.10	0.04
P67	population-males aged 15 years and more non-labour force	0.35	**0.71**	0.38	0.19	0.22	0.34	0.08	-0.04
P68	population-Total of 15 years and more housewares/s	0.32	0.49	0.46	0.27	0.26	0.21	0.21	0.12
P69	population-Total of 15 years and more students	0.38	0.28	**0.78**	0.13	0.01	0.17	0.12	0.21
P70	population-Total males of 15 years and more students	0.34	0.25	**0.79**	0.10	0.02	0.16	0.09	0.19
P71	population-Total of 15 years and more in other state	0.23	0.39	0.21	0.38	**0.62**	0.06	0.05	-0.02
P72	population-Total males of 15 years and more in other condition	0.24	0.26	0.22	0.39	**0.64**	0.11	0.04	-0.11
P73	population moving Daily in the municipality of habitual dwelling	**0.73**	0.33	0.47	0.20	0.09	0.15	0.20	0.12
P74	population moving daily out of the municipality of habitual dwelling	**0.75**	0.33	0.35	0.09	0.02	0.16	0.13	-0.09
P75	population-Total of 15 years and more earners of income from work or capital	0.29	**0.86**	0.20	0.15	0.11	0.29	0.06	-0.02
P76	population-Total males of 15 years and more earners of income from work or capital	0.30	**0.81**	0.22	0.11	0.09	0.39	0.07	-0.08

2.3 Results of cluster analysis

Table S4. Groundwater monitoring stations of aquifer A and B and their categorization based on cluster analysis.

well number	station in aquifer B	CBZ cluster in aquifer B	station in aquifer A	CBZ cluster in aquifer A
1	B1	CLB1	A1	CLA2
2	B2	CLB4	A2	CLA1
3	B3	CLB3	A3	CLA1
4	B4	CLB3	A4	CLA4
5	B5	CLB2	A5	CLA1
6	B6	CLB3	A6	CLA1
7	B7	CLB5	A7	CLA3
8	B8	CLB2	A8	CLA2
9	B9	CLB4	A9	CLA4
10	B10	CLB4	A10	CLA4
11	B11	CLB4	A11	CLA1
12	B12	CLB5	A12	CLA3
13	B13	CLB5	A13	CLA1
14	B14	CLB1	A14	CLA2
15	B15	CLB1	A15	CLA4
16	B16	CLB3	A16	CLA4
17	B17	CLB2	A17	CLA3
18	B18	CLB4	A18	CLA2
19	B19	CLB2	A19	CLA2
20	B20	CLB2	A20	CLA2
21	B21	CLB4	A21	CLA3

Table S5. Descriptive statistics. This table reports summary statistics of the variables in each cluster of aquifer B.

CBZ clusters in aquifer B		Statistic	Std. Error
CLB 1	Mean	1.9033	1.07
	Median	1.6100	
	Variance	3.487	
	Std. Deviation	1.86736	
	Minimum	0.20	
	Maximum	3.90	
	Range	3.70	
	Skewness	0.689	1.225
CLB 2	Mean	8.9	0.65
	5% Trimmed Mean	9.01	
	Median	9.41	
	Variance	2.15	
	Std. Deviation	1.46	
	Minimum	7.33	

	Maximum	10.40	
	Range	3.06	
	Interquartile Range	2.89	
	Skewness	-0.34	0.91
	Kurtosis	-3.01	2
CLB 3	Mean	16.24	0.10
	5% Trimmed Mean	16.24	
	Median	16.26	
	Variance	0.043	
	Std. Deviation	0.20	
	Minimum	15.99	
	Maximum	16.47	
	Range	0.48	
	Interquartile Range	0.40	
	Skewness	-0.41	1.01
	Kurtosis	-0.74	2.61
CLB 4	Mean	14.04	0.47
	5% Trimmed Mean	14.09	
	Median	14.51	
	Variance	1.37	
	Std. Deviation	1.17	
	Minimum	12.13	
	Maximum	15.08	
	Range	2.95	
	Interquartile Range	2.12	
	Skewness	-1.088	0.845
	Kurtosis	-0.272	1.74
CLB 5	Mean	26.59	2.59
	Median	25.34	
	Variance	20.13	
	Std. Deviation	4.48	
	Minimum	22.86	
	Maximum	31.57	
	Range	8.71	
	Skewness	1.156	1.22

Table S6. Descriptive statistics. This table reports summary statistics of the variables in each cluster of aquifer A

CBZ clusters in aquifer A		**Statistic**	**Std. Error**
CLA1	Mean	18.91	2.09
	5% Trimmed Mean	18.86	

	Median	18.68	
	Variance	26.33	
	Std. Deviation	5.13	
	Minimum	13.60	
	Maximum	25.10	
	Range	11.50	
	Interquartile Range	10.53	
	Skewness	0.10	0.84
	Kurtosis	-2.49	1.74
CLA2	Mean	6.37	1.41
	5% Trimmed Mean	6.47	
	Median	7.50	
	Variance	12.05	
	Std. Deviation	3.47	
	Minimum	1.53	
	Maximum	9.40	
	Range	7.87	
	Interquartile Range	6.70	
	Skewness	-0.565	0.84
	Kurtosis	-1.94	1.74
CLA3	Mean	82.61	9.00
	5% Trimmed Mean	82.73	
	Median	83.64	
	Variance	324.3	
	Std. Deviation	18.008	
	Minimum	65.03	
	Maximum	98.16	
	Range	33.13	
	Interquartile Range	32.09	
	Skewness	-.045	1.01
	Kurtosis	-5.74	2.61
CLA4	Mean	41.13	2.11
	5% Trimmed Mean	41.19	
	Median	41.80	
	Variance	22.26	
	Std. Deviation	4.719	
	Minimum	34.57	
	Maximum	46.60	
	Range	12.03	
	Interquartile Range	8.81	
	Skewness	-.435	0.913
	Kurtosis	-0.748	2