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Rajovic, N., Grubor, N., Cirkovic, A. et al. (15 more authors) (2024) Insights into relationship of environmental inequalities and multimorbidity: a population-based study. Environmental Health, 23. 99.

https://doi.org/10.1186/s12940-024-01133-8

https://doi.org/10.1186/s12940-024-01133-8
Environmental Health

RESEARCH Open Access

Insights into relationship of environmental inequalities and multimorbidity: a population-based study

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Abstract

Background Substantial inequalities in the overall prevalence and patterns of multimorbidity have been widely reported, but the causal mechanisms are complex and not well understood. This study aimed to identify common patterns of multimorbidity in Serbia and assess their relationship with air pollutant concentrations and water quality indicators.

Methods This ecological study was conducted on a nationally representative sample of the Serbian population. Data were obtained from the European Health Interview (EHIS) Survey, a periodic study designed to assess population health using widely recognized standardized instruments. The study included 13,069 participants aged 15 and older, randomly selected through a multistage stratified sampling design. Multimorbidity was defined as having two or more self-reported diagnoses of chronic non-communicable diseases. Latent class analysis (LCA) was performed to identify clusters of multimorbidity. Concentrations of particulate matter (PM10), sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), and ozone (O3), as well as water quality indicators, were obtained from the Serbian Environmental Protection Agency.

Results The overall prevalence of multimorbidity was 33.4% [32.6%—34.2%]. Six latent classes of multimorbidity were identified: Healthy, Multicondition, Cardiovascular, Metabolic syndrome, Respiratory, and Musculoskeletal. Annual increases in PM10 and SO2 concentrations, as well as daily increases in O3 concentrations, significantly raised the odds of having multimorbidity (OR = 1.02, 95% CI 1.02–1.03; OR = 1.01, 95% CI 1.00–1.02 and OR = 1.03, 95% CI 1.02–1.03, respectively). A pattern of increased risk was observed with rising levels of water contamination. Exposure to physico-chemical, microbiological and combined contamination was associated with a 3.92%, 5.17% and 5.54% higher probability, respectively, of having multiple chronic conditions. There was strong evidence that air pollutants, as well as chemical and microbial water contamination, were significantly associated with higher odds of the most common clusters of multimorbidity identified by LCA.

Conclusion There is compelling evidence of an association between multimorbidity and environmental pollution, suggesting that exposure to air pollutants and water contaminants may contribute to disease accumulation

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and help explain geographically and socioeconomically patterned inequalities. These findings underscore the need for extensive studies that simultaneously measure both multimorbidity and pollution to explore their complex interrelationships.

Keywords Multimorbidity, Latent class analysis, Disease clusters, Inequalities, Air pollution, Water pollution

Introduction

In societies facing considerable demographic aging, multimorbidity – defined as the coexistence of two or more chronic diseases in an individual – becomes an increasingly pressing public health issue [1]. Recent estimates suggest that approximately 50 million people in the European Union are affected by multimorbidity [2]. This condition often results in diminished physical functioning, polypharmacy, increased hospitalization rates, reduced quality of life, depression, and heightened mortality risk, thus imposing a substantial economic strain on healthcare systems [3]. Despite its significance, the standardization of multimorbidity definitions and clinical practices remains insufficient due to its complex and variable nature across different populations [4, 5].

The evaluation of multimorbidity patterns and associated risk factors can be approached through various methodologies [6–8]. Traditional approaches, which focus solely on counting the number of chronic conditions, often fail to adequately inform healthcare policy due to the diverse combinations of conditions experienced by individuals [1, 9]. The conventional definition of multimorbidity – two or more chronic conditions – has been criticized for its lack of detailed information about the specific combinations of conditions affecting individuals, which is crucial for effective patient management [10]. Additionally, the inclusion of less impactful conditions, such as well-managed hypertension, pre-diabetes, and mildly elevated cholesterol, may obscure the true impact of multimorbidity on patient well-being [11].

Recent advancements advocate for a paradigm shift towards recognizing multimorbidity as a collection of disease clusters, thereby enabling a more systematic approach to understanding and managing the condition [1, 9]. Emerging research supports the application of latent class analysis (LCA), a modeling technique that identifies population heterogeneity and classifies individuals based on the likelihood of belonging to specific classes of disease patterns [12, 13].

While individual characteristics such as gender, age, socioeconomic status, and health-related behaviors are well-established predictors of multimorbidity, there is limited evidence on the influence of environmental factors [1, 14, 15]. Air pollution and water contamination, both significant public health concerns, are increasingly recognized as contributing factors. According to the World Health Organization (WHO), ambient air pollution is responsible for approximately 4.2 million deaths annually, with this number expected to rise [16]. Despite reductions in pollutant emissions in the European Union over the past two decades, air pollution levels remain problematic, affecting both short-term and long-term health outcomes [17, 18]. Short-term exposure exacerbates existing conditions and triggers acute illnesses, while long-term exposure has more severe and delayed health consequences [19]. Increased exposure to air pollutants is linked to a rise in chronic conditions such as pulmonary insufficiency, chronic asthma, cardiovascular diseases, and overall mortality [20]. Similarly, water quality issues, exacerbated by industrialization, agriculture, and urbanization, pose a critical public health challenge [21]. The UNESCO World Water Development Report 2021 highlights that unsafe drinking water, poor sanitation, and inadequate hand hygiene contribute to approximately 829,000 annual deaths due to diarrhea [22]. Given these concerns, it is crucial to undertake future studies to better understand the relationships between environmental factors, such as air pollution and water contamination, and the prevalence and patterns of multimorbidity. Thus, the aim of this study was to identify common patterns of multimorbidity and to assess their complex relationship with air and water pollution in a representative sample of the Serbian population.

Material and methods

Study sample

The data analyzed in this ecological study were obtained from the European Health Interview Survey (EHIS) [23], conducted on a nationally representative sample of the Serbian population during 2019. The EHIS is a periodic survey designed to assess the health of the population using widely recognized standardized instruments, specifically interview surveys, to collect reliable data on health status, health protection, and the determinants of health within the European Union (EU). The study instrument was culturally adapted and validated for Serbian population. The survey was conducted in cooperation with the Statistical Office of the Republic of Serbia, the Ministry of Health of the Republic of Serbia, and the Institute of Public Health of Serbia "Dr Milan Jovanović Batut". The survey was approved by the Ethics Committee of the Institute of Public Health of Serbia (n° 3607/1), and ethical standards were in accordance with the International Declaration of Helsinki [24]. The participants were presented with a written document that included relevant information regarding the study's objectives and the extent of their rights. A written signature was obtained from each participant who agreed to participate in the study. To ensure participant anonymity, measures were implemented to exclude any data that could potentially reveal their identities. This practice adhered to the Law on Official Statistics, wherein the requisite identification information was systematically eliminated and substituted with a unique code.

A stratified, two-stage cluster sampling method was used to obtain a nationally representative sample. Stratification was undertaken according to the four statistical regions in Serbia (Vojvodina, Sumadija and Western Serbia, Southern and Eastern Serbia and the Belgrade region), and the type of settlement (urban or other). The first stage involved selecting random samples of census districts with a probability proportional to their size using clustering sampling techniques. In the second stage, a sample of households were randomly selected with equal probability. Out of 6,000 households invited, a sample of 5,114 households was realized (response rate: 85.23%). The inclusion criteria were all persons aged 15 years and over who were living in non-institutional (private) households in the territory of the Republic of Serbia and who represented the usual population. Individuals who lived in collective households were excluded. Detailed information on the Serbian EHIS 2019 sampling procedures, calculation of the sample size, and population inclusion and exclusion criteria can be found elsewhere [25]. Patients or the public were not involved in research's design, conduct, reporting, or dissemination plans.

Defining multimorbidity state and clusters of multimorbidity

Multimorbidity was defined as two or more diagnoses from the list of 17 self-reported chronic non-communicable diseases provided in EHIS 2019: 1) Hypertension; 2) Lower spine deformity or other chronic back problem (back pain); 3) Cervical deformity or other chronic problem with the cervical spine; 4) Hyperlipidemia; 5) Arthrosis (excluding arthritis); 6) Coronary artery disease or angina pectoris; 7) Allergy (excluding allergic asthma); 8) Diabetes mellitus; 9) Depression (or chronic anxiety); 10) Renal disorders; 11) Chronic bronchitis, COPD (Chronic obstructive pulmonary disease), Emphysema; 12) Urinary incontinence; 13) Asthma (including allergic asthma); 14) Stroke (cerebral bleeding or thrombosis) or chronic consequences of the stroke; 15) Myocardial infarction or chronic consequences of the myocardial infarction; 16) Malignancies; and 17) Liver cirrhosis.

LCA was performed to define clusters of multimorbidity, using scripts in the poLCA from the R package. The 17 chronic health conditions listed above were used as observed indicators. The optimal number of latent classes was determined using the lowest Bayesian information criterion (BIC) and Akaike information criterion (AIC) [26, 27]. Clinical judgment and interpretability were also implemented in selecting the optimal model. Based on their highest computed probability of membership, each participant was assigned to one class. Average posterior probabilities > 70% indicated optimal fit [28]. Used tolerance for convergence was 1e-12 and the number of repetitions per model was 10. Entropy was used as a metric for assessing class differentiation by computing the posterior probabilities for assigning each observation to the latent classes. The entropy values range from 0, which represents random classification, to 1, which signifies a perfect assignment. Models with values about 0.8 are generally regarded as satisfactory [29].

Air pollution measurement

The study looked at the levels of PM10 particles, sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), and ozone (O3) in the air for 2019. The levels were obtained from the state network of air quality monitoring stations, governed by the Environmental Protection Agency of the Ministry of Environmental Protection, and follow the rules set out in the Regulation on conditions for monitoring and air quality requirements [30]. The total number of ambient air quality monitoring stations across the country that provided data in 2019 were: PM10 (36), SO2 (41), NO2 (35), CO (29), and O3 (19). All used measuring techniques are defined as reference methods. An Additional file 1. shows used standards in more detail.

Data on air pollutants were directly assigned to respondents from municipalities that had a monitoring station with available data for the study period. To address the issue of a smaller number of valid measuring stations for air pollutant concentrations compared to the number of municipalities included in the EHIS 2019, values were interpolated (< 10%). For respondents from municipalities without monitoring stations, pollutant values were assigned from the nearest monitoring station based on geographical longitude and latitude, using cubic interpolation. Cubic interpolation was selected over nearest and linear methods due to its lower approximation error, particularly for boundary municipalities (those not surrounded by other municipalities, located near the borders of Serbia), and was performed in the Python programming language. An Additional file 2. shows the air pollutant concentration averaging periods and their limits in the Regulation on conditions for monitoring and air quality requirements, and Additional file 3. reports measured air pollutant concentration range for 2019.

Water quality measurement

The Environmental Protection Agency of the Republic of Serbia provided water quality indicators for 2019 [31]. The following indicators were assessed: physico-chemical water quality (risk levels: acceptable, partially acceptable, bad, very bad, and alarming) and microbiological water quality (risk levels: insignificant, small, moderate, large, and huge). Based on the physico-chemical and microbiological properties, the water quality was classified as [31]:

1. satisfactory (less than 5% of microbiologically contaminated samples and less than 20% of physico-chemically contaminated samples annually)
2. physico-chemical contamination (physico-chemical contamination in more than 20% of tested samples annually),
3. microbiological contamination (microbiological contamination is present in more than 5% of tested samples annually) and
4. "combined" contamination (physico-chemical contamination in more than 20% of tested samples and microbiological contaminations in more than 5% of tested samples annually).

Data on water contamination indicators were directly assigned to respondents from municipalities that had a measuring station with available data for the study period. There was no imputation for missing data on water quality indicators.

Statistical analysis

Numerical variables were presented as means with standard deviations. Categorical variables were presented with absolute numbers and percentages. In addition, 95% confidence intervals (CI) were calculated. Chi-squared test was used for testing associations between two independent groups according to categorical variables. The distribution of multimorbidity was assessed according to sex, age, quintiles of household's monthly income per person (with the 1st quintile indicating lowest and the 5th quintile indicating the highest level of income), and four regions in Serbia (Vojvodina, Belgrade, Šumadija and Western Serbia, South and Eastern Serbia). Household monthly income per person was calculated by taking the total gross household monthly income divided by total number of family members living together. LCA was conducted to identify clusters of multimorbidity, as previously described. After LCA, we performed a Bayesian categorical multi-logistic regression to assess the relationship between age and predicted class membership. We also investigated the empirical distribution of specific diseases and disease burden by plotting percent changes across defined statistical regions of the Republic of Serbia. Additionally, based on domain knowledge, we constructed multiple directed acyclic graphs (DAG) to identify the total causal effects of different predictors on multimorbidity risk and avoid the 'Table 2' fallacy [32]. An Additional file 4. shows DAG in more details. Our primary target of inference was the association of socio-demographic determinants of health, air pollutant concentrations and water contamination indicators with multimorbidity and the most common clusters of multimorbidity. We estimated the association of age, income, education, chemical and microbiological water quality, ozone, sulfur dioxide, and the presence of particulate matter of less than 10 μm with multimorbidity by fitting a varying-intercept multilevel Bayesian logistic regression model. We pre-specified age as a nonlinear term and assumed the monotonicity of income, education, and water contamination with respect to multimorbidity odds.

We presented the posterior distributions which relate to covariate-adjusted estimates of multimorbidity odds by different risk factors. The posterior distributions communicate the probability of the relevant quantity of interest conditional on the observed data. We also explicitly calculated contrasts between risk factor levels and their reference value with other covariates held at their mean where relevant.

The posterior distribution was estimated using Hamiltonian Markov Chain Monte Carlo (MCMC), as implemented in Stan version 2.32.2. When deriving point estimates from the posterior distributions, we used the median. We assessed convergence by inspection of trace plots and R-hat values, which should be below 1.01 [33], and Effective Sample Size (ESS), which should be greater than 1000 [34]. Models were compared by assessing out-of-sample predictive performance using leave-one-out cross-validation approximated by Pareto smoothed importance sampling [35]. Weakly informative priors were selected to provide minimal regularization and so that the parameters span scientifically plausible values. Additionally, posterior predictive checks and stable reliability diagram calibration plots were used to assess model fit [36]. We computed weighted expectations using importance weights obtained from the PSIS smoothing procedure when assessing calibration. An Additional file 5. shows the MCMC trace plot visualized and Additional file 6. presents the CORP reliability diagram. The statistical analysis was done in R version 4.3.2.

The packages utilized were: brms, marginal effects, and ggdist.

Results

Multimorbidity in study population

The demographic characteristics of the Serbian study population, the number of morbidities and the proportion of the population with multimorbidity are shown in Table 1. The study population included a slightly higher proportion of women (51.2%) than men (48.8%) and considerably more people with lower secondary education (55.3%). The mean number of morbidities in the study population was 1.34 and 33.4% of the population had multimorbidity. The distribution of the relative multimorbidity burden and relative disease prevalence among the sampled statistical regions of the Republic of Serbia is presented in Figs. 1 and 2. Some diseases show no regional predilection as evidenced by a more homogenous distribution, while others exhibit a clear regional predominance.

In our study, we found a significant decline in odds of having multimorbidity with higher levels of education. The observed odds were highest for a 'primary' education level. Attaining a 'secondary' level of education was linked to a substantial decrease in odds, observed as a -6.74% reduction (95% CI [-9.02, -4.48]). Further attainment of 'tertiary' education was associated with a -10.44% decrease in odds compared to baseline (95% CI [-13.12, -7.66]). The pronounced drop from 'primary' to 'secondary' education levels represents the larger of the two differences in odds. We also found a step-wise decrease in odds across income quintiles. Individuals in the second income quintile were observed to have a -2.2% reduction in multimorbidity odds compared to individuals in the lowest income quintile (95% CI [-4.67, -0.3]). Individuals in the third quintile saw a -3.47% reduction in odds (95% CI [-6.05, -1.23]), the fourth quintile showed a -5.31%

Table 1 Demographics and prevalence of multimorbidity

	% (*n*)	Mean number of morbidities (SD)	Percent (95% CI) with multimorbidity
All persons	100.0 (13,166)	1.34 (1.8)	33.4 (32.6–34.2)
Sex			
Male	48.8 (6,423)	1.14 (1.68)	28.8 (27.7–29.9)
Female	51.2 (6,743)	1.54 (1.97)	37.8 (36.6–38.9)
Age, years			
15–24	1519 (11.5)	0.13 (0.44)	2.4 (1.7–3.2)
25–44	3574 (27.1)	0.42 (0.92)	9.9 (9.0–10.9)
45–64	4371 (33.2)	1.47 (1.81)	37.5 (36.1–38.9)
65–84	3419 (26.0)	2.56 (2.08)	63.9 (62.3–65.5)
85 +	283 (2.1)	2.73 (2.14)	64.3 (58.7–69.9)
Educational level			
Primary	3525 (26.8)	2.02 (2.18)	48.2 (46.5–49.8)
Secondary	7287 (55.3)	1.12 (1.65)	28.7 (27.6–29.7)
Higher	2354 (17.9)	1.03 (1.57)	25.9 (24.1–27.7)
Income per capita			
1st quintile (lowest)	2715 (20.6)	1.58 (2.08)	37.7 (35.9–39.5)
2nd quintile	2694 (20.5)	1.44 (1.90)	35.2 (33.3–37.0)
3rd quintile	2661 (20.2)	1.36 (1.85)	34.4 (32.6–36.2)
4th quintile	2637 (20.0)	1.20 (1.67)	31.0 (29.3–32.8)
5th quintile (highest)	2459 (18.7)	1.10 (1.62)	28.2 (26.4–30.0)
Regions			
Belgrade	3055 (23.2)	1.27 (1.85)	31.7 (30.0–33.3)
Vojvodina	2960 (22.5)	1.50 (1.95)	36.5 (34.7–38.2)
Šumadija and Western Serbia	4231 (32.1)	1.13 (1.63)	29.3 (27.9–30.6)
Southern and Eastern Serbia	2920 (22.2)	1.56 (1.97)	38.1 (36.4–39.9)

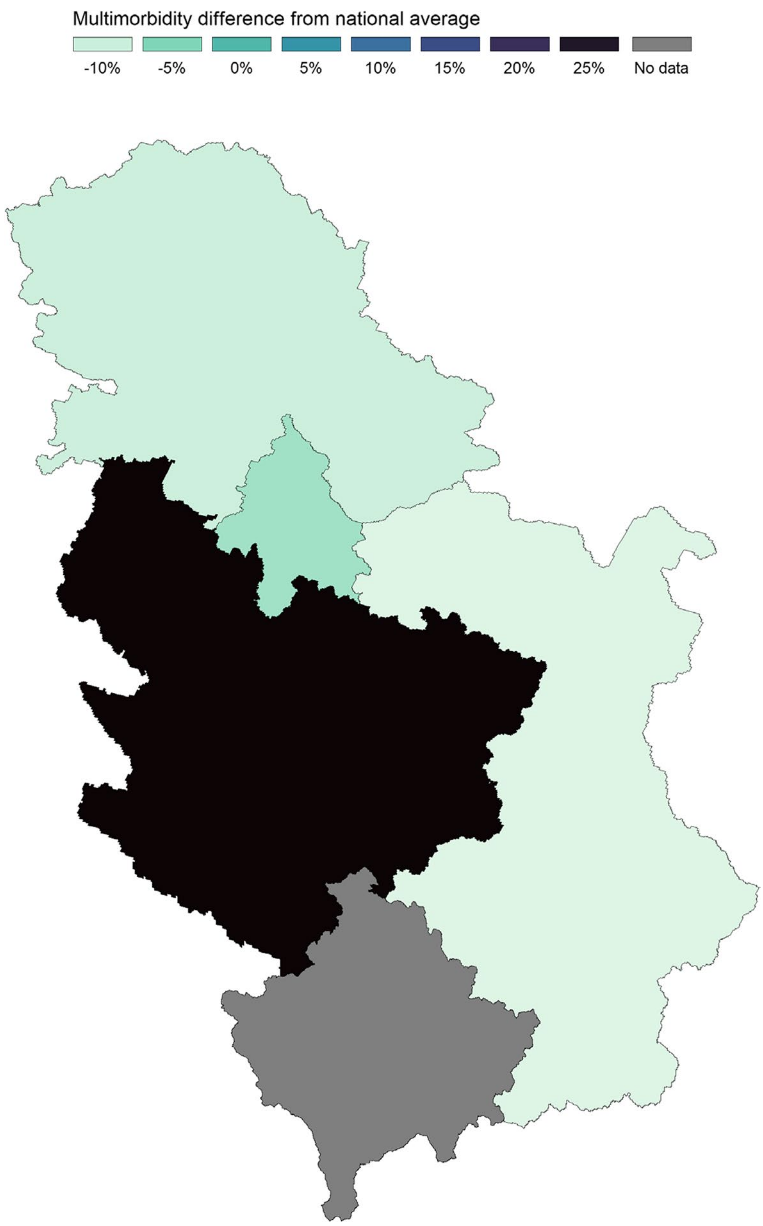

Fig. 1 The distribution of the relative multimorbidity burden among the sampled statistical regions of the Republic of Serbia. Shaded regions represent differences from national average given in percent

reduction (95% CI [-8.04, -2.66]), and individuals in the highest income quintile (5th quintile) experienced a -6.84% decrease in odds (95% CI [-9.99, -3.92]) compared to lowest income quintile. Average adjusted posterior distributions of multimorbidity by educational attainment and income quintiles is presented in Additional file 7.

Latent classes of multimorbidity patterns

A six classes model of multimorbidity was identified by LCA use (Fig. 3). Additional file 8. shows a comparison of fit statistics for models with different numbers of classes ranging from two to ten. There was an important drop in the BIC and AIC values from the two-class to the three-class model. The six-class model yielded the lowest BIC value (BIC = 94,419.09) and, although the lowest AIC corresponded to the ten-class model (AIC = 93,293.04), further inspection showed that none of the average posterior probabilities for the first six classes was below 0.7. In addition, since AIC monotonically dropped with an increase in class number, we

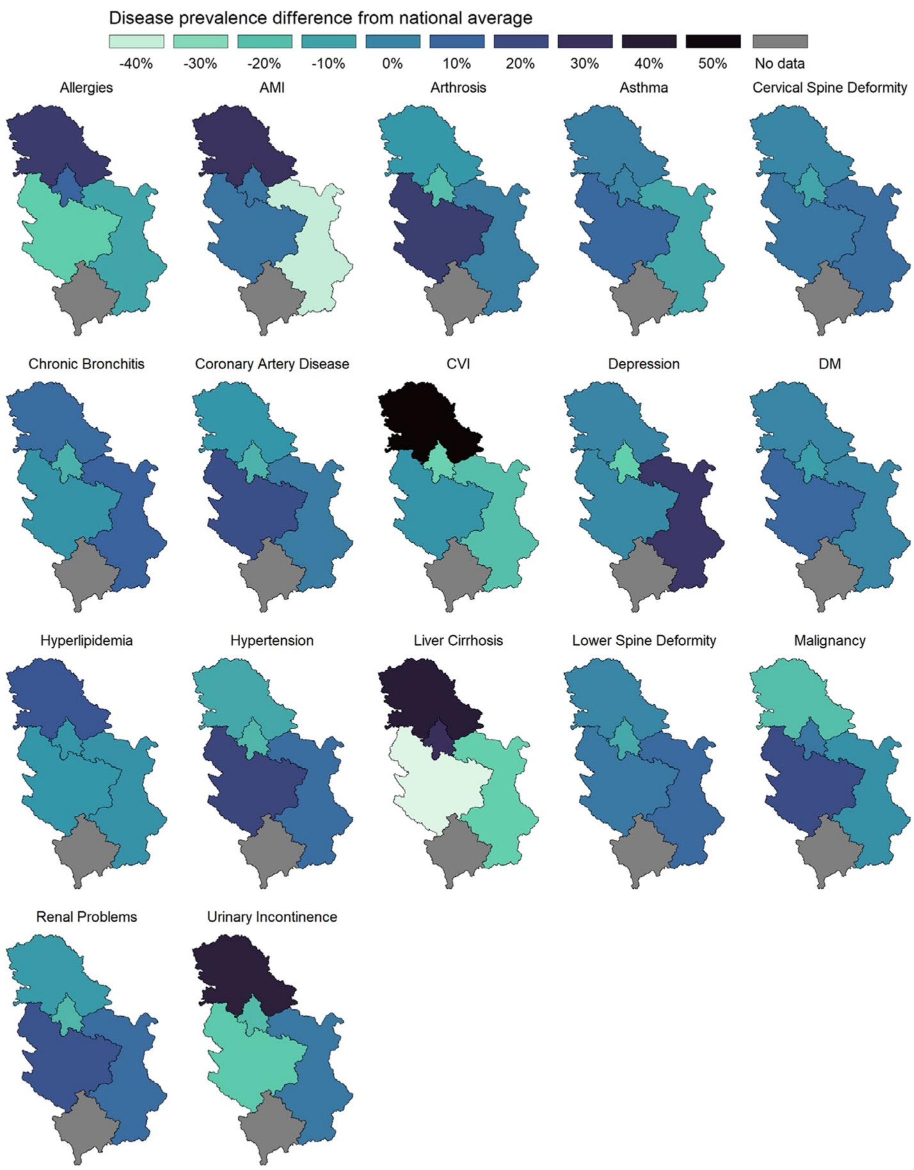

Fig. 2 The distribution of relative disease prevalence among the sampled statistical regions of the Republic of Serbia. Shaded regions represent differences from national average given in percent

have selected BIC as the primary criterion and the six-class model was finally chosen over the others. Figure 3 presents latent class models and chronic conditions assigned to each class model. The entropy of LCA indicated a satisfactory model (0.78).

Six latent classes of multimorbidity identified using the LCA were: Healthy ($n=7581$), Multicondition ($n=588$), Cardiovascular ($n=200$), Metabolic syndrome ($n=2821$), Respiratory ($n=275$) and Musculoskeletal ($n=1701$). The latent model class labelled as "Healthy" was composed of participants with a substantially lower prevalence of all chronic diseases. The "Multicondition" latent model class was complex multimorbidity state, comprising those with high probabilities of almost all chronic conditions. "Cardiovascular" model class had high membership probability of coronary artery disease or angina pectoris, hypertension and myocardial infarction or chronic consequences of myocardial infarction, diabetes mellitus and hyperlipidemia. The latent model class labelled as "Metabolic syndrome" was populated by those with high probability of hypertension, diabetes mellitus and hyperlipidemia, the "Respiratory" class by those with high probability of asthma (including allergic asthma), chronic bronchitis, COPD (Chronic obstructive

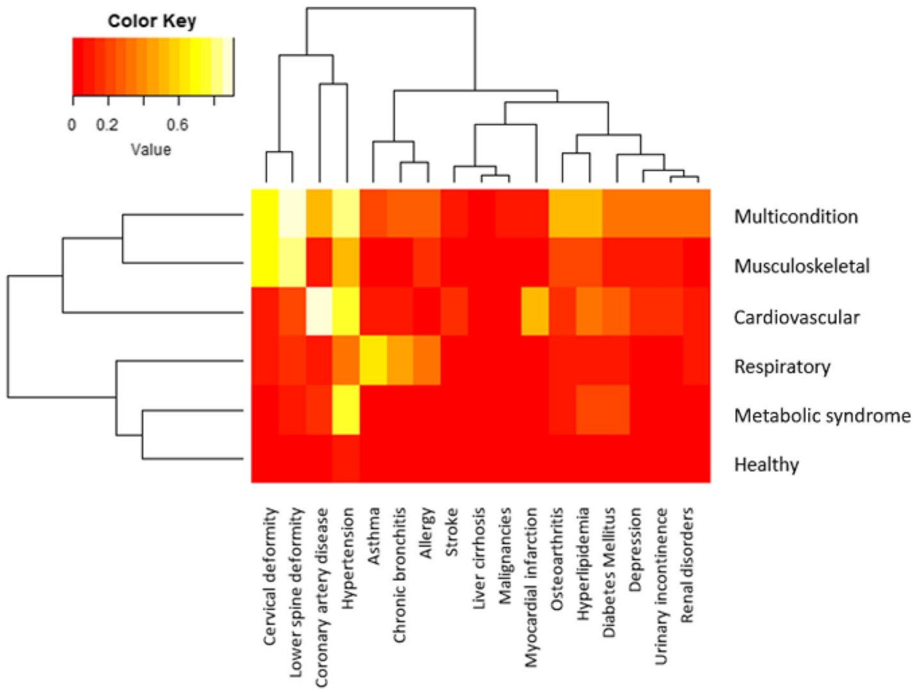

Fig. 3 Heatmap of latent class models. A clustered heatmap displays the posterior probabilities from the latent class model. Columns represent individual disease observations, and rows correspond to the latent classes. The heatmap colors reflect the probability that a subject belongs to a given latent class, with warmer colors indicating higher probabilities. Appended dendrograms to the left and top of the heatmap illustrate the hierarchical clustering of categories based on their class membership probabilities. The dendrogram branches indicate the relative similarity between subjects, with shorter branch lengths representing closer groupings

pulmonary disease), and emphysema, hypertension and allergies, whereas the "Musculoskeletal" latent class model included those with high probability of lower spine deformity or other chronic back problem (back pain), cervical deformity or other chronic problem with the cervical spine and hypertension. Item response probabilities that allow assessing the distinctness of the identified six latent classes are presented in Additional file 9. For graphical representations, a heatmap and dendrogram were built for visualization of distances and latent class models (Fig. 3). The probability of multimorbidity cluster membership as a function of age is presented in Additional file 10.

Association of air pollutant concentrations and water quality indicators with multimorbidity

The findings indicate that increase of PM10, SO2, and O3 concentrations significantly increases the odds of having multimorbidity. Specifically, the population-averaged marginal odds ratio for PM10 was 1.02 (95% CI [1.02–1.03]). Similarly, a marginal increase in SO2 was associated with a population-averaged odds ratio of 1.01 (95% CI [1.00–1.02]). Lastly, O3 exposure was linked to an odds ratio of 1.03 (95% CI [1.02–1.03]). A significant negative correlation was found between O3 and NO2 concentrations (r = -0.108; $p < 0.001$). These results underscore the compounding effect of air pollutants on the odds of having multimorbidity. In addition to relative odds estimates, Fig. 4. presents marginal estimates of absolute risks, illustrating average increases in the probability of multimorbidity presence as indicated by the y-axis label. All marginal estimates are covariate-adjusted (age, sex, income, education).

The study further explored the impact of physicochemical and microbial water contamination on the probability of having multimorbidity. A pattern of increased risk was observed with rising levels of water contamination. Individuals in areas with satisfactory water quality served as a baseline. Exposure to physico-chemical contamination was associated with a 1.18 (95% CI [1.03–1.24]) increase in the odds ratio of multimorbidity presence, microbiological contamination exposure resulted in a 1.18 (95% CI [1.07–1.29]) increase in the odds of multimorbidity, and combined contamination levels corresponded to 1.19 higher odds of having multiple chronic conditions (95% CI [1.08–1.31]). In addition to relative odds ratio estimates, Fig. 5 presents marginal estimates of absolute risks, illustrating average increases in the probability

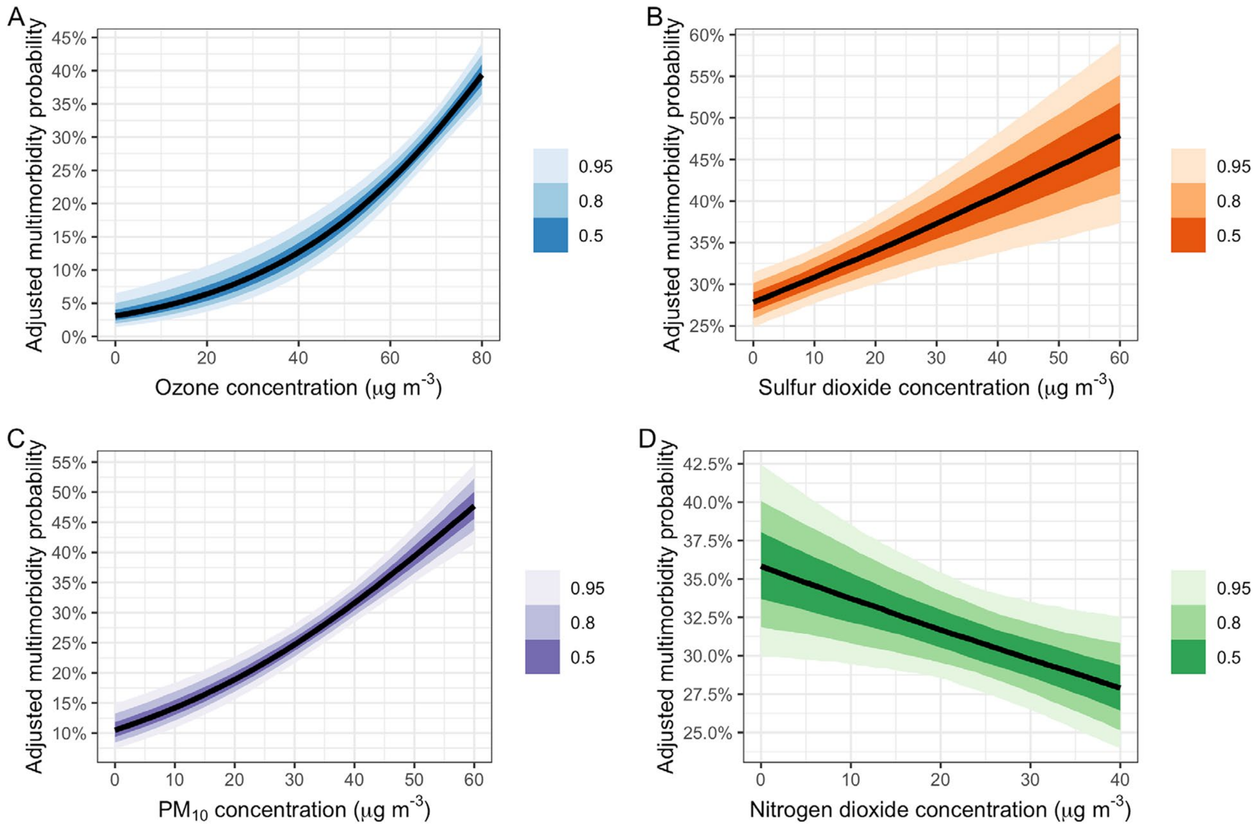

Fig. 4 Association between ambient air pollutants (ozone, sulfur dioxide, nitrogen dioxide and PM10) and increasing probability of multimorbidity. All marginal estimates are covariate-adjusted (age, sex, income, education)

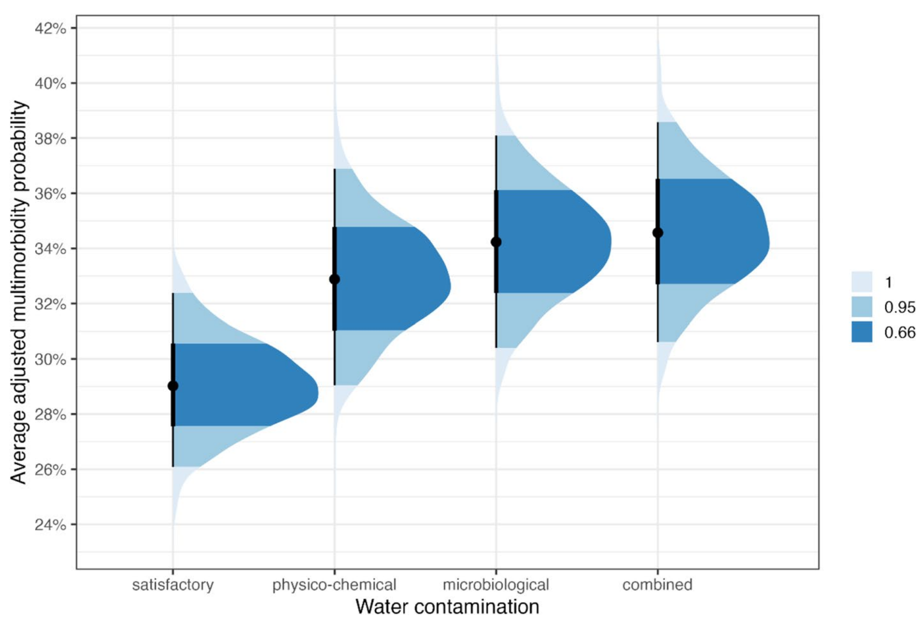

Fig. 5 Average adjusted posterior distributions of multimorbidity probability by chemical and microbial contamination. Water contamination (chemical and microbial) increases the expected probability of multimorbidity. Shaded areas represent conventional credible intervals. All marginal estimates are covariate-adjusted (age, sex, income, education)

of multimorbidity presence as indicated by the y-axis label. All marginal estimates are covariate-adjusted (age, sex, income, education).

Association of air pollutant concentrations and water quality indicators with clusters of multimorbidity

The findings demonstrate that increase of SO2, PM10 and O3 concentrations significantly increases the odds of having Multicondition (OR: 1.02, 1.02 and 1.08, respectively) and Musculoskeletal (OR: 1.01, 1.02 and 1.08, respectively) clusters of multimorbidity. Exposure to the increased levels of SO2 significantly rises the odds of having Respiratory cluster (OR: 1.02), while the increase of PM10 and O3 concentrations rises the odds of having Metabolic syndrome cluster (OR: 1.00 and 1.01, respectively) (Table 2). The reverse relationship between NO2 levels and presence of Multicondition (OR: 0.97) and Musculoskeletal (OR: 0.98) cluster was reported.

Physico-chemical contamination of water significantly increases the odds of having Multicondition (OR: 1.81), Musculoskeletal (OR: 1.39) and Cardiovascular cluster (OR: 1.99) of multimorbidity. Exposure to the microbiological water contamination significantly increased the odds of having Multicondition (OR: 2.05), Musculoskeletal (OR: 1.57), Cardiovascular (OR: 1.78), Respiratory (OR: 1.54) and Metabolic syndrome cluster (OR: 1.23), while combined water contamination significantly rises the odds of having Multicondition (OR: 1.84) and Cardiovascular (OR: 1.99) clusters of multimorbidity (Table 2).

Discussion

The results of this study demonstrated that more than one-third of the general population in Serbia was classified as having multimorbidity. The study also identified six latent classes of multimorbidity through LCA: Healthy, Multicondition, Cardiovascular, Metabolic syndrome, Respiratory and Musculoskeletal. Furthermore, the presence of various air pollutants, along with chemical and microbial water contamination indicators, provides compelling evidence of their substantial influence on the odds of having multimorbidity.

The appropriate method of identifying and analyzing clusters of diseases represents an on-going debate among the scientific community. This has led to an incomplete and fragmented insight into the nature of multimorbidity and its impact on individuals, communities, and

Table 2 Association of air pollutant concentrations and water quality indicators with clusters of multimorbidity

	Multicondition			**Musculoskeletal**			**Cardiovascular**		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Air pollutants									
SO2	1.02	1.01, 1.03	**0.003**	1.01	1.00, 1.02	**0.024**	0.99	0.97, 1.02	0.638
PM10	1.02	1.01, 1.04	**< 0.001**	1.02	1.01, 1.03	**< 0.001**	1.01	0.99, 1.03	0.407
O3	1.08	1.06, 1.11	**< 0.001**	1.08	1.07, 1.09	**< 0.001**	1.03	1.00, 1.06	0.069
NO2	0.97	0.95, 0.98	**< 0.001**	0.98	0.97, 0.99	**< 0.001**	1.00	0.97, 1.03	0.990
Water quality									
Satisfactory	ref								
Physico-chemical contamination	1.81	1.30, 2.52	**< 0.001**	1.39	1.11, 1.73	**0.004**	1.99	1.14, 3.45	**0.015**
Microbiological contamination	2.05	1.54, 2.72	**< 0.001**	1.57	1.31, 1.88	**< 0.001**	1.78	1.12, 2.83	**0.015**
Combined contamination	1.84	1.40, 2.41	**< 0.001**	1.17	0.98, 1.40	0.081	1.99	1.31, 3.02	**0.001**
	Respiratory			**Metabolic syndrome**					
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***			
Air pollutants									
SO2	1.02	1.00, 1.03	**0.040**	1.00	0.99, 1.01	0.499			
PM10	1.01	0.99, 1.02	0.456	1.01	1.00, 1.01	**0.050**			
O3	1.01	0.99, 1.04	0.334	1.02	1.01, 1.03	**0.002**			
NO2	1.00	0.98, 1.02	0.958	0.99	0.98, 1.00	0.058			
Water quality									
Satisfactory	ref								
Physico-chemical contamination	1.14	0.71, 1.85	0.584	1.16	0.94, 1.42	0.163			
Microbiological contamination	1.54	1.08, 2.21	**0.017**	1.23	1.06, 1.44	**0.008**			
Combined contamination	1.12	0.78, 1.60	0.543	1.04	0.90, 1.21	0.572			

OR Odds Ratio, *CI* Confidence Interval

reference group for odds ratio calculations was Healthy cluster ($n = 7581$)

health care services [10]. Additionally, issues arise when comparing the methodologies used in different research, where some rely on clinical records and others on self-report; some mention only a small number of conditions, while others provide extensive lists of diseases. Several multi-country systematic reviews were conducted in order to gather information on the prevailing clusters of conditions, where a significant amount of research has focused on clusters consisting of just two conditions. These studies have identified depression, cardiometabolic, and musculoskeletal disorders as the most prevalent components of multimorbidity clusters worldwide. However, it is important to acknowledge that the available evidence suggests that the occurrence of certain combinations of conditions is probably greatly influenced by the specific environment and population in which the research is conducted [6, 37, 38]. However, very few of the published studies used different approaches to compare methods and identify differences in results, consequently increasing the reliability of their findings [10, 39]. Systematic reviews found that hierarchical clustering and factor analysis were the most common methods. LCA, an approach that classifies individuals using a probabilistic model based on the observed values of all included variables, on the other hand, was used only in a few studies [6–8, 40]. Olaya et al. conducted a study to describe the patterns of multimorbidity in a representative sample of Spanish adults using the LCA method [41]. Based on the presence or absence of 11 chronic conditions, this study found three clinically and statistically distinct latent classes of multimorbidity: the "cardiorespiratory/mental/arthritis" class, the "healthy" class, and the "metabolic/stroke" class. In a cross-sectional study on a sample of 4,574 senior Australians, Islam et al. [10] identified four clusters of diseases: "healthy" individuals, "asthma/bronchitis/arthritis/osteoporosis/depression and anxiety", "high blood pressure (HBP)/diabetes", and "cancer", with stroke and heart disease either creating a separate group or "attaching" to other groups in different analyses. Moreover, the Australian study sample revealed that HBP and arthritis were the two predominant chronic diseases in both multimorbid triplets and comorbid pairs. Park et al. [42] found three groups of multimorbidity patterns in the general South Korean population. The first group was mostly healthy, the second group had heart and blood vessel diseases like dyslipidemia, hypertension, diabetes mellitus, and stroke, and the third group had asthma, arthritis, allergic rhinitis, thyroid disease, and depression. Whitson et al.'s study [43], which included Americans aged 65 + years, identified six latent classes, similar to our study results. Classes were determined based on 13 conditions, and participants were assigned to classes based on the highest calculated probability of membership to: "minimal disease", "non-vascular", "vascular", "cardio-stroke-cancer", "major neurologic disease", and "very sick" class. Multimorbidity clusters in our study were based on 17 chronic conditions which were classified in following clusters: Healthy, Multicondition, Cardiovascular, Metabolic syndrome, Respiratory and Musculoskeletal.

Evidence indicates that a low level of education and living in a deprived area are associated with an increased probability of multimorbidity [44]. The systematic review and meta-analysis of 24 studies indicated that a low education level, compared to a high education level, was linked to a 64% higher likelihood of multimorbidity, with considerable heterogeneity among studies, partially attributable to the methods used for multimorbidity assessment. Rising deprivation was consistently linked to a increasing risk of multimorbidity, while the evidence regarding income was inconclusive [44]. In our study, secondary education mitigated most of the odds, indicating that early educational interventions might be particularly effective in reducing the likelihood of developing multiple chronic conditions. The income analysis reveals a pattern illustrating a consistent step-wise reduction in the odds of multimorbidity with each higher income quintile. Increases in income further lower multimorbidity odds for each level of attained education in our study.

Environmental pollutants, such as those affecting air and water quality, increase the risk of chronic conditions [45–47], and may contribute to the accumulation of chronic diseases, leading to multimorbidity. A new cross-sectional study looking at links between air pollution and multimorbidity in the UK Biobank found that long-term exposure to NO2 and PM2.5 pollutants was linked to higher rates of multimorbidity, the severity of multimorbid conditions, and the most of multimorbidity clusters [48]. Results on over 360,000 adults from the UK Biobank revealed that exposure to higher levels of NO2 and PM2.5 was associated with nine and ten patterns of multimorbidity, respectively, out of 11 identified patterns. The strongest associations were observed for respiratory, cardiovascular, and neurological multimorbidity and both NO2 and PM2.5 pollutants. Ronaldson et al. [48] used fully adjusted logistic regressions to assess the relationship between air pollution and multimorbidity patterns, finding a link between higher exposures to PM10 pollutants and multimorbidity pattern consisting of painful conditions. These results indicate that the chance of having a multimorbid condition increases with higher exposure to air pollution, therefore implying that air pollution could affect multiple body systems. In our study, higher levels of PM10 were significantly associated with higher multimorbidity odds in a representative sample of the Serbian population (OR: 1.02 (95% CI

[1.02–1.03]). In particular, the increase of PM10 concentrations significantly increased the odds of having Multicondition and Musculoskeletal clusters (OR: 1.02 and 1.02, respectively).

The results of a recently conducted study by Luo et al. [49] showed a relationship between cardiometabolic multimorbidity and air pollution. This large prospective cohort study, which included 410,494 middle- and old-age participants from the UK Biobank, showed that exposure to air pollution was associated with a higher risk of almost all phases of cardiometabolic multimorbidity progression, which included the development of first cardiometabolic disease, transition from first cardiometabolic disease to cardiometabolic multimorbidity, and death from baseline and first cardiometabolic disease [49]. Our study results demonstrated that higher concentrations of PM10 particles and O3 increased the odds of having Metabolic syndrome cluster of multimorbidity (OR: 1.01 and 1.02, respectively).

Recently, Su et al. [50] used a nationally representative sample of all Chinese people over 60 years old to study how long-term exposure to PM2.5 and O3 affects cardiovascular and metabolic diseases. According to Su et al. [50], being exposed to PM2.5 steadily raised the risk of cardiometabolic diseases and various cardiometabolic multimorbidity clusters. They also found that the O3 air pollutant became a major risk factor for cardiometabolic multimorbidity after a certain dose. Additionally, the study found a significant positive correlation between the prevalence of diabetes, hypertension, and cardio-cerebrovascular diseases, as well as the prevalence of different subtypes of cardiometabolic multimorbidity, and PM2.5 concentrations. It was found that for every 10 units increase in PM2.5 levels, there was a 2.2% higher risk of diabetes and high blood pressure, a 5.4% higher risk of cardiovascular diseases and high blood pressure, a 5.6% higher risk of cardiovascular diseases and diabetes, and a 7.6% higher risk of diabetes, hypertension, and cerebrovascular diseases. Although there wasn't a strong overall link between long-term exposure to the O3 pollutant and different groups of cardiometabolic multimorbidity. Su et al. [50] found that the risk of cardiovascular diseases, diabetes, and all types of cardiometabolic multimorbidity was significantly higher in the group that was exposed to high levels of O3 (88–99.5 μg/m3). In addition to Su et al.'s [50] findings, our study revealed a statistically significant relationship between O3 air pollutants and multimorbidity, with higher O3 concentrations significantly associated with higher multimorbidity odds in a representative sample of the Serbian population (OR: 1.03 (95% CI [1.02–1.03]). The studies conducted by Luo et al. [49] and Su et al. [50] did not consider the effects of other pollutants, such as carbon monoxide and sulfur dioxide, despite long follow-up periods and large sample sizes that allowed the establishment of a causal association between multimorbidity and air pollution exposure. Our study measured the concentrations of both carbon monoxide and sulfur dioxide, and confirmed the relationship between sulfur dioxide and multimorbidity (OR: 1.01 (95% CI [1.00–1.02]). In particular, exposure to the increased levels of SO2 significantly rises the odds of having Multicondition (OR: 1.02), Musculoskeletal (OR: 1.01) and Respiratory cluster (OR: 1.02).

A special emphasis should be placed on the results of our study providing evidence of association between ground level ozone and multimorbidity. Ozone pollution is a global health hazard with increasing concentrations and a growing disease burden. The disease burden is expected to continue due to the rising concentrations and improved understanding of ozone effects beyond the lung [51]. However, ascertaining chronic ozone exposure remains inconclusive, and co-exposure to other air pollutants like PM2.5 and PM10 makes it challenging to examine chronic effects. Future studies should incorporate advanced technologies to monitor and compute ozone exposures [51]. Control policies are needed, especially in developing countries where PM2.5 and PM10 reductions are primarily focused. In our study, a clear relationship between O3 exposure and multimorbidity was found (OR: 1.03 (95% CI [1.02–1.03]), particularly with Multicondition (OR:1.08), Musculoskeletal (OR:1.08) and Metabolic syndrome cluster (OR:1.02). A significant negative correlation that was found between O3 and NO2 concentrations ($p < 0.001$) is consistent with previous literature findings [52].

In addition to clean air, access to safe drinking water is crucial for health and further society development, as inadequate water and sanitation services expose individuals to health risks. Poor water management in urban, industrial, and agricultural areas leads to contaminated drinking water, affecting millions of people. Poor drinking water quality is the leading cause of morbidity and mortality in developing countries, emphasizing the importance of clean drinking water [22]. Based on the survey conducted by the World Health Organization (WHO), 80% of global diseases and 50% of child mortality worldwide can be attributed to inadequate drinking water quality. Additionally, there are over 50 diseases that are directly caused by poor drinking water quality. Unfortunately, despite the fact that much of the literature focuses on water pollution and a specific disease, there is a lack of research findings that systematically examine the impact of water pollution on human health and disease heterogeneity. Our study findings that a pattern of increased risk correlates with escalating contamination of water further support these findings. Exposure to physico-chemical contamination, microbiological and combined contamination was associated with a 3.92%, 5.17% and 5.54% higher probability of having multimorbidity. Especially, physico-chemical contamination increased the odds of having Multicondition (OR: 1.81), Musculoskeletal (OR: 1.39) and Cardiovascular cluster (OR: 1.99), while exposure to the microbiological contamination increased the odds of having Multicondition (OR: 2.05), Musculoskeletal (OR: 1.57), Cardiovascular (OR: 1.78), Respiratory (OR: 1.54) and Metabolic syndrome cluster (OR: 1.23). Combined water contamination rose the odds of having Multicondition (OR: 1.84) and Cardiovascular (OR: 1.99) clusters.

Recommendations

To promote equity in health and healthcare, it is vital to ensure that both healthcare providers and the public are aware of the prevalence and interconnections of multimorbidity, including the impacts of various health conditions, demographic factors, and environmental influences. Effective strategies may vary by geographical region, as solutions that are successful in one area may not be suitable for another due to differing regional priorities and needs [53]. Therefore, countries should leverage localized data to pinpoint specific focus areas at national or regional levels. This can be accomplished by gathering input from patients and professionals, analyzing local health statistics, and reviewing relevant literature in relation to local conditions.

To improve healthcare management for individuals with multiple conditions, several key actions should be considered [53]: implementing policy changes, adopting a systematic approach, identifying individuals who need additional support, prioritizing care coordination and self-management support, and simplifying treatment regimes. In Serbia, for instance, enhancing primary care within the framework of national healthcare coverage is crucial. Primary care providers should be trained as "expert generalists" and adopt a patient-centered approach tailored to those with multiple conditions. This involves integrating postgraduate training that covers multimorbidity concepts into both undergraduate medical education and ongoing healthcare training programs.

A systematic approach should improve communication and coordination across different healthcare levels and sectors, including primary, secondary, and tertiary care, as well as integrating health and social care. Guidelines should focus on managing multiple rather than single conditions. Care coordination should employ integrated electronic medical systems to identify individuals requiring additional support, while also promoting self-management strategies to empower patients in taking charge of their health. Simplifying treatment regimes and ensuring patient understanding of their treatments will enhance management of chronic diseases. Accepting multimorbidity as a typical rather than exceptional condition will facilitate the development of effective healthcare delivery for patients with multiple chronic conditions.

Strengths and limitations

The strength of our study lies in its ecological design utilizing a large nationally representative sample employing a wide age range of study participants (15 years and older). Ecological studies are commonly used to measure prevalence of diseases; they are easy to conduct using a routinely collected data, and may generate hypothesis on the relationship between environmental factors and health outcomes. In addition, the inclusion of additional chronic conditions such as lower spine deformity and other chronic back problems (i.e., back pain), as well as cervical deformity and other chronic problems with the cervical spine, enabled us to identify patterns of multimorbidity beyond those previously published. Obtained model for multimorbidity probabilities is accurate and suitable for interpretation. The model's ability to correctly assign risk probabilities was assessed using the CORP approach suggested by Dimitriadis et al. [36]. Model-assigned values are then compared to empirically observed rates at automatically calculated optimal intervals to ensure the developed model is reliably assigned multimorbidity risk probabilities. Consequently, both overestimation and underestimation were assessed. However, when interpreting our findings, it is important to take into account some limitations. The limitations of ecological study design include presence of a bias and the lack of adjustment for major confounders such as smoking habits and the inability to infer causality. In addition, the observed weak correlations between the cardiovascular and respiratory clusters and most air pollutants may be attributed to the limited number of individuals who have only one condition within these clusters, and a substantial number of participants with cardiovascular and respiratory diseases classified within the Multicondition and Metabolic syndrome clusters. Furthermore, the used EHIS survey protocol incorporates a restricted selection of chronic conditions, chosen for their significant prevalence and consequential influence on health outcomes. Therefore, our study did not assess certain diseases (e.g., infectious diseases, thyroid disease, cataracts), and the inclusion of supplementary chronic conditions could potentially lead to distinct patterns. Lastly, the identification of chronic diseases in our study relied on self-reported data, which introduces the possibility of inaccuracies. However, previous large-scale population-based studies have extensively employed self-reported measures of chronic diseases, demonstrating a satisfactory level of accuracy, as evidenced by existing literature [54, 55].

Future directions

The complex interaction between specific pollutants and multimorbidity requires large pools of heterogeneous data. Real-time data that combines air and water pollution-related figures and health records (admissions, exacerbations) can aid in identifying the public health impact of air pollution on a national, municipal, or local level. More importantly, real-time data would be critical for designing effective interventions that are specific to the population affected by the specific pollutants. In the absence of clear real-time evidence, comprehensive studies exploring the long-term effect of environmental pollutants on disease accumulation would be essential to reducing the burden of multimorbidity.

Conclusion

The global burden of disease has increased over the past decades due to demographic aging and increased exposure to environmental pollutants. Our study revealed a clear relationship between multimorbidity and its clusters with pollution exposure, indicating that exposure to air pollutants and contaminated water may lead to disease accumulation. These findings underscore the critical need for comprehensive research that incorporates measurements of both multimorbidity and pollution. Such studies are essential to reveal their complex interrelationship, thereby aiding environmental and healthcare policymakers in implementing preventative strategies to mitigate harmful environmental pollutant levels and alleviate the global burden of multimorbidity. Tackling multimorbidity and its relationship with environmental pollution should be one of the most important challenges for health systems globally and nationally.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-024-01133-8.

Additional file 1: Measurement of the levels of PM10 particles, sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), and ozone (O3) in the air for 2019.

Additional file 2: The air pollutant concentration averaging periods and their limits in the Regulation on conditions for monitoring and air quality requirements.

Additional file 3: The measured air pollutant concentration range for 2019.

Additional file 4: The multiple directed acyclic graphs (DAG).

Additional file 5: Markov Chain Monte Carlo (MCMC) Trace Plots for Selected Model Parameters.

Additional file 6: CORP model calibration curve.

Additional file 7: Average adjusted posterior distributions of multimorbidity by educational attainment and income quintiles.

Additional file 8: A comparison of fit statistics for models with different numbers of classes.

Additional file 9: Item response probabilities that allow assessing the distinctness of the identified six latent classes.

Additional file 10: The probability of multimorbidity cluster membership as a function of age.

Acknowledgements
Not applicable.

Authors' contributions
All authors made substantial contribution to the conception and design of the work and participated in the data acquisition, analysis and interpretation. NR, NG, OM, MN were responsible for data visualization. AM, EG, DM and NM have done project administration. All authors were involved in developing the first draft of the manuscript and take part in critical revision of the paper. All authors approved the final version of the manuscript.

Funding
This research was funded by the UKRI Global Challenges Research Fund (Project Reference No: 164294), and Ministry of Science, Innovation and Technological Development of the Republic of Serbia (Grant No. 200110 and 200007). The data from the European Health Interview Survey (EHIS) was provided by the Institute of Public Health of Serbia "Dr Milan Jovanović Batut". The work was supported by the Ministry of Health, Republic of Serbia and World Health Organization, Country Office Serbia.

Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Institute of Public Health of Serbia (date: 10.06.2021; n° 3607/1). Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 11 July 2024 Accepted: 15 October 2024
Published online: 14 November 2024

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