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Urban Air Pollution Associated with the Incidence of Autoimmune Thyroid Diseases

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ABSTRACT

Background: Endocrine disrupting air pollutants such as sulphur dioxide (SO₂), carbon monoxide (CO), nitrogen dioxide (NO₂), fine particle matter (PM_{2.5}), and ozone (O₃) can affect thyroid gland function on the level of synthesis, metabolism, and the action of its hormones. **Objective:** The aim of this study was to establish whether increased air pollution could contribute to an increased incidence of autoimmune thyroid diseases (AITD). **Methods:** A retrospective analysis was conducted of the medical records of 82000 patients at the University Clinical Centre in Tuzla, Bosnia and Herzegovina. The target group of this study comprised a total of 174 patients from the Lukavac area. Daily data on concentrations of air pollutants were collected from the air quality monitoring station located in Lukavac. The study covered the period from 2015 to 2020. **Results:** The results of the monitoring confirmed the presence of air pollutants in concentrations above the permitted limits throughout the entire observed period. Concentrations of PM_{2.5}, SO₂, NO₂, CO, and O₃ were in the range of 1.90–431.40 µg/m³, 3.60–620.50 µg/m³, 3.40–66.20 µg/m³, 48.00–7002.00 µg/m³, and 0.70–89.40 µg/m³, with means of 64.08 µg/m³, 77.48 µg/m³, 22.57 µg/m³, 1657.15 µg/m³, and 31.49 µg/m³, respectively. During the six-year period, 174 cases of AITD were registered, of which 150 (86.21%) were women and 24 (13.79%) men. Hashimoto's thyroiditis was found in 33 patients (18.97%), whilst 141 patients (81.03%) were diagnosed with atrophic thyroiditis. The highest total incidence of autoimmune thyroiditis was recorded in 2017, when it reached 99.49, 95% CI. **Conclusion:** The effects of chronic exposure to a mixture of air pollutants on the function of the thyroid gland are still not sufficiently well-known, but the numerical tendency towards a higher incidence of AITD in this study, albeit without statistical significance (p>0.05), still underlines the need for additional research.

Keywords: autoimmune thyroiditis, air pollutants, endocrine disruptors, incidence.

1. BACKGROUND

Environmental pollutants disrupt the function of the thyroid gland through several mechanisms, including the synthesis, metabolism, secretion and action of thyroid hormones (1-4). Most of them reduce the level of circulating thyroid hormones or disrupt their action, although some may also affect the pituitary gland and thyroid stimulating hormone (TSH), and even partially be an agonist of thyroid hormone receptors. In addition, many environmental agents disrupt the absorption of iodine, which is essential for the biosynthesis of thyroid hormones. The usual model for the onset of autoimmune thyroid disease (AITD) includes basic genetic predisposition and triggers, which launch a cascade of events and maintain the process, culminating in hypo-function or hyper-function of the thyroid (5). There are a large number of factors relating to the subject and living environment which contribute to the development of AITD (6-9). The most important of these are stress, iodine intake, smoking, drugs, radiation, and air pollution.

The air pollutants with the most public health significance include carbon monoxide (CO), sulphur dioxide (SO₂), nitrogen dioxide (NO₂), ozone (O₃), and fine particle matter (PM_{2.5}). The consequences for health of exposure to the complex mixture of these air pollutants primarily include the occurrence of irritation, disturbance of the sense of smell, respiratory, cardio-vascular or autoimmune disease, and carcinomas (10-15). On the other hand, the endocrine disruptive effect of air pollutants has still not been sufficiently researched (6-9). An understanding of the connection between air pollutants

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and risk of AITD has particularly important implications for public health and disease prevention. Existing studies have focused on evaluating the connection between air pollutants and thyroid dysfunction, however, with relatively limited number of samples (6-9).

The quantitative assessment of the health effects of air pollution and its correlation with epidemiological data has become very important around the world, especially in developing countries. Bosnia and Herzegovina (B&H), primarily its industrial north-eastern region, is continually affected by air pollution, but also a large number of patients with AITD (16-18).

2. OBJECTIVE

Therefore, this study was designed to obtain information on the possible influence of exposure to mixtures of air pollutants with the number of new patients suffering from AITD in the period from 2015 to 2020.

3. MATERIALS AND METHODS

Field of research

The town of Lukavac (44°33'1" N, 18°31'54"E) is an inhabited industrial town in north-eastern B&H, with a total area of 337 km². According to the census of 2013, the town of Lukavac had a population of 44,520 inhabitants. The area is characterised by frequent excessive air pollution, especially during the winter. In 2018 it was included on the list of the most polluted towns in Europe with PM_{2.5} for 2018 at an annual average of 55.6 µg/m³ (19). Air pollution with NO₂, SO₂, O₃, CO, PM_{2.5}, and PM₁₀ particles is mostly the result of local industry (the thermal power plant, soda industry, cement, and coke industries) as well as households using coal for heating.

Study population

A retrospective analysis was conducted of the medical records of 82000 patients at the Thyroid Diseases Department of the Radiology and Nuclear Medicine Clinic, of the University Clinical Centre (UCC) in Tuzla, B&H. The inclusion/exclusion criteria in the study were the same as in our previous study (17). People included in the study were patients older than 14 years, of both gender, with all forms of clearly defined AITD, living in the area of Lukavac, and in whom the disorder was diagnosed in the period from January 2015 to December 2020. The target group of this study comprised a total of 174 patients. The Ethics Committee of the UCC approved the study.

Diagnosis of AITD

For making a diagnosis and classification of the disorder we used the electrochemiluminescence method (ELCIA) (Elecsys Cobas 411 (Rosche Diagnostics, Mannheim, Germany) which determined the serum level of thyroid and pituitary hormones, and antibodies. According to the protocol already described (17), and in line with the WHO guidelines, in order to confirm the diagnosis, palpitation and visual examination of the thyroid were also applied.

Exposure to air pollutants

In the Tuzla Canton (TC) since 2003 continuous air quality monitoring have been made of the basic param-

eters through five stationary and one mobile air quality monitoring stations. The data are up-dated every hour on the basis of the values obtained from the Air Quality Monitoring System installed for the region of TC. The Ministry of Spatial Planning and Environment Protection is responsible for keeping the data and maintaining the system, pursuant to the current legislation (20, 21). Daily data on concentrations of SO₂, CO, NO₂, PM_{2.5}, and O₃ in the ambient air are available on the TC government's web site: <http://www.vladatk.kim.ba/izvjesta-ji-o-kvalitetu-zraka> (21). This study collected data from the stationary air quality monitoring station located in Lukavac in the period from 01.01.2015. to 31.12.2020.

Statistical analysis

In the analysis of the collected data we performed standard descriptive statistical methods and Pearson correlation analysis, using the SPSS 21 program (IBM SPSS, Chicago, Illinois, USA). Values of p<0.05 were considered to be statistically significant.

The statistical analysis of the epidemiological data was described in a previously published study (18). The incidence rates were obtained by retrospective analysis of the data collected over the six-year observed period.

4. RESULTS

The results of the monitoring confirmed the presence of all five main air pollutants, and confirmed their excessive concentrations over the entire observed period (Table 1).

Figure 1 shows the average and maximum values of the five indicators of ambient air quality in the area of Lukavac over the six-year period. The concentration of fine particle matter, less than 2.5 µm in diameter in the observed period, ranged from 1.90 to 431.40 µg/m³, with a mean value of 64.08 µg/m³. The lowest concentrations of PM_{2.5} were recorded in 2016 and 2020, and the highest concentration of PM_{2.5} was measured in 2017. According to the legislation of the Federation of B&H and the WHO guidelines, the maximum permitted limit value (MPLV) of PM_{2.5} is 25 µg/m³ (22). Figure 1a is a graph showing air pollution with PM_{2.5}. The results of monitoring show that in all the years observed, the MPLV for PM_{2.5} was exceeded.

The air quality monitoring stations in our study confirmed that the MPLV for SO₂ was also exceeded in all observed years (Figure 1b). The lowest concentration of SO₂ was recorded in 2019, when it was 3.60 µg/m³. In the winter of the following year, the highest concentration of SO₂ was recorded, almost 8 times higher than the six-year average. The maximum concentration of SO₂ in 2020 was 620.50 µg/m³, while the average concentration over the observed period i was 77.48 µg/m³. Table 1 shows that the average annual concentration of SO₂ in the ambient air in the area of Lukavac exceeded the MPLV prescribed by B&H legislation in each of the years observed.

The concentration of NO₂ in our research ranged from 3.40-66.20 µg/m³. The minimum and maximum concentrations of NO₂ were recorded in 2016. The six-year average concentration of NO₂ in Lukavac (22.57 µg/m³)

Air pollutant	Year	Mean	SD	Min	Max	MPLV's WHO limit	MPLV's B&H regulation
PM _{2.5} (µg/m ³)	2015	118.11	119.35	6.20	430.50	25	25
	2016	69.46	88.92	1.90	381.40		
	2017	67.57	95.19	4.00	431.40		
	2018	62.31	67.40	4.40	272.10		
	2019	46.16	47.7	3.30	191.80		
	2020	47.83	51.15	1.90	225.20		
SO ₂ (µg/m ³)	2015	110.64	122.19	3.90	433.70	80	50
	2016	61.30	51.20	11.50	252.60		
	2017	101.05	105.21	11.80	508.10		
	2018	68.56	47.90	8.10	195.50		
	2019	56.64	42.70	3.60	162.00		
	2020	77.89	106.15	8.30	620.50		
NO ₂ (µg/m ³)	2015	23.33	13.82	4.90	47.80	20	40
	2016	18.22	12.85	3.40	66.20		
	2017	24.60	12.81	10.00	60.60		
	2018	23.78	14.78	3.60	62.50		
	2019	23.47	11.07	9.50	53.80		
	2020	22.91	10.65	9.80	48.20		
CO (µg/m ³)	2015	2057.33	1368.34	294.00	4758.00	2500	3000
	2016	1448.18	1094.21	322.00	5177.00		
	2017	1207.83	1539.20	48.00	7002.00		
	2018	1014.99	1172.93	99.00	5056.00		
	2019	2462.50	1713.16	263.00	5070.00		
	2020	2550.92	865.89	1809.00	5269.00		
O ₃ (µg/m ³)	2015	14.69	10.46	3.90	40.50	-	-
	2016	23.85	14.38	0.90	54.50		
	2017	38.17	22.05	6.80	80.00		
	2018	26.96	17.43	4.70	61.20		
	2019	37.81	25.14	1.50	89.40		
	2020	42.33	23.61	0.70	88.20		

Table 1. Descriptive statistical analysis of ambient air pollution in Lukavac

was above the WHO limit of 20 µg/m³, but below the local MPLV of 40 µg/m³. The highest concentration of this pollutant measured exceeded the annual limit values in all observed years (Figure 1c).

In Lukavac CO was present in concentrations which can seriously harm people's health. The concentration of CO ranged from 48.00-7002.00 µg/m³. The highest concentration of CO was recorded in 2020, when it reached 2550.92 µg/m³ and was above the WHO limit (Figure 1d). During the remaining period observed, the value of the average annual concentration did not exceed the defined limits, although the maximum concentrations detected in all the years were 1.90-2.80 time higher than the WHO limits, and 1.59-2.33 more than the MPLV prescribed by B&H legislation.

The highest concentrations of O₃ were recorded in 2019 (89.40 µg/m³) and 2020 (88.20 µg/m³), whilst the average annual concentrations were in the following or-

der: 2020>2017>2019>2018>2016>2015. A significant increase in concentrations in the air is noticeable from 2017 onwards. The annual MPLV's for O₃ in the air are not prescribed by the current Regulations, nor are the WHO limits clearly defined. However, the WHO has defined a maximum average eight-hour daily O₃ concentration of 60-100 µg/m³ which was frequently exceeded, especially in 2019 and 2020.

Table 2 shows the Pearson correlation coefficient between the pollutants. The concentration of PM_{2.5} is strongly correlated with SO₂ (r=0.568, p=0.000), NO₂ (r=0.723, p=0.000) and CO (r=0.674, p=0.000). The concentration of SO₂ also strongly correlates with CO (r=0.536, p=0.000), whilst it correlates moderately with NO₂ and O₃ (0.25≤r≤0.5). A moderate and weak correlation was recorded between NO₂ and O₃, and CO and O₃. The Pearson correlation coefficient revealed that PM_{2.5}

	SO ₂		NO ₂		CO		O ₃	
	r	p	r	p	r	p	r	p
PM _{2.5}	0.568	0.000	0.723	0.000	0.674	0.000	0.081	0.355
SO ₂			0.536	0.000	0.476	0.000	0.204	0.020
NO ₂					0.567	0.000	0.310	0.000
CO							0.197	0.030

Table 2. Pearson's correlation coefficient analysis of concentrations of air pollutants

Year	New patients			Incidence rate
	Hashimoto	Atrophic	Total	
2015	8	28	36	83.3
2016	3	13	16	37.02
2017	13	30	43	99.49
2018	5	35	40	92.55
2019	2	24	26	60.16
2020	2	11	13	30.08

Table 3. Incidence rate and number of new patients by year

and O₃ are not correlated with each other (r=0.081, p=0.355).

From 2015-2020, 164 cases of AITD were registered in Lukavac, of which 150 (86.21 %) were women and 24 (13.79 %) men. The ratio of women to men was 25:4. Hashimoto's thyroiditis was found in 33 patients (18.97 %), whilst 141 patients (81.03 %) were diagnosed with atrophic thyroiditis. The highest total incidence of autoimmune thyroiditis was recorded in 2017, when it reached 99.49, 95% CI. The incidence rate of new patients did not show linear growth, and by years it occurred in the following order: 2017>2018>2015>2019>2016>2020 (Table 3). The total incidence over the 6-year period was 67, 95% CI.

The data analysis did not show any statistically significant correlation between the number of new patients with AITD and the average concentrations of the five air pollutants observed (Table 4). However, it was not established whether there was a rise in the incidence of AITD in the years in which the highest values of air pollutants were recorded.

5. DISCUSSION

Although traditionally exposure to environmental air pollutants is related to respiratory and cardiovascular diseases, several studies have confirmed our hypothesis that breathing polluted air may lead to deterioration of AITD and thyroid function (14, 22-26). However, the patho-physiological mechanisms linking pollution of ambient air with the function of the thyroid are still unknown. It is supposed that the mechanism may be connected to a response to oxidative stress (21, 27, 28). On the other hand, there are many better described studies examining the negative effect of air pollution on the im-

munological response of respiratory mucosa where the mechanisms are clearer, and the results indicate a disturbance in oxidation-reduction homeostasis (29). Air pollutants stimulate proinflammatory immune responses in several classes of immune cells. Unhealthy air may improve the adaptive immune response of T helper lymphocytes (30). Although the manifestation of a strong immune response in the lungs is the first line of action of pollutants, the question still arises about the spread of the immune response, such as for example the possible inhibition of T suppressor cells, which are also one of the main links in genetic predisposition for AITD. In this

Thyroiditis	PM _{2.5}		SO ₂		NO ₂		CO		O ₃	
	r	p	r	p	r	p	r	p	r	p
Hashimoto's	0.30	0.56	0.61	0.20	0.47	0.34	-0.30	0.54	-0.30	0.63
Atrophic	0.24	0.64	0.50	0.31	0.57	0.23	0.47	0.35	-0.40	0.42
Total	0.39	0.58	0.59	0.22	0.60	0.21	0.25	0.64	-0.40	0.43

Table 4. Pearson's correlation analysis of concentrations of air pollutants and the number of new patients

situation, T helper cells have a great deal to do, both in the activation of B lymphocytes which create enhanced thyroid antibodies and so also interferon μ (31). On the basis of this presumption, we researched whether the polluted air in Lukavac affects the incidence of AITD.

In our study, the disease was significantly more frequent in women than in men (25:4). It has been reported that women are more sensitive to polluted air and that they have a greater chance of dying from pollution than men (32). One of the explanations may be that women more often suffer from AITD (31). Another reason is that oestrogen and progesterone may contribute to the gender disparity (33), but further studies are needed to confirm this.

The total incidence of AITD per 100,000 of the population of TC in the six-year observed period was: in women 123.74, 95% CI; in men 16.25, 95% CI, or a total of 71.25, 95% CI. The highest recorded incidence was in women in 2017 (183.93/10⁵) (17). Our results showed that the highest total incidence in Lukavac was recorded in 2017, and was 99.49, 95% CI, in which women were predominant. Although it was expected that the incidence of AITD in Lukavac would be higher due to the industrial pollution in that town, the results did not confirm this in comparison with the TC region as a whole.

As mentioned earlier, there were no previous studies giving a detailed analysis of the potential risks from air

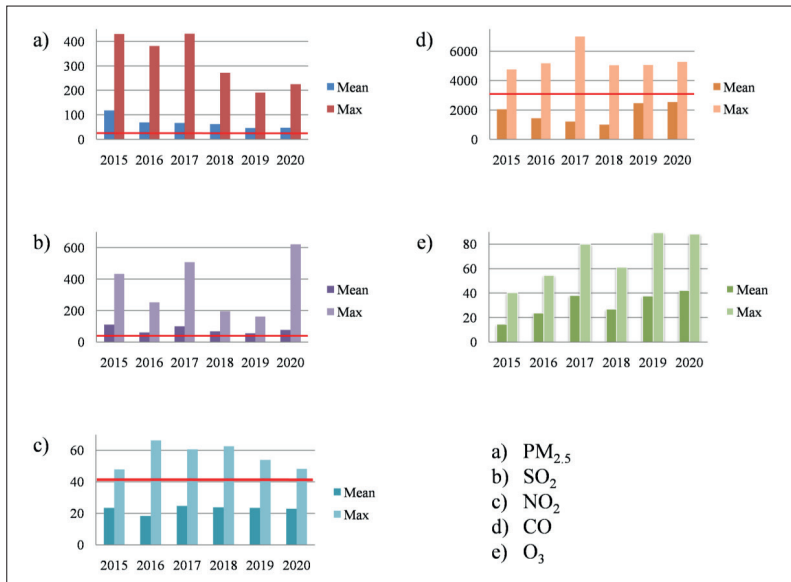


Figure 1. Mean and maximum values of pollutant concentrations (µg/m³) over the years. The red line marks the MPLVs of air pollutants according to the current legislation.

pollutants for the incidence of AITD. Our study analysed each of the 5 main air pollutants (PM_{2.5}, NO₂, SO₂, CO, and O₃) whose average concentrations were not statistically correlated with an increased risk of AITD amongst the population of the region in question (Table 4). However, the highest incidence of AITD was recorded in 2017 when the mean values of PM_{2.5}, NO₂, O₃, and SO₂ were amongst the highest in the observed period, much higher than the proposed WHO guidelines for air quality (34). Our results were partially complementary with the existing group of evidence focused on connections between air pollutants and thyroid function (14, 24, 35, 36). On the other hand, the lowest incidence of new thyroid patients was recorded in 2020, probably as a result of the smaller number of examinations at the height of the COVID-19 pandemic and not because of the state of air pollution.

There is no clearly defined no-observed adverse effect level of exposure to PM_{2.5}. However, there is an obvious dose-dependent response to exposure to high concentrations of PM_{2.5} and increased morbidity and mortality (12). Although the results of monitoring in our study show that the MPLV level was exceeded in all the years in question, there was no significant effect of the mean PM_{2.5} value on the incidence of AITD. However, the lowest values of PM_{2.5} concentrations recorded in 2016 and 2020 were accompanied by the lowest incidence of AITD, whilst the highest concentration of PM_{2.5} measured in 2017 was accompanied by the highest incidence of AITD. Earlier research reported the inverse correlation between exposure to PM_{2.5} and free thyroxine (FT4) levels in pregnant women (24). In a study from 2018, the results unambiguously show that there was no correlation between the level of thyroid-stimulating hormone (TSH) and exposure to PM_{2.5} (14). In a large sample from 5 cohort studies in Europe and the United States of America (USA), we learned that exposure to PM_{2.5} in the first trimester of pregnancy correlated with mild thy-

roid dysfunction, and that pregnant women with greater exposure to NO and PM were more likely to be positive for thyroid peroxidase antibodies (TPOAb) (37). The latest research from the USA in 2021 confirmed a correlation between increased concentrations of PM_{2.5} in polluted air and the incidence of thyroid carcinoma after 2 and 3 years of exposure (30).

Although our study records continually excessive levels of SO₂ above the WHO guidelines, it still does not show a correlation between the concentrations of this air pollutant with thyroid ailments. There was no linear growth in SO₂ concentrations over the observed period, although the concentration in 2020 was 8 times higher than the six-year average. However, although there is a limited number of studies confirming the endocrine disrupting action of SO₂ on the thyroid gland in animal studies, there is still insufficient evidence of the same effect on a human population (38, 39). In Korean research from 2020, the effect of other pollutants on serum values of thyroid hormones was noticed, but not of SO₂ (40).

Although genetic and environmental factors contribute to the aetiology of AITD, there is no reliable information about the toxic manifestations of NO₂ in the thyroid gland in humans. The results of our study also did not confirm any significant effect of NO₂ in relation to the occurrence of AITD. In the cohort study mentioned above, exposure to NO_x and NO₂ was not related to low or high levels of TSH during pregnancy, but pregnant women with higher exposure to NO and PM were more often positive for TPOAb. Consistent findings about the zero association of NO_x with thyroid function suggest that the connection between air pollutants and thyroid function mainly relate to PM (37). The pollutants monitored in Greece, PM₁₀ and NO₂, did not have a significant effect on TSH, but the same results show a positive relationship of dose response between PM_{2.5} and TSH (41).

Although the effects of CO poisoning can be seen in all organs, the heart and brain are most sensitive to tissue hypoxia caused by CO intoxication (42). However, the effects of CO poisoning also include changes in the function of endocrine organs. A national cohort study from Taiwan confirmed that exposure to CO increases the risk of developing hypothyroidism (36). Although our study does not show the effect of ambient air CO on the incidence of AITD, a study of adult Koreans shows a significant correlation between these parameters and high concentrations of TSH and low FT4. An analysis stratified by age showed the stronger effect of exposure to NO₂ and CO in older people than in younger adults. Exposure to these air pollutants correlated with concentrations of TSH and FT4 in serum in people who were overweight or obese, but not in people with normal weight (40).

Several studies indicate a correlation between exposure to O₃ and endocrine organ diseases in humans, including the pancreas, thyroid and the adrenal gland (26-28). Our research did not show any correlation between exposure to O₃ and the total incidence of AITD. Earlier studies on animals showed that the risk of lung toxicity caused by O₃ was significantly higher in hyperthyroid conditions, and suggest that lung sensitivity to damage caused by exposure to O₃ may be significantly affected by the individual's thyroid hormone status (43). On the other hand, results from an American study suggest that prenatal exposure to PM is linked with a higher concentration of TT4 in neonates, whilst prenatal exposure to NO₂, O₃ and polluted air caused by traffic was not consistently connected with TT4 concentrations in neonates (35).

Currently there is no scientific consensus on the toxic manifestations of polluted ambient air on the thyroid gland. A particular problem in interpreting the results of toxic mixtures of substances is their possible interaction in the environment, but also *in vivo* (44), whereby the final effect may be greater or less than expected (45). This may also be one of the reasons for the impossibility of drawing a final conclusion in relation to this issue.

The strong correlation between the ambient air pollutants in our study shows that these pollutants have a similar origin. Previous studies confirm that traffic, industrial activity and households contribute most to air pollution (46, 47). Bearing in mind that the area of the TC is characterized as one of the most polluted areas in Europe, it was of great interest to assess the health risk and the correlation between the resident's exposure to outdoor polluted air and the incidence of AITD.

Limitations of the study

A particular problem in studying the effect of the multi-component mixture of chemicals present in the air is the fact that the composition of ambient air has not been completely defined, and this study covered only five key air pollutants. A further problem is the impossibility of predicting their mutual interaction in the environment, but also *in vivo*. Moreover, the limitations of this study are also seen in the scarce data from the pre-industrial period when the level of air pollution in the area in question was significantly lower. The lack of epidemiological data on the number of patients with AITD in the period before 2015 also contributes to this. Therefore, this study may serve as a good starting point for further research in the field of epidemiology, environmental toxicology, health ecology, and human health risk assessment.

6. CONCLUSION

Ubiquitous environmental pollution, especially in developing countries, contributes to increased concern about its possible effect on the health of the population. The thyroid gland may be one of the targeted points of the toxic action of many environmental pollutants; however there are scarce data about the effects air pollutants may show on the level of this endocrine organ. Epidemiological research into AITD in an area with many years of high levels of air pollution, such as the area of Luka-

vac, demonstrates the responsibility of researchers to identify possible biological effects related to exposure to polluted air. The results of this study show that although there is no statistically significant effect of chronic exposure to the mixture of various pollutants in the polluted air on the function of the thyroid gland, the numerical tendency towards a higher incidence of AITD still underlines the need for further research on this topic.

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