

Lower air ozone concentration is associated with clinical remission in type 1 diabetes diagnosed in adulthood: a prospective, observational study in Wielkopolska region, Poland

Wiktoria Cieplucha^{1*} , Aleksandra Cieluch^{1*}, Kamila Jaz¹, Justyna Flotyńska¹, Aleksandra Nowicka¹, Aleksandra Cieplucha², Dorota Zozulińska-Ziółkiewicz¹, Aleksandra Uruska¹

¹ Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznań, Poland

² First Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

KEY WORDS

air pollution, clinical remission, public health, type 1 diabetes

ABSTRACT

INTRODUCTION Clinical remission in type 1 diabetes (T1D) results from metabolic compensation after insulin implementation and is caused by various factors.

OBJECTIVES Our aim was to investigate an association between air pollution defined based on ozone concentration in the month of T1D diagnosis and the early course of the disease, that is, glucose metabolism and the occurrence of remission.

PATIENTS AND METHODS This prospective, observational analysis included 96 adult patients with newly diagnosed T1D. The study group was divided according to the occurrence of remission at 12 months after the diagnosis. The levels of ambient ozone measured within the month of T1D diagnosis were calculated using the official data of Poland's Chief Inspectorate of Environmental Protection. Remission was defined according to the following formula: actual glycated hemoglobin (HbA_{1c})(%) level + [4 × insulin dose (units/kg per 24 h)] – value defining partial remission ≤9.

RESULTS The remission rate after 12 months was higher in the group where ozone concentration was below or equal to the median for the study population ($P < 0.001$). Moreover, the patients in the group where ozone levels were above the median, presented lower C-peptide levels ($P = 0.01$), higher HbA_{1c} concentration ($P = 0.005$), and higher daily insulin requirements ($P = 0.02$) after 12 months from the diagnosis. Also, in the group of participants achieving remission, the ambient ozone level was lower ($P < 0.001$). In a multivariable logistic regression analysis, the increased ozone concentration in the month of diagnosis was the variable that influenced the lack of remission after 12 months, independently of sex and smoking ($P < 0.001$).

CONCLUSIONS Increased ozone level may exacerbate metabolic outcomes and reduce remission in T1D.

INTRODUCTION Type 1 diabetes (T1D) is a chronic disease affecting children and adults, characterized by destruction of pancreatic β cells. Pathogenesis of T1D is complex, including autoimmunity, genetic, and environmental factors.^{1,2} In T1D, absolute insulin deficiency occurs due to B-cell damage by autoimmune processes. However, soon after

diagnosis and implementing insulin treatment and a healthy lifestyle, some patients restart to produce endogenous insulin in residual β islet cells. Then, their requirement for exogenous insulin might be decreased or even eliminated. This phenomenon is called remission or “honeymoon period,” and has many advantages for T1D patients,

Correspondence to:
Wiktoria Cieplucha, MD,
Department of Internal Medicine
and Diabetology, Poznan University
of Medical Sciences,
ul. Mickiewicza 2, 61-834 Poznań,
Poland, phone: +48 61 224 52 70,
email: wiktoria.cieplucha@gmail.com

Received: March 2, 2023.

Revision accepted:

September 1, 2023.

Published online: January 2, 2024.

Pol Arch Intern Med. 2024;

134 (1): 16636

doi:10.20452/pamw.16636

Copyright by the Author(s). 2024

*WC and AC contributed equally to this work.

WHAT'S NEW?

In this study, we have proved that increased ozone concentration may contribute to a lack of remission after 12 months in people with newly diagnosed type 1 diabetes (T1D). Moreover, ozone may impact glycemic control, pancreatic cell function, and daily insulin dose, as it activates the stress hormone pathway, resulting in metabolic decompensation. To our knowledge, no study has addressed the relationship between air pollution and remission in T1D in adults. Our results indicated a new area to focus on to enhance the chances of remission and improve quality of life in patients with diabetes. In addition, air pollution is a global health threat, and our paper further confirms the need to improve air quality worldwide.

such as fewer microvascular complications³ and better insulin sensitivity.⁴ The remission phase occurs due to temporary metabolic compensation after initiating insulin treatment.⁵⁻⁷ Additionally, β -cell recovery or regeneration⁸ and modulation of the islet autoimmunity⁹ occur during the remission. Nevertheless, the mechanism of remission is still not fully understood; its occurrence is highly individual and depends on many factors.¹⁰⁻¹²

Ambient air pollution is one of the leading global health risks.¹³ The most investigated type of air pollution in the context of diabetes is traffic-related air pollution, which includes a variety of contaminants, for example, particulate matter (PM) below 10 μm and below 2.5 μm in diameter (PM₁₀, PM_{2.5}), sulfate and nitrogen compounds, polycyclic aromatic hydrocarbons, and ground-level ozone (O₃). Ground-level ozone is a major component of smog formed during an interaction of various air pollutants with sunlight. Zhang et al¹⁴ called it a major health hazard worldwide.

Poor-quality air promotes development of autoimmune diseases, including T1D.¹⁵ Zhao et al¹⁶ pointed out that air pollution triggers abnormal immune responses in the body, which contribute to the pathogenesis of T1D. Besides, air pollution may influence genetics by affecting epigenetic mechanisms.¹⁷ Pancreatic β cells are prone to oxidative stress, which leads to their dysfunction and death in T1D.¹⁸ Furthermore, air pollution can promote oxidative effects, that is, generation of free oxygen radicals resulting from exposure to ozone, which are capable of damaging β cells.¹⁹ Animal studies showed that ozone impairs β -cell function and induces oxidative stress, adipose tissue inflammation, and glucose intolerance.^{20,21}

To our knowledge, no study has addressed the relationship between air pollution and T1D remission in adults.

Therefore, our work aimed to investigate the relationship between air pollution in the month of T1D diagnosis and early course of the disease, as characterized by glucose metabolism, and the occurrence of remission.

PATIENTS AND METHODS Study population

The analysis included 96 patients (34 women and 62 men), at a median (interquartile range

[IQR]) age of 28 (20–33) years, inhabitants of Wielkopolska region in Poland, who participated in the prospective, observational Insulin Therapy and Lipoproteins Profile in Type 1 Diabetes Study (InLipoDiab1). The adults with newly diagnosed T1D were consecutively recruited between June 2015 and September 2018. The participants did not have any comorbidities. Their demographic characteristics, that is, weight, body mass index, smoking status, medical history, and laboratory data, including the levels of glycated hemoglobin (HbA_{1c}), were collected at baseline (during hospitalization due to hyperglycemia and ketosis) and after 12 months of observation. At 12 months from the diagnosis, pancreatic β -cell function was assessed by measuring serum C-peptide (CPE) levels. Positive specific autoantibodies: islet cell antibodies, glutamic acid decarboxylase antibodies, and tyrosine phosphatase antibodies, confirmed the autoimmune etiology. The patients were treated with intensive insulin therapy administered with insulin pens. The study was registered at ClinicalTrials.gov (NCT02306005). It was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Poznan University of Medical Sciences (NCT02306005). All participants gave their written, informed consent.

Calculation of air pollution concentration Air concentrations of ozone were collected from the official data of the Chief Inspectorate for Environmental Protection in Poland.²² The monitoring stations were deployed around the Wielkopolska region. The O₃ levels were measured at 5 different sites. The measurements were obtained every hour using automatic methods. The average air pollutant concentrations in the month of the diagnosis were obtained by calculating daily measurements collected during each month. The date of the T1D diagnosis was used to assign the patient to relevant monthly air pollution concentrations. The levels of contaminants were calculated using the data from the monitoring station the closest to the patient's permanent residence address. The study group was divided according to the median ozone concentration for the study population, and for further statistical analysis the patients were classified into 2 groups depending on the date of T1D diagnosis. The cold season group included diagnoses established in autumn and winter, and the warm season group those established in spring and summer, as per the Dfb climate classification by Köppen.²³

Diabetes metabolic control and remission criteria

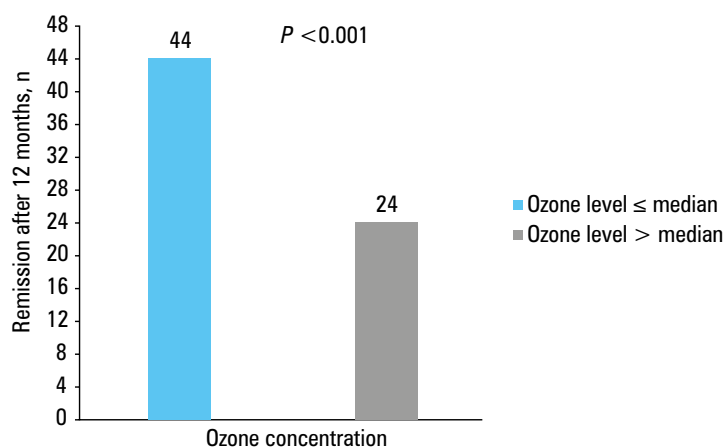
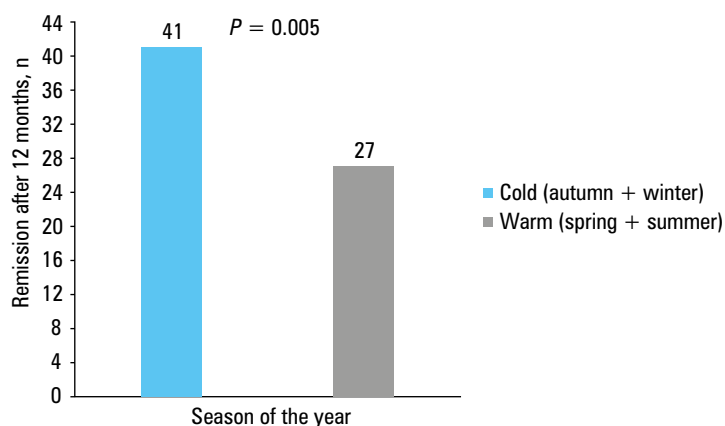
The HbA_{1c} concentration was measured in the whole blood and assessed by a turbidimetric inhibition immunoassay (Cobas 6000, Roche Diagnostics, Basel, Switzerland). Fasting plasma glucose (FPG) and postprandial glucose (PPG) were measured using capillary plasma with a glucometer. PPG was calculated as mean glycemia measured thrice, 2 hours after the main meals throughout the day.

TABLE 1 Clinical and biochemical characteristics of the study group

Parameter	With remission (n = 68)	Without remission (n = 28)	P value
Men, n (%)	44 (65)	18 (64)	0.97
Smoking, n (%)	14 (20.6)	9 (32)	0.23
Age at diagnosis, y	29 (25.5–34)	27.5 (23–30.5)	0.03
Weight, kg			
Baseline	68.3 (57–78.2)	67.5 (56.6–77)	0.61
After 12 months	72.1 (62.1–80.9)	68.9 (59.4–76.8)	0.28
BMI, kg/m ²			
Baseline	22.3 (19.9–23.6)	22.3 (18.6–24.1)	0.84
After 12 months	23.2 (20.6–25.3)	22.2 (20.1–25)	0.49
HbA _{1c} , %			
Baseline	11.3 (9.8–12.6)	11.6 (10.2–12.3)	0.99
After 12 months	6.3 (5.8–6.8)	8.1 (7.4–9.5)	<0.001
FPG, mmol/l			
Baseline	7.5 (6.9–8.7)	9.3 (7.9–9.9)	<0.001
After 12 months	6.7 (6.1–7.8)	8.3 (7.4–9)	0.007
PPG, mmol/l			
Baseline	9.4 (8.4–10.6)	10.1 (9.3–11.1)	0.12
After 12 months	6.7 (6.1–7.8)	8.5 (7–9.8)	0.003
CPE after 12 months, nmol/l	1.2 (0.7–1.7)	0.6 (0.2–1)	<0.001

Values are presented as median (interquartile range) unless indicated otherwise.

Abbreviations: BMI, body mass index; CPE, C-peptide; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; PPG, 2-hour postprandial glycemia

**FIGURE 1** Number of patients in remission after 12 months in a whole group of 96 individuals**FIGURE 2** Number of patients in remission after 12 months according to the season in which type 1 diabetes was diagnosed in a whole group of 96 individuals

Mean fasting glucose and mean postprandial glucose were calculated as a mean from measurements during the participant hospitalization at diagnosis and a few days before visiting the outpatient clinic 12 months after the diagnosis. Clinical remission was defined as actual HbA_{1c} (%) level + [4 × insulin dose (units/kg per 24 h)] – value defining partial remission ≤9.²⁴

Statistical analysis Statistical analysis was performed using Statistica v. 13.0 software (StatSoft, Tulsa, California, United States). The Kolmogorov–Smirnov test with the Lilliefors correction was used to check if the quantitative variables were normally distributed. Nonparametric tests were used for further analyses, if the analyzed parameters did not follow a normal distribution. The results were presented as numbers, percentages, medians, and IQRs. The Mann–Whitney test was used for the continuous variables, and the χ^2 test for categorical variables to assess the differences between the groups. We applied a multivariable logistic regression model to assess the influence of selected parameters (sex, age at T1D diagnosis, smoking status, and ozone concentration) on the lack of remission. The Spearman correlation coefficient was calculated to determine the relationship between air ozone concentration and HbA_{1c} levels. A P value below 0.05 was considered significant.

RESULTS After 12 months of observation, clinical remission was present in 68 participants (71%). As shown in **TABLE 1**, the patients in remission were slightly older at the time of diagnosis ($P = 0.03$), and they presented lower HbA_{1c} ($P < 0.001$) and higher CPE ($P < 0.001$) levels, both measured after 12 months of observation. FPG levels measured at baseline ($P < 0.001$) and after 12 months of intensive insulin therapy ($P = 0.007$) were higher in the group without remission. PPG levels after 12 months were also higher among the nonremitters ($P = 0.003$).

Median (IQR) ozone concentration in the month of T1D diagnosis was significantly higher among the nonremitters than among those in remission (61.5 [50–70.4] $\mu\text{g}/\text{m}^3$ vs 38.5 [28.1–57.1] $\mu\text{g}/\text{m}^3$; $P < 0.001$).

We observed the remission more often in the group of patients where the ambient ozone level was below or equal to the median (median O₃, 45.2 $\mu\text{g}/\text{m}^3$; IQR, 29.9–63; 65% vs 35%; $P < 0.001$) (**FIGURE 1**). The remission was also more frequent when T1D was diagnosed in the cold season (60% vs 40%; $P = 0.005$) (**FIGURE 2**). Moreover, in the group with ambient ozone concentrations above the median, CPE levels were lower ($P = 0.01$), daily insulin requirement was higher ($P = 0.02$), and HbA_{1c} levels measured after 12 months were higher ($P = 0.005$) in comparison with the group with O₃ concentration below the median (**FIGURES 3–5**). The multivariable logistic regression model revealed that ozone

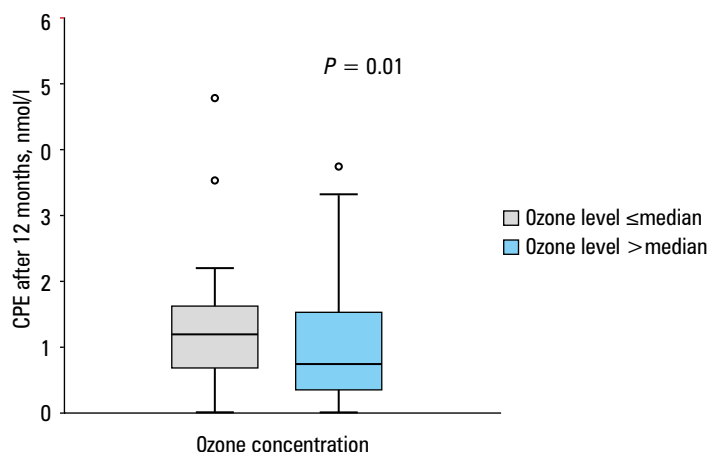


FIGURE 3 C-peptide (CPE) and ozone level
Whiskers indicate the minimal and maximal values, boxes indicate the interquartile range, central line represents the median, and circles represent outliers.

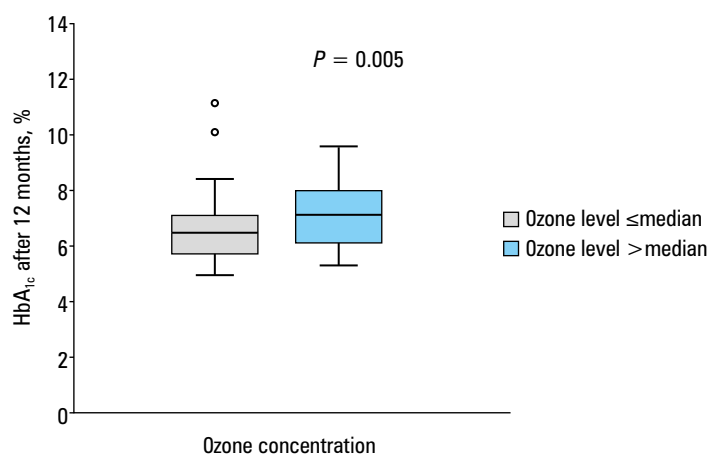


FIGURE 4 Glycated hemoglobin (HbA_{1c}) and ozone level
Whiskers indicate the minimal and maximal values, boxes indicate the interquartile range, central line represents the median, and circles represent outliers.

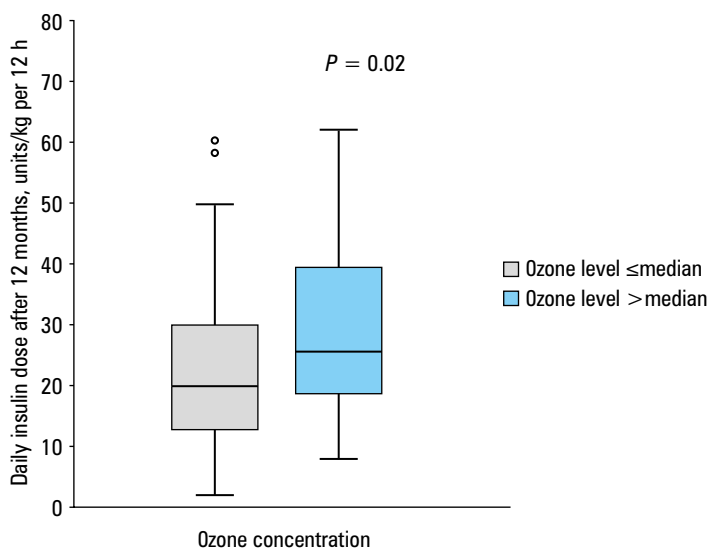


FIGURE 5 Daily insulin dose and ozone level
Whiskers indicate the minimal and maximal values, boxes indicate the interquartile range, central line represents the median value, and circles represent outliers.

concentration, independently of sex and smoking status, impacted remission after 12 months from the diagnosis ([TABLE 2](#)). The higher the ozone level in the month of diagnosis and the older the patient, the lower the odds for remission (odds ratio [OR], 1.06; 95% CI, 1.03–1.09; $P < 0.001$ and OR, 0.88; 95% CI, 0.79–0.98; $P = 0.02$, respectively). Also, we found a weak positive correlation between ozone concentrations within the month of T1D diagnosis and the levels of HbA_{1c} measured at 12 months from the diagnosis ($R = 0.34$; $P < 0.001$).

DISCUSSION This study supports the hypothesis that air pollution resulting in higher ozone air concentration may have an unfavorable impact on the course of disease in adult patients diagnosed de novo with T1D. Previous studies on air pollution affecting T1D were primarily performed in children, and focused on the correlation between poor-quality air and the incidence of T1D. Hathout et al²⁵ found that children diagnosed with T1D had higher exposure to O₃ and SO₄ than healthy children ($P < 0.001$, $P = 0.006$, respectively). Furthermore, Di Ciaula²⁶ proved that PM₁₀ concentrations in Apulia (Italy) played a crucial role in the number of new T1D diagnoses in children, mainly above the age of 5. A study from Sweden²⁷ indicated that living in an area with elevated levels of air pollution (O₃, NO_x) during pregnancy is associated with an increased risk of T1D in offspring. The authors found that mothers of children who developed T1D, more often lived in the areas with higher NO_x levels during the third trimester or with higher ozone levels in the second trimester of their pregnancy. All mentioned studies showed a relationship between air quality and T1D. Additionally, our finding that the remission rate was higher in the cold season of the year is in line with our main conclusion that ozone concentration may contribute to the remission 12 months after the T1D diagnosis. The ozone levels in colder seasons are usually lower than in the summer, when solar radiation is stronger, and more ground ozone is formed.¹⁴

The metabolic alterations caused by ozone are similar to fight-or-flight responses involving adrenal-derived hormones.²⁸ Miller et al²⁹ showed that ozone exposure in humans was related to increased levels of fatty acids in the circulation and increased concentrations of cortisol and corticosterone, suggesting activation of the neurohormonal stress response pathway. Elevated levels of circulating stress hormones result in diminished pancreatic insulin secretion, and regulate a wide array of processes associated with glucose metabolism characterized by fasting hyperglycemia, glucose intolerance, and increased hepatic gluconeogenesis.^{20,28-32}

The ozone impact on insulin resistance is, however, controversial. Some studies claimed that ozone does not affect impaired insulin sensitivity.^{20,28} In contrast, Vella et al³³ demonstrated that exposure of rats to ozone induced whole-body

TABLE 2 A multivariable logistic regression model with the lack of remission after 12 months from the diagnosis as a dependent variable

Parameter	OR	95% CI	P value
Ozone, above median	1.06	1.03–1.09	<0.001
Age at diagnosis, y	0.88	0.79–0.98	0.02
Male sex	0.76	0.25–2.29	0.61
Smoking	0.37	0.12–1.17	0.09

Abbreviations: OR, odds ratio

insulin resistance and oxidative stress through muscle c-Jun N-terminal kinase activation, which might be associated with high ozone concentration and long-time exposure.

Furthermore, Zhong et al²¹ found that ozone triggers a specific immune response in the exposed mice, that is, an increase in the levels of tumor necrosis factor α , interferon γ , and a marker for natural killer cells. Decreased levels of those biomarkers were reported by Tang et al³⁴ at the beginning of the remission phase in T1D.

Smoking was another critical issue while discussing air pollution as a risk factor for lack of remission. Nicotine intake is associated with poorer glycemic control, decreased insulin sensitivity, and it impacts the length of the remission phase.^{35,36} In this study, we demonstrated the smoking-independent effect of ozone on remission, which gave a new insight into the determinants of the early course of T1D.

Our study shows the consequences of ozone-induced metabolic effects. The patients from the group with ozone concentrations above the median had lower levels of CPE, higher daily insulin requirements, and higher levels of HbA_{1c}. These findings support the thesis that increased ozone concentration may contribute to worse metabolic outcomes and reduced remission in T1D. Although the exact mechanisms have not been fully explored, higher ozone level in the month of T1D diagnosis may escalate β -cell dysfunction, evoke immune changes, and disturb temporary metabolic compensation. In addition, activation of the neuroendocrine pathway and the role of corticosteroids are crucial in mediating the glucose metabolic effect.³⁷ Thus, ozone exposure treated as a stress factor exacerbates metabolic impairment.²⁸

The ozone concentration values in the official 5-year air quality assessment in the Wielkopolska region in the years 2014–2018, provided by the regional department of the Chief Inspectorate for Environmental Protection in Poland³⁸ exceeded the acceptable level or fell between the acceptable level and the upper assessment threshold. In that report, the ozone influence on people's health was taken into consideration. Therefore, public health policies and governments should pay more attention to air quality, as the air pollution-related burden of disease is significant.^{39–41} Moreover, people living in more polluted regions should be aware of their poorer prognosis. They may try to act more actively in other areas, such as diet, physical

activity, and smoking cessation, all of which have proven to improve remission chances.^{10,12,36,42} Finally, it should be a part of a health care professional's job to outline to newly-diagnosed patients the key areas to focus on to increase the chance of remission and a better course of the disease.⁴³

The main limitation of our study is that the contaminant concentration was only measured outdoors at the monitoring station closest to patients' permanent residence, and there are only a few stations in Wielkopolska. In this study, we did not account for patient travels and indoor pollution levels. This is a pitfall of many epidemiologic air pollution studies based on measurements from the open-air monitoring stations. Another limitation regarding the assessment of air pollution is the occurrence of weather-dependent variables, such as humidity, wind, or solar radiation, that may impact the level of air pollution concentration. In the present study, we investigated the air pollution levels in the calendar month of diagnosis, as we suspected a possible relationship between poor air quality and metabolic decompensation in adults developing T1D. Therefore, we studied the association of ozone levels and early course of T1D by checking the presence of significant remission at 12 months after the diagnosis. Further studies concerning more time-specified and prolonged air pollution measurements, with more advanced and personalized air pollution level calculations are required to provide more insights into the relationship between poor air quality and early course of T1D in adults.

Conclusions Increased ozone concentration within the month of T1D diagnosis may contribute to a lack of remission after 12 months. In addition, higher ozone level might be associated with metabolic decompensation in this population. Metabolic decompensation is more likely in the group of patients experiencing higher ozone levels in the month of T1D diagnosis. Since the remission phase is highly beneficial for T1D patients, identifying its modifiable risk factors might be crucial to improve the disease trajectory.

ARTICLE INFORMATION

ACKNOWLEDGMENTS We want to thank the participants of the InLipoDiab1 study and all the staff involved in the data collection.

FUNDING The Poznan University of Medical Sciences funded the InLipoDiab1 study at the Faculty of Medicine (Grant for Young Scientists No. 502-14-02234382-99658; to AU and AC).

CONTRIBUTION STATEMENT Conceptualization: WC, AU; methodology: WC, AC, AU; formal analysis: WC, AC, KJ, Aca, AU; validation: WC, AC, KJ, AN, ACa; investigation: WC, AC, KJ, JF, AN; resources: WC, AC, KJ, JF, AN; writing original draft: WC, AC; visualization: WC; supervision: DZZ, AU; writing – review and editing: AU, project administration: AU

CONFLICT OF INTEREST None declared.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only.

HOW TO CITE Cieplucha W, Cieluch A, Jaz K, et al. Lower air ozone concentration is associated with clinical remission in type 1 diabetes diagnosed

REFERENCES

- 1 Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet Lond Engl.* 2001; 358: 221-229. [↗](#)
- 2 Aasbjerg K, Nørgaard CH, Vestergaard N, et al. Risk of diabetes among related and unrelated family members. *Diabetes Res Clin Pract.* 2020; 160: 107997. [↗](#)
- 3 Niedzwiecki P, Pilacinski S, Uruska A, et al. Influence of remission and its duration on development of early microvascular complications in young adults with type 1 diabetes. *J Diabetes Complications.* 2015; 29: 1105-1111. [↗](#)
- 4 Niedzwiecki P, Pilacinski S, Uruska A, Zozulinska-Ziolkiewicz D. Clinical remission of type 1 diabetes predicts higher insulin sensitivity at 7 years from diagnosis of the disease. *Diabetes Technol Ther.* 2020; 22: 577-583. [↗](#)
- 5 Kara Ö, Esen I, Tepe D. Factors influencing frequency and duration of remission in children and adolescents newly diagnosed with type 1 diabetes. *Med Sci Monit.* 2018; 24: 5996-6001. [↗](#)
- 6 Schölin A, Berne C, Schvarcz E, et al. Factors predicting clinical remission in adult patients with type 1 diabetes. *J Intern Med.* 1999; 245: 155-162. [↗](#)
- 7 Muhammad BJ, Swift PG, Raymond NT, Botha JL. Partial remission phase of diabetes in children younger than age 10 years. *Arch Dis Child.* 1999; 80: 367-369. [↗](#)
- 8 Pozzilli P, Maddaloni E, Buzzetti R. Combination immunotherapies for type 1 diabetes mellitus. *Nat Rev Endocrinol.* 2015; 11: 289-297. [↗](#)
- 9 Karges B, Durinovic-Belló I, Heinze E, et al. Immunological mechanisms associated with long-term remission of human type 1 diabetes. *Diabetes Metab Res Rev.* 2006; 22: 184-189. [↗](#)
- 10 Niedzwiecki P, Zozulinska-Ziolkiewicz D. Clinical remission of type 1 diabetes. *Clin Diabetol.* 2013; 2: 185-190.
- 11 Zhong T, Tang R, Gong S, et al. The remission phase in type 1 diabetes: changing epidemiology, definitions, and emerging immuno-metabolic mechanisms. *Diabetes Metab Res Rev.* 2020; 36: e3207. [↗](#)
- 12 Rydzewska M, Kulesza M, Olszewska M, et al. Clinical determinants of the remission phase in children with new-onset type 1 diabetes mellitus in two years of observation. *Pediatr Endocrinol Diabetes Metab.* 2019; 25: 6-16. [↗](#)
- 13 Lelieveld J, Pozzer A, Pöschl U, et al. Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective. *Cardiovasc Res.* 2020; 116: 1910-1917. [↗](#)
- 14 Zhang JJ, Wei Y, Fang Z. Ozone pollution: a major health hazard worldwide. *Front Immunol.* 2019; 10: 2518. [↗](#)
- 15 Di Ciaula A. Association between air pollutant emissions and type 1 diabetes incidence in European countries. *Adv Res.* 2014; 2: 409-425. [↗](#)
- 16 Zhao CN, Xu Z, Wu GC, et al. Emerging role of air pollution in autoimmune diseases. *Autoimmun Rev.* 2019; 18: 607-614. [↗](#)
- 17 Shukla A, Bunkar N, Kumar R, et al. Air pollution associated epigenetic modifications: transgenerational inheritance and underlying molecular mechanisms. *Sci Total Environ.* 2019; 656: 760-777. [↗](#)
- 18 Lenzen S. Oxidative stress: the vulnerable beta-cell. *Biochem Soc Trans.* 2008; 36: 343-347. [↗](#)
- 19 Hathout EH, Beeson WL, Nahab F, et al. Role of exposure to air pollutants in the development of type 1 diabetes before and after 5 yr of age. *Pediatr Diabetes.* 2002; 3: 184-188. [↗](#)
- 20 Miller DB, Snow SJ, Henriquez A, et al. Systemic metabolic derangement, pulmonary effects, and insulin insufficiency following subchronic ozone exposure in rats. *Toxicol Appl Pharmacol.* 2016; 306: 47-57. [↗](#)
- 21 Zhong J, Allen K, Rao X, et al. Repeated ozone exposure exacerbates insulin resistance and activates innate immune response in genetically susceptible mice. *Inhal Toxicol.* 2016; 28: 383-392. [↗](#)
- 22 Measurement data archives of the Chief Inspectorate for Environmental Protection in Poland. <http://powietrze.gios.gov.pl/pjp/archives>. Accessed September 18, 2020.
- 23 Kottke M, Grieser J, Beck C, et al. World map of the Köppen-Geiger Climate Classification updated. *Meteorologische Zeitschrift.* 2006; 15: 259-263. [↗](#)
- 24 Mortensen HB, Hougaard P, Swift P, et al. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care.* 2009; 32: 1384-1390. [↗](#)
- 25 Hathout EH, Beeson WL, Ischander M, et al. Air pollution and type 1 diabetes in children. *Pediatr Diabetes.* 2006; 7: 81-87. [↗](#)
- 26 Di Ciaula A. Type 1 diabetes in paediatric age in Apulia (Italy): incidence and associations with outdoor air pollutants. *Diabetes Res Clin Pract.* 2016; 111: 36-43. [↗](#)
- 27 Malmqvist E, Larsson HE, Jönsson I, et al. Maternal exposure to air pollution and type 1 diabetes - accounting for genetic factors. *Environ Res.* 2015; 140: 268-274. [↗](#)
- 28 Snow SJ, Henriquez AR, Costa DL, Kodavanti UP. Neuroendocrine regulation of air pollution health effects: emerging insights. *Toxicol Sci.* 2018; 164: 9-20. [↗](#)
- 29 Miller DB, Ghio AJ, Karoly ED, et al. Ozone exposure increases circulating stress hormones and lipid metabolites in humans. *Am J Respir Crit Care Med.* 2016; 193: 1382-1391. [↗](#)
- 30 Peterhoff M, Sieg A, Brede M, et al. Inhibition of insulin secretion via distinct signaling pathways in alpha2-adrenoceptor knockout mice. *Eur J Endocrinol.* 2003; 149: 343-350. [↗](#)
- 31 Gibson TB, Lawrence MC, Gibson CJ, et al. Inhibition of glucose-stimulated activation of extracellular signal-regulated protein kinases 1 and 2 by epinephrine in pancreatic beta-cells. *Diabetes.* 2006; 55: 1066-1073. [↗](#)
- 32 Fichna M, Fichna P. Glucocorticoids and beta-cell function. *Endokrynol Pol.* 2017; 68: 568-573. [↗](#)
- 33 Vella RE, Pilon NJ, Zarrouki B, et al. Ozone exposure triggers insulin resistance through muscle c-Jun N-terminal kinase activation. *Diabetes.* 2015; 64: 1011-1024. [↗](#)
- 34 Tang R, Zhong T, Wu C, et al. The remission phase in type 1 diabetes: role of hyperglycemia rectification in immune modulation. *Front Endocrinol.* 2019; 10: 824. [↗](#)
- 35 Tonstad S. Cigarette smoking, smoking cessation, and diabetes. *Diabetes Res Clin Pract.* 2009; 85: 4-13. [↗](#)
- 36 Pilacinski S, Adler AI, Zozulinska-Ziolkiewicz, et al. Smoking and other factors associated with short-term partial remission of type 1 diabetes in adults. *Diabet Med.* 2012; 29: 464-469. [↗](#)
- 37 Thomson EM, Pilon S, Guénette J, et al. Ozone modifies the metabolic and endocrine response to glucose: reproduction of effects with the stress hormone corticosterone. *Toxicol Appl Pharmacol.* 2018; 342: 31-38. [↗](#)
- 38 Five-year assessment of air quality in the Wielkopolskie Voivodship. Voivodeship report for the years 2014-2018. Chief Inspectorate for Environmental Protection, Regional Department of Environmental Monitoring in Poznań 2019 [in Polish]. <https://powietrze.gios.gov.pl/pjp/rwms/publications/card/391>. Accessed March 1, 2023.
- 39 Malashock DA, Delang MN, Becker JS, et al. Global trends in ozone concentration and attributable mortality for urban, peri-urban, and rural areas between 2000 and 2019: a modelling study. *Lancet Planet Health.* 2022; 6: 958-967. [↗](#)
- 40 Dąbrowiecki P, Chciałowski A, Dąbrowiecka A, et al. Air pollution and long-term risk of hospital admission due to chronic obstructive pulmonary disease exacerbations in Poland: a time-stratified, case-crossover study. *Pol Arch Intern Med.* 2023; 133: 16444. [↗](#)
- 41 Kuźma Ł, Pogorzelski S, Struniawski K, et al. Effect of air pollution on the number of hospital admissions for acute coronary syndrome in elderly patients. *Pol Arch Intern Med.* 2020; 130: 38-46. [↗](#)
- 42 Jamiolkowska-Sztabkowska M, Głowińska-Olszewska B, Łuczynski W, et al. Regular physical activity as a physiological factor contributing to extend partial remission time in children with new onset diabetes mellitus-two years observation. *Pediatr Diabetes.* 2020; 21: 800-807. [↗](#)
- 43 Phillips A. Supporting patients with type 1 diabetes. *Br J Nurs.* 2016; 25: 330-334. [↗](#)