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Scientific Inquiry

Year 11-12

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Australian Government Department of Defence

Government of South Australia Department for Education

SASTA South Australian Science Teachers Association

Investigating the correlation between atopic dermatitis prevalence and pollution levels

Research Question

To what extent is there a correlation between atopic dermatitis prevalence in children aged 0-14 (per 100,000 people) and air pollution levels, as measured by the ozone (O_3) air quality index?

Introduction

Atopic dermatitis (AD), more commonly known as eczema, is an autoimmune disease that mainly affects the skin. It is characterised by itchy, dry patches of skin, as well as redness, which can lead to skin cracking and weeping clear fluid (Nancy Garrick 2017). AD can be chronic and usually begins in early childhood where it affects 10-20% of children worldwide, making it a disease with a significant burden on the population (Page, Weston & Loh 2016).

I was diagnosed with eczema as a child, but apart from using eczema creams, I never found out the exact causes behind my flare-ups. Because I grew up in Shanghai, China – a city with high levels of pollution, my parents had theories that my allergic reaction was in part due to chemical pollutants. As a result, I wanted to investigate if air pollution had any involvement in triggering the onset of eczema, particularly given that air pollution is a problem in many cities worldwide.

Background Information

Currently, the exact cause of AD is unknown, but possible reasons that have been proposed include genetics, immune system disorders and environmental factors (Nancy Garrick 2017). The skin, being the body's largest organ in the integumentary system, acts as the body's first line of defence against foreign substances, such as pathogens and air pollutants. The epidermis – the outermost layer of the skin – is the first target of air pollutants. It consists of 4-5 layers of skin cells called keratinocytes, which stack on top of each other in layers to form a "barrier".

The epidermal barrier is maintained through a few mechanisms. First, the keratinocytes secrete lipid compounds, such as phospholipids and cholesterol into the intercellular space (Dijkhoff et al. 2020). Second, proteins such as keratin and filaggrin, and membrane proteins such as desmosomes and tight junctions bind the keratinocytes together (Vietri Rudan & Watt 2022). Lastly, the skin produces natural moisturising factors to maintain hydration. Together, these factors are important for the water-resistant properties of the skin, preventing excess water uptake and loss. Air pollutants can damage or downgrade the expression of the linking proteins and lipid molecules. This impairs the skin barrier, making it dry and prone to infection, as seen in atopic dermatitis patients (see Figure 1 below).

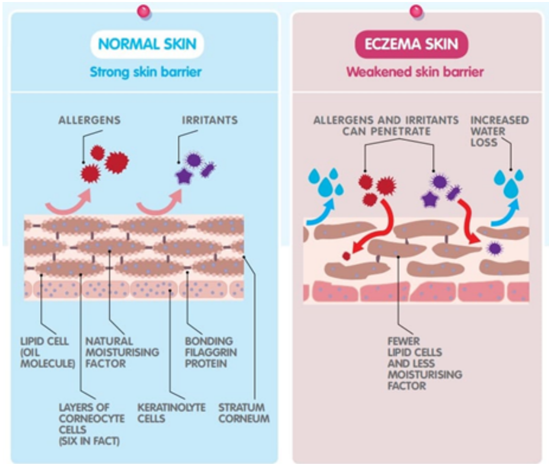


Figure 1: Normal epidermal structure compared to epidermis affected by atopic dermatitis (Brown 2021)

Air pollution consists of many factors, including particulate matter, nitrous oxides, carbon monoxide, cigarette smoke, and tropospheric ozone (O_3) (Kathuria et al. 2017). Tropospheric ozone (O_3) is a secondary pollutant present at ground level, which forms from car pollution. NO_2 from car exhausts can react with sunlight to form NO and O_3 (US EPA 2016). This makes ozone highly prevalent in urbanised environments, especially densely populated cities that have many cars, buses and trucks (Mancebo & Wang 2015). Ozone, being a powerful oxidant, has already been extensively in its damaging effects on the respiratory system. While the ozone's effects on the skin are not well studied, a study by Xu et al. has found an association between ozone exposure and hospital visits for skin conditions (Fuks et al. 2019). This suggests that tropospheric ozone pollution is potentially a global health concern, especially in the development and aggravation of atopic dermatitis.

This leads to my research question: to what extent is there a correlation between ozone air pollution levels and atopic dermatitis prevalence?

Hypothesis

Hypothesis: There will be a positive correlation between the ozone air quality index (AQI) level and the prevalence of atopic dermatitis per 100,000 people.

As stated by Fuks et al. in 2019, "experimental evidence suggests a positive correlation of O3 exposure with oxidative damage, impaired antioxidant defence and proinflammatory response in the skin". This suggests that the damage caused by ozone affects the skin's ability to act as a barrier, and therefore suggests a positive correlation between ozone exposure and atopic dermatitis symptoms.

Approach to the Research Question

To standardise the data across different countries, the rate of prevalence per 100,000 people was chosen as the metric. Prevalence refers to "a measure of the total number of people in a specific group who have (or had) a certain disease during a given period of time" (National Cancer Institute 2011). Using "number" as the metric means that countries with larger populations will seem like they have a higher AD prevalence, which is problematic. Using “rate” keeps the eczema rate is kept relative to the total population of the country, and thus standardises the data.

All air pollution data from the database were given in terms of the United States Environmental Protection Agency Air Quality Index (US EPA AQI) (World Air Quality Index 2023). The Air Quality Index (AQI) is a measurement of air pollution that standardises pollutant concentration against a common scale. In this case, the scale boundaries were developed by the US EPA, as seen in Figure 2 below (Airnow, 2021). From here onwards, the AQI value will be referred to as AQI.

Air Quality Index (AQI) Values	Levels of Health Concern	Colors
0 to 50	Good	Green
51 to 100	Moderate	Yellow
101 to 150	Unhealthy for Sensitive Groups	Orange
151 to 200	Unhealthy	Red
201 to 300	Very Unhealthy	Purple
301 to 500	Hazardous	Maroon

Figure 2: Table of US EPA AQI categories (Wikipedia Contributors 2021)

Both atopic dermatitis prevalence and AQI were averaged over five years – 2015 to 2019. This was minimise any random errors in the collection of data in a country in a particular year, thus improving the accuracy of the data.

Data sources

Two extensive and reliable databases were used for this experiment:

- 2019 Global Burden of Disease Study (IHME 2022)
- World Air Quality Index historical database (World Air Quality Index 2023)

The IHME database was chosen as it was the most comprehensive and accessible database for atopic dermatitis data. The IHME data consists of both primary and secondary sources. The primary data is collected using government medical records, and surveys and interviews done by trained data collectors in the local countries. The secondary data comes from various studies done by other organisations, which the IHME adds to their database. Although there could be bias from both the primary and secondary sources, the large sample size reduces the effects of random error.

Similarly, the World Air Quality database was chosen as it was the most comprehensive database available. The WAQI database had measurements from more than 10,000 stations around the world, meaning the sample size was very large. Moreover, for each station, there was data available for every day of each year, further increasing the sample size, and reducing the effects of random error.

Moreover, both databases have data from the years 2015-2019, making them suitable for this investigation.

Variables

The independent variable is the level of O_3 in ambient, outdoor air, given using the US EPA Air Quality Index (AQI)

The dependent variable is the prevalence of atopic dermatitis (given as rate per 100,000 people)

Inclusion criteria

Confounding variables are variables that are not the independent variable but influence the dependent variable. Factors that may cause atopic dermatitis, other than air pollution, include age, prenatal conditions and genetics. To minimise the effects of some confounding variables, an inclusion criteria was developed.

The age range was chosen based on which group is most sensitive to air pollution and at risk for atopic dermatitis. As 80% of people grow out of eczema by adolescence, children before puberty are most likely to be affected by eczema. Furthermore, according to Phases I and III of the International Study of Asthma and Allergies in Childhood, “the prevalence of eczema in children aged 6 to 7 years and 13 to 14 years is increasing in both developing and developed countries”. Children in the age range of 0-14 years seemed to be most at risk and were therefore chosen for this investigation.

Countries with a population larger than 1 million were used in the statistical test, as they were more likely to provide accurate data on AD prevalence. A population that is too small could cause random errors, where the population is, by chance, a misrepresentation of the actual AD rate.

The following inclusion criteria were put in place:

Table 1: Inclusion criteria for investigation

Variable	Inclusion criteria
Age	0-14 years
Population	Greater than 1 million
Time	2015-2019

Uncontrolled variables

Diet, prenatal conditions and genetics were confounding variables that were not controlled in this investigation. Due to globalisation, many developed countries are home to multiple different ethnicities, which makes it difficult to restrict the sample size to only people of the same ethnicity. Similarly, as diet and prenatal conditions vary drastically depending on the person, it was impossible to control in a database study.

Safety, environmental and ethical considerations

There were no safety and environmental considerations associated with the experiment, apart from the ethical use of data, per the guidelines set by the database organisation, such as copyright laws and commercial use.

Methodology

1. Using Excel 2019, the average ozone AQI of all stations in a country in 2015 is calculated. This is repeated for every country for which there is data.
2. The average O3 AQI is calculated in the same way for the years 2016, 2017, 2018 and 2019.
3. The median AD prevalence is found for every country for which there is an average ozone AQI.
4. Countries with air pollution and atopic dermatitis (AD) data for all five years from 2015 to 2019 are selected. Other countries are removed.
5. Countries with a population smaller than 1 million are removed from the dataset.
6. The average air pollution from 2015-2019 is calculated for each country.
7. The average AD rate from 2015-2019 is calculated for each country.
8. The remaining countries are combined in a table and a scatter plot is drawn, with air pollution on the x-axis and AD prevalence on the y-axis.
9. Pearson's moment correlation value is found using the =PEARSON() formula.

Results

Raw data

Figure 3: Screenshot of unprocessed AD data for some countries

2015		2016		2017		2018		2019	
location_r	val	location_r	val	location_r	val	location_r	val	location_r	val
Papua Nev	140.2283	China	2357.602	China	2368.279	China	2419.109	Afghanista	2215.233
Ecuador	187.5663	Tonga	3215.593	Tonga	3215.686	Tonga	3215.518	Albania	4697.458
Estonia	532.9451	Micronesi	3205.358	Micronesi	3204.327	Sri Lanka	2943.306	Algeria	2219.99
Venezuela	134.4274	Armenia	11030.14	Armenia	11029.47	Armenia	11017.85	American	3193.784
Tunisia	99.2061	Sri Lanka	2946.783	Sri Lanka	2945.4	Solomon I	3179.723	Andorra	7893.422
Zimbabwe	95.10016	Vietnam	3141.947	Vietnam	3144.103	Kazakhsta	11234.56	Angola	2145.31

Figure 4: Screenshot of a section of air pollution data for the Republic of Korea in 2015

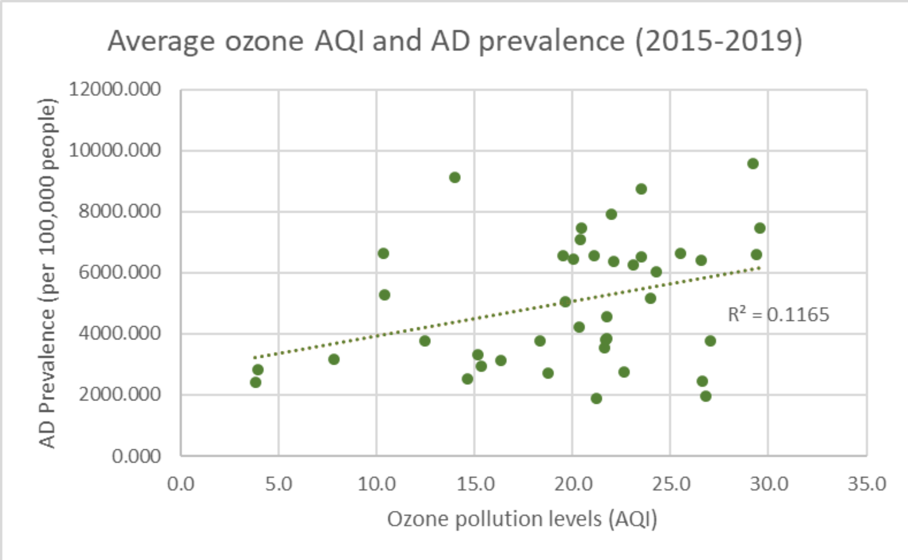
Date	Country	CountryCode	City	Specie	count	min	max	median
28/04/2015	Republic of Korea	KR	Jeonju	o3	154	7.3	48.1	26.4
2/06/2015	Republic of Korea	KR	Jeonju	o3	169	4	60.9	30.4
31/01/2015	Republic of Korea	KR	Jeonju	o3	138	1.6	30.4	20
3/02/2015	Republic of Korea	KR	Jeonju	o3	120	0.8	29.6	6.4
23/03/2015	Republic of Korea	KR	Jeonju	o3	111	1.6	41.6	24.8
13/04/2015	Republic of Korea	KR	Jeonju	o3	168	16	45.6	35.2
17/04/2015	Republic of Korea	KR	Jeonju	o3	168	3.2	48.8	22.4
22/03/2015	Republic of Korea	KR	Jeonju	o3	168	8	66.1	35.2

Processed Data

Table 2: Average O3 AQI and atopic dermatitis prevalence in all countries from 2015-2019

Country	Average O3 AQI value	Average AD prevalence (per 100,000 people)	Country	Average O3 AQI value	Average AD prevalence (per 100,000 people)
Iran	21.2	1873.735	Hungary	19.6	5049.496
China	26.8	1948.868	United States Of America	24.0	5164.512
Colombia	3.8	2403.404	Chile	10.4	5274.935
Mexico	26.6	2448.511	Spain	24.3	6049.377
Thailand	14.7	2537.909	Cyprus	23.1	6249.035
Romania	18.8	2711.312	Germany	22.1	6365.369
Taiwan	22.6	2761.189	Portugal	26.6	6398.003
Peru	4.0	2845.086	Netherlands	20.1	6466.788
India	15.3	2936.691	Finland	23.5	6533.122
Turkey	16.3	3116.630	Belgium	19.5	6548.122
Bolivia	7.8	3151.348	Switzerland	21.1	6554.905
Canada	15.2	3304.311	Israel	29.4	6602.053
Poland	21.6	3561.764	Sweden	25.5	6641.430
Brazil	12.5	3756.307	Singapore	10.4	6653.224
Serbia	18.3	3779.833	United Kingdom	20.4	7096.155
Croatia	27.0	3781.311	Italy	29.6	7479.409
Bulgaria	21.7	3813.099	Norway	20.5	7482.312
Czech Republic	21.8	3845.820	Denmark	22.0	7921.382
Lithuania	20.4	4235.379	France	23.5	8742.938
Australia	21.8	4560.900	Mongolia	14.0	9139.812
			Japan	29.2	9572.282

Figure 5: Graph of the correlation between average O3 air quality index and atopic dermatitis prevalence from 2015 to 2019



A scatter plot was constructed from the data. The line of best fit has an R2 value of 0.12, showing a very weak, positive correlation between the average O3 AQI in a country and the prevalence of AD. The graph shows a large scatter, with most of the data points concentrated at 20-25 O3 AQI and 4000-8000 cases of AD per 100,000 people.

Statistical Testing

Pearson's product-moment correlation was used as the most appropriate test for determining the strength and direction of the linear correlation between the two variables – AD and air pollutant levels.

O_3 and AD prevalence have an R score of 0.342, indicating a moderate positive correlation between the two variables, as shown by the R^2 value in figure 2 above.

Null hypothesis (H_0): There is no correlation between atopic dermatitis prevalence and O3 levels

Alternative hypothesis (H_1): There is a correlation between atopic dermatitis prevalence and O3 levels

A hypothesis test was used to determine the significance of the correlation between the two variables. The level of significance was chosen to be 0.05. A P-value less than 0.05 is statistically significant, as it shows that there is a less than 5% chance that the null hypothesis is true.

The sample size was calculated using the Excel =COUNT() function, and the degrees of freedom (N) can be calculated as the $sample\ size\ -\ 2$ (Turney 2022).

Table 3: Sample size and degrees of freedom for ozone

Pollutant	Sample size	Degrees of Freedom (N)
O3	41	39

Using Excel, the Pearson's coefficient for both O3 was calculated, and the results are as follows:

Table 4: Calculation of significant of Pearson's coefficient for each pollutant

Pollutant	Pearson's coefficient (R score)	P-value (Social Science Statistics 2019)	Significance
O_3	0.342	0.0289	$P<0.05$

The P-value for both pollutants are smaller than the p-value of 0.05, meaning that we can reject the null hypothesis and accept the alternative hypothesis. This supports the Pearson's coefficient (R-score) above, showing that there is a significant correlation between atopic dermatitis and tropospheric ozone levels.

Conclusion

Evaluation

Overall, the results support the hypothesis and suggest that to a small extent, average ozone levels are correlated with an increased prevalence of atopic dermatitis in children aged 0-14. The correlation, although weak, is statistically significant, with a Pearson's moment correlation coefficient 0.34. The weak correlation, however, indicates that there are errors, as well as other factors involved in the triggering of atopic dermatitis (AD).

Scientific context

Ozone is the strongest oxidant in chemical pollutants, meaning that it reacts easily with the proteins and lipids present in the epidermis. In particular, ozone can react with the double bonds in the lipids in a process called lipid peroxidation (Fuks et al. 2019). This process forms reactive oxygen species – molecules that can start a chain reaction of oxidation reactions throughout the skin, causing oxidative damage to the keratinocytes (Ferrara et al. 2021). Although the skin contains antioxidants – such as vitamins C and E – to prevent the perpetuation of the oxidation reactions, they will eventually be depleted by prolonged exposure to ozone. As antioxidants are important for healthy skin, the lack of antioxidants may explain why atopic dermatitis causes poor skin conditions.

Moreover, oxidative damage can trigger inflammasomes – protein complexes in the skin, which are part of the body's first line of defence (Tang & Zhou 2020). The role of inflammasomes is to activate proinflammatory proteins, signalling that there has been an infection or tissue damage. This can have several inflammatory effects, such as cell apoptosis and recruitment of immune cells, such as neutrophils and macrophages (Tang & Zhou 2020). Inflammation in the skin can lead to the redness and itchiness that is seen in eczema-affected skin.

It is also important to note that none of the countries had an average ozone AQI above 50, or in an "unhealthy" range (see figure 2). This suggests that on average, people were exposed to a "healthy" level of ozone, which in part explains why ozone is not strongly correlated with atopic dermatitis.

Strengths and Limitations

The strengths of this investigation largely lie in the very large and extensive database used, which largely decreases the chance of any random error. The air pollution data was an average of at least one air-quality monitoring station for each country for every day from 2015 to 2019. The atopic dermatitis data was taken from IHME, which conducts large-scale data collection around the world, meaning that the sample size was not limited, unlike in clinical studies.

As for limitations, many random and systematic errors would have impacted the final correlation strength and direction.

Firstly, the data on AD prevalence is affected by systematic errors, as it is based on reports from government administrative data, censuses and surveys from third parties (IHME 2016). Government administrative data involves hospital and healthcare data, which can be limited in its accuracy, especially in less developed countries. As AD is not a life-threatening illness in most cases, some families may choose not to visit the doctor. As a result, many cases of eczema could go unrecorded. Surveys on the other hand could cause random error, as they are distributed to members of the public who are not experienced in diagnosing AD in themselves or their children. If people misdiagnose their skin condition for AD, then surveys would be incorrect in estimating the prevalence of eczema in a population.

In addition, a systematic error is the fact that wealthier countries could be overrepresented, while countries with poorer healthcare systems may have underestimated the prevalence of AD in their country. The results show that the countries with the highest AD prevalence are Italy, Denmark, France, Mongolia and Japan, all of which have ‘very high’ HDI, except Mongolia, with a ‘high’ HDI (World population review 2022). This suggests that their healthcare systems are more accessible to everyone in the population, and therefore they have a more accurate count of AD cases in the country.

There are random errors in the collection of air pollution data. The air quality monitors that collect data around the world for the WAQI can be set up by both the government and independent organisations. Air quality monitors could've been uncalibrated and consequently over-measured or under-measured the concentration of pollutants. Another factor is selection bias, in which the set-up of the air quality monitors is not representative of the air quality in which the majority of the population lives, but rather in a relatively over- or under-polluted part of the country.

Finally, other uncontrolled variables could also have had an impact on AD prevalence. Other sources of pollution, such as cigarette smoke and chemicals from renovations, have been shown in numerous studies to be correlated to an increased risk of AD symptoms (Drakaki & Antoniou 2014). Some countries might favour smoking more than others which can all contribute to AD prevalence.

The investigation design also does not take into consideration that ozone may only be involved in exacerbating the symptoms of those already diagnosed with eczema, rather than triggering the disease itself. As atopic dermatitis is an autoimmune disease, and partially due to genetic factors, it is unlikely ozone is the sole cause of the disease. This explains the weak correlation, as well as the high scatter of the graph.

Improvements and Extensions

It is difficult to remove bias from the data on atopic dermatitis, especially when using online databases. However, the correlation study can be separated into only ‘very high’ HDI or ‘high’ HDI countries to reduce the effects that HDI may have on data collection and underrepresentation of AD prevalence. Countries with ‘very high’ HDI would be the most suitable, as their healthcare systems are set up in a way such that cases of AD are more likely to be reported.

Another improvement would be to investigate the correlation between AD and air pollution within a single country, using the ozone AQI from different cities and towns. This would minimise the effect of confounding variables, such as genetics, especially when done in a mostly monocultural country where people are more likely to be genetically similar (ie. Japan or China). Furthermore, the effect of diet as a confounding variable may also be minimalised due to cultural preferences and having the same national food safety standards. Moreover, as the location is much more specified (eg. Melbourne, instead of Australia) air quality monitoring stations would be much more representative of the population that lives nearby. Although calibration of the stations may still be a problem, cities in large countries have many stations per city, and therefore taking the average already reduces any random error.

It would be beneficial to investigate the extent of the correlation between AD severity and ozone exposure as an extension. Instead of using ‘prevalence’ as the metric used to quantify the AD rate in a country, DALY’s can be used instead. Prevalence only takes into account the number of people diagnosed with AD and not the severity of the condition while DALYs (disability-adjusted life years) – a measure of the number of years of full health lost to disease – may be a better indicator of severity.

In addition, a clinical trial can be conducted to establish a stronger, more direct link between the two variables. People with atopic dermatitis can be exposed to varying concentrations of ozone to determine if it exacerbates symptoms. However, there are many ethical considerations associated with a clinical trial that need to be considered, including patient health and consent.

Conclusion

To answer the research question: to a small extent, there is a correlation between AD prevalence in children aged 0-14 years and ozone AQI in 41 countries globally. This is justified both internally and externally: the Pearson correlation coefficient of 0.342, which is statistically significant; and external studies also support the conclusion. However, this investigation was limited in accuracy and reliability by the chosen database and therefore requires further research to fully establish the link between ozone and atopic dermatitis.

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