Intrauterine and Early Life Exposure: Determinants of Adolescent Atopy

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Abbreviations: PSY (psychological), ENV (environmental), MIC (microbial), OR (odds ratio), CI (confidence interval), SE (standard error), AD (atopic dermatitis), AR (allergic rhinitis), PPV (positive predictive value), FDR (false discovery rate), TP (true positive), FP (false positive)

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I. Abstract

Pediatric allergies present a variety of challenges. For parents, they can mean psychological and fiscal burdens. For children, they can mean years of health struggles and long-term physical damage. These diseases, such as asthma and atopic dermatitis, are common in childhood, often developing in a progression known as the atopic march. With the goal of elucidating the relationship between prenatal and early-life exposure and development of atopic disease, this project conducted a systematic literature review and meta-analysis on a number of influential factors. Exposure to maternal psychological distress, ambient air pollution, and gut dysbiosis were examined in this study, which employed the restricted maximum-likelihood (REML) method for analysis. The findings reveal significant impacts of exposure to maternal distress and pollution on the likelihood of developing allergies, as well as notable perturbations in the microbiome composition of atopic mother-child dyads. Meta-regression identified particularly sensitive windows of exposure, effects on allergy types, and significantly damaging pollutants. These results have socioeconomic implications given existing inequalities in healthcare; in particular, this research serves to underscore the influence of early-life events on long-term health disparities. To increase understanding of these risks, the results of this analysis were used to build a predictive model for new parents. Two general linear models were trained on the meta-analytic data, separately evaluating exposure to distress and air pollution. The program's interface uses an entry system for parents to gauge the risk of atopic disease in their children, helping them plan for possible health outcomes.

II. Introduction

With increasing prevalence of allergic diseases worldwide, understanding the factors that affect early immunological establishment is vital. The early-life period is when sensitivity of the developing immune system and microbiome is at its highest. Looking beyond exposures in childhood leads to the question posed by maternal exposures. Dependency, particularly on mothers, extends well beyond gestation and into the first few years of a child's life, meaning it is important to examine the effects of threatening exposures in both prenatal and postnatal periods.

To understand this issue, it is first necessary to understand the mechanisms of atopic diseases. These diseases are the manifestation of dysregulated T helper type 2 (Th2) cells. Upon first exposure to an allergen, the Th2 cells stimulate B cells to produce immunoglobulin E (IgE) antibodies specific to those allergens, a process known as sensitization. When exposure occurs again, the IgE antibodies activate mast cells and basophils, leading to release of chemical mediators such as the pro-inflammatory cytokines interleukins 4, 5, and 13. These cause allergic reaction symptoms as well as eosinophilia, where an excess of eosinophils accumulate and cause tissue damage; this is a biomarker of atopic disease (Nelson et al, 2022). The term atopy refers to a genetic predisposition to elevated levels of IgE, which makes one more sensitive to a diverse possibility of allergens, and its presence is influenced by a number of factors. An overview of the atopic march's manifestations and the studied causes is shown in Figure 1.

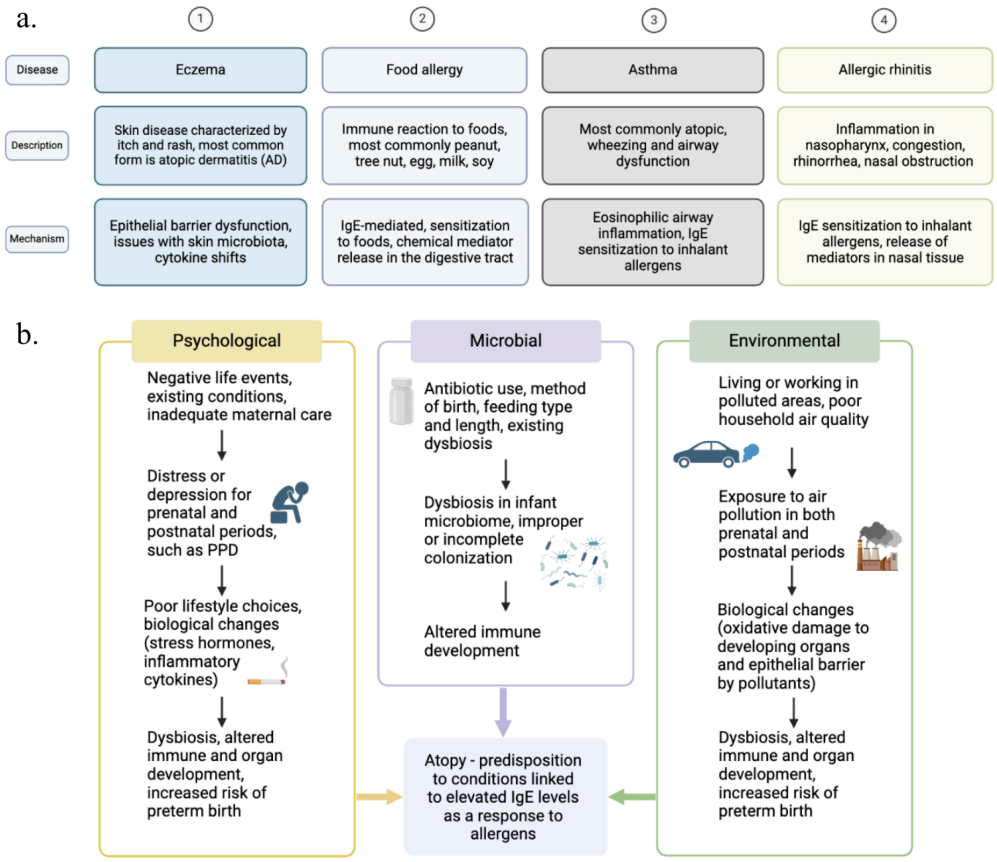

Figure 1. Summary of the atopic march and investigated influential factors. a) Throughout early life and childhood, atopic diseases typically develop in a certain progression b) Each of the factors affects atopy through multiple pathways and mechanisms (Comberiati et al, 2017; Gür Çetınkaya & Murat Şahıner, 2019; Elghoudi & Narchi, 2022; Pawankar et al, 2011)

The first category of interest is maternal psychological distress. There is a plethora of biological changes associated with stress and depression, many of which can have major impacts on the health of a fetus or infant. A major biomarker of stress is an increased level of cortisol, a hormone capable of passing through the placental barrier. Its presence is capable of altering fetal development, specifically the hypothalamic-pituitary-adrenal (HPA) axis through another hormone called corticotropin-releasing hormone (CRH). The HPA axis plays a crucial role in neuroendocrine functions, as its regulation is critical for proper development of both the central and autonomic nervous systems. Along with the HPA axis, these systems modulate immune responses. The ANS, for example, influences atopic sensitization and manifestation through neurotransmitters. Glucocorticoids (GCs) are another type of hormone released during stress, which can affect fetal organ development. Additionally, high GC levels increase the risk of preterm birth or low birth weight, both of which are correlated with underdeveloped organs and organ systems (Suh et al, 2017). Outside of purely biological factors, stress can lead to certain life choices, such as smoking and drinking, which can impair mental and physical health.

The second category examined is air pollution. Nearly the entire global population (99%) breathes in unhealthy air (WHO, 2022), including 93% of the world's children (WHO, 2018). Ambient air pollution is known to be damaging to many aspects of health, especially when

exposure occurs in utero as these cells are more sensitive to damage. For instance, traffic- and industrial-related pollutants such as particulate matter (PM) and ozone have been linked to airway inflammation and asthma exacerbation. As shown by Stieb et al (2012), maternal exposure to many of these pollutants is also linked to preterm birth and low birth weight, which correlates with underdeveloped organs through oxidative damage. Furthermore, children are particularly susceptible to pollution's effects due to a multitude of factors, including increased time outside and underdeveloped physiological defenses. In addition to direct impact on allergic diseases like asthma, exposure can have many indirect effects by negatively impacting organ development in childhood and increasing risk of respiratory infections by damaging the immune system and response (Aithal et al, 2023). Although the exact mechanism by which pollution affects allergic diseases is not completely known, possibilities include activation of an inflammatory response or epigenetic alterations, potentially similar to those linked to maternal smoking (Voynow & Auten, 2015).

The last category is the microbiome. The collection of microorganisms in an individual plays a vital role in overall health and exists in nearly all parts of the body, such as in the gastrointestinal tract and skin. Its role in immune development marks it as a key player in atopy. Composition typically stabilizes around age 3, indicating the importance of early life events in determining long-term health trajectory. Birth type is one of the earliest determinants of gut flora composition; cesarean-born infants are not colonized by the maternal vaginal flora and are at a higher risk of developing allergic disease. Another is feeding, as breastmilk is one of the main pathways for maternal flora to enter children (Wu et al, 2023) and thus influence both gut and nasopharyngeal microbiota. Its composition is also influenced by that of the maternal microbiome, which in turn is affected by diet, lifestyle, antibiotic use, and many other factors. Household environment can also be of impact, especially when examining the lung microbiome. For instance, houses with pets may contain a more diverse bacterial and allergen community, and this early exposure can have a protective effect (Lynch & Boushey, 2016). An imbalance in microbiota composition is referred to as dysbiosis and is associated with a myriad of conditions, including many allergic diseases. As a result, probiotics have been suggested as possible treatments to correct imbalances in the gut flora of atopic children. However, the existing literature contains conflicting results about the impact of dysbiosis on atopy.

The goal of this study is to increase specificity of knowledge by identifying particularly susceptible windows. The size and diversity of this research allows it to be applicable on a large scale (a process for which the framework is set here), which in turn allows for implementation of more effective solutions. The multiple aspects examined here can help to comparatively analyze the many factors that play a role of development of atopic diseases.

III. Methodology

Search strategy

Three databases were manually searched for relevant studies: PubMed, Science Direct, and Google Scholar. Keywords used in searching included both exposure (stress, maternal stress, postpartum depression, etc) and outcome (atopy, childhood allergy, allergy, atopic disease, etc) terms. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed throughout to ensure transparency during the study selection process, as displayed in Figure 2. Zotero was used to hold, sort, and organize the studies. After removal of duplicates, titles and abstracts were examined; irrelevant studies, literature reviews, and secondary analyses were removed. 76 studies were subject to a full-text review, and 45 were

included in the final analysis. 15 measured psychological distress, 16 measured exposure to air pollution, and 14 measured gut dysbiosis.

Inclusion/exclusion criteria

The search used the PICO (Population, Intervention, Comparison, Outcome) framework to set inclusion criteria as follows:

> *Population*: Mother-child dyads
> *Intervention*: None (PSY, ENV), none or randomized control trial (MIC)
> *Comparison*: Healthy and exposed dyads
> *Outcome*: Development of atopic disease (eczema, AD, AR, or asthma) in the child during early life or adolescence, reported in the form of odds ratios (PSY, ENV) or relative abundance (MIC)

These criteria were used to eliminate irrelevant studies, such as clinical trials and studies examining only food allergy. Food allergy was excluded due to significant distinctions in its pathophysiology when compared to the others, particularly for this study's measured exposures. Its presence in this meta-analysis may have led to a significant increase in heterogeneity and reduced accuracy of results, hence the choice to leave it out.

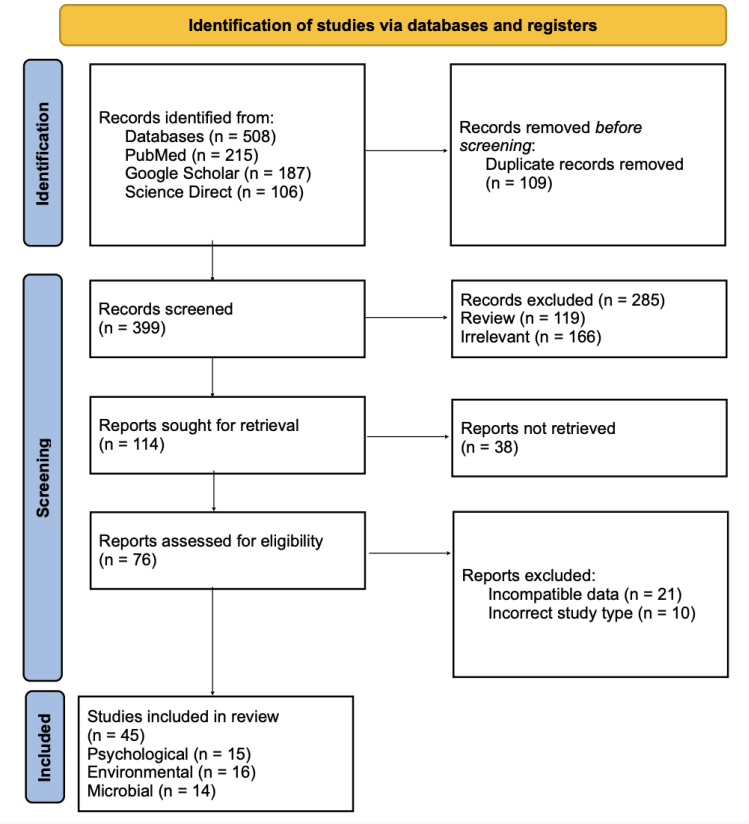

Figure 2. Reporting the number of studies identified and eliminated at successive points, the PRISMA flowchart details the process of study selection.

Data extraction

From each study (PSY, ENV), the author, year, country, sample size, measure, effect size, and outcome were extracted. Descriptive characteristics of each study can be found in Table 1. Additionally, each data point (often multiple from one study) was assigned an ID for the purpose of analysis. Data was cleaned and preprocessed using spreadsheet software, a process that included calculating standard error and variance for each data point. From each study (MIC), the measured species and the corresponding change out of five options (increase, decrease, no change, inconsistent, no data) were extracted.

Primary Author	Year	Country	Sample size (n)	Measure	Outcome
El-Heis	2017	UK	2871	Preconception stress affecting health, stress in daily living	Eczema at 12 months
Kawaguchi	2022	Japan	6056	Prenatal and/or postnatal distress	Atopic dermatitis between 1 and 2 years
Sausenthaler	2009	Germany	2516	Stress-related factors during pregnancy	Eczema by 6 years
Wang	2015	Taiwan	18,024	Postpartum depression, high stress levels	Atopic dermatitis at 3 years
Zhou	2017	France	1139	Clinical significant depression during pregnancy	Allergic rhinoconjunctivitis at 5 years
Shi	2022	China	4178	Stress in early and late pregnancy	Eczema at 2 months, allergic rhinitis at 2 years, persistent allergy
van der Leek	2020	Canada	12587	Prenatal, recurrent postpartum, and late-onset postpartum distress	Atopic dermatitis at 5 years, asthma at 7 years
de Marco	2012	Italy	3854	Stressful life events during pregnancy	Eczema, wheeze, asthma, allergic rhinitis (3-14 years)
Puosi	2021	Finland	1305	Prenatal high and decreasing/moderate and increasing anxiety, postnatal consistently high depression	Wheeze ever at 2 years, eczema at 2 years
Cookson	2009	UK	5810	Anxiety and 18 and 32 weeks gestation	Asthma at 7 1/2 years
Lee	2016	US	989	5 or more prenatal or postnatal negative life events	Asthma by 6 years
Zhou	2023	China	3131	Anxiety in at least 1, 2, or 3 trimesters	Asthma by 4 years

Table 1. Relevant characteristics extracted for each study include year of publication, study size, measured outcome, and country. Shown above are characteristics of the first 12 studies, and the full table is available here

Data analysis

All quantitative analysis (PSY, ENV) was performed using the R package metafor (Viechtbauer, 2010). The package provides a variety of models for meta-analysis, each with its pros and cons. The restricted maximum-likelihood (REML) model was selected for its unbiased handling of random effects, as there was significant variance between studies. Accurate estimation of variance is particularly important in cases with significant heterogeneity, which applies to both categories. The REML estimator also showed a significantly better fit compared to a fixed-effects (FE) model when judging by the 5 given goodness-of-fit measures (log-likelihood,

deviance, Akaike Information Criterion, Bayesian Information Criterion, and corrected Akaike Information Criterion).

In addition to the overall meta-analytic model, various other tests and methods were used to both visualize and quantify other parameters. The main purposes of such analyses were to assess the quality and sensitivity of the data. An influence test was performed on the full datasets, using eight measures of weight to identify particularly influential studies. Funnel plots were used for visual assessment and Egger's test for quantitative analysis of publication bias. Normal quantile-quantile (QQnorm) plots were used for visual assessment and the Shapiro-Wilk test for quantitative analysis of distribution. Bootstrapping was performed to ensure reliability of results; kernel density plots and histograms were used to visualize the resulting distribution. Baujat plots were used to detect potentially outlying studies through each study's contribution to the Q-statistic for heterogeneity. The effects of such outlying studies on heterogeneity (I^2) and on the overall effect size were visualized with a GOSH (graphical display of study heterogeneity) plot.

This method of analysis was not applicable to MIC due to the nature of the data. Instead, the data was analyzed through aggregation and subsequent comparative analysis. Due the size and diversity of the microbiome, there was significant variation in the measured species, as well as the taxon reported. Of the broader taxa, the most commonly reported types were at the phylum and genus level. Thus the data was aggregated at these levels, using 4 of the most abundance phyla and 5 of the most abundant genera. Each category was then analyzed separately based on the mode of the five changes.

By comparing each change to the mode, the data was categorized and subsequently suitable for quantitative analysis. For each category, the positive predictive value (PPV) and false discovery rate (FDR) were calculated, each expressed as a percentage. The number of true positives (TP) was equal to the number of changes that agreed with the mode, whereas the number of false positives (FP) was equal to the number of changes that did not agree with the mode, excluding studies with no data.
PPV: (TP)/(TP +FP) * 100
FDR: (FP)/(TP + FP) * 100

Application
The purpose of the program is to publicize the results of this research in a way where it is available to anyone. However, its results should be regarded with caution as it lacks the input of many other important factors, such as family history of atopic diseases. Thus the final model should only be regarded as a framework and as something that could likely be improved in the future with further review and analysis.

Multiple external datasets were required to create a model analyzing ambient air pollution. The EPA provided recent (2022) data on air quality per Core Based Statistical Area (CBSA). As this is not a well-known location metric, it was necessary to find the corresponding ZIP codes for each CBSA. This crosswalk was obtained per the US Housing and Urban Development website (HUD USER); it linked ZIP codes to GEOIDs (identifiers of CBSAs). In order to conduct geospatial nearest-neighbor search, the latitude and longitude coordinates per CBSA were needed, and this was obtained from the US Census website. Finally, the program required the

limits on air quality that gave the baseline of what crossed the line as a health risk. This data was also obtained per the EPA, and gave concentration limits for each pollutant. As both the original air quality dataset and the limit dataset were from the EPA, there was uniformity in pollutants and their measurements, and no additional information or conversions were needed.

In order to obtain sufficient data to train the general linear models (GLMs), bootstrapping was performed. As touched on in the *Data analysis* section above, bootstrapping is a technique in which random subsets are drawn from an existing dataset, creating many more available samples compared to the original data.

In the bootstrapping process, 2500 random samples were drawn from the original PSY and ENV data. Nonparametric bootstrapping was used for its robustness and lack of assumption regarding distribution of the original dataset, a choice supported by the analysis of data distribution in both categories (detailed further in the Results section). These samples were then used to train the GLM. Performance was evaluated using mean squared error (MSE) and k-fold cross-validation.

The program interface allows a user to enter perceived distress levels during gestation/early life as well as a ZIP code. The level of distress was inputted into the model, and the returned result came in the form of an OR. Exposure to ambient air pollution was more complicated as a location could not be entered directly into the GLM. Instead, the entered location was treated as a central point, and a BallTree model was used to find the geographic nearest-neighbors. This was the optimal model due to its compatibility with the Haversine metric, which is favored for 3-dimensional distance calculations (Agrawal, 2021). Data from the nearest locations was then used to determine the average air quality in an area, which could then be entered into the model. Again, the result came in the form of an OR.

The final result, a cumulative OR, comes from multiplying the results of both exposures. In the program, it is expressed as a percentage increase in likelihood for greater understanding. Additionally, the program returns online resources to provide additional support for new parents, which are especially beneficial for those without access to high-quality in-person healthcare.

IV. Results

Psychological distress increases likelihood of atopy

The summary result is displayed in Figure 4. Maternal psychological distress, accounting for all forms and across all windows, was associated with increased risk of atopic disease (OR = 1.33, 95% CI 1.26, 1.40, $p < .0001$). Results displayed statistical significance despite moderate heterogeneity ($I^2 = 47.53\%$).

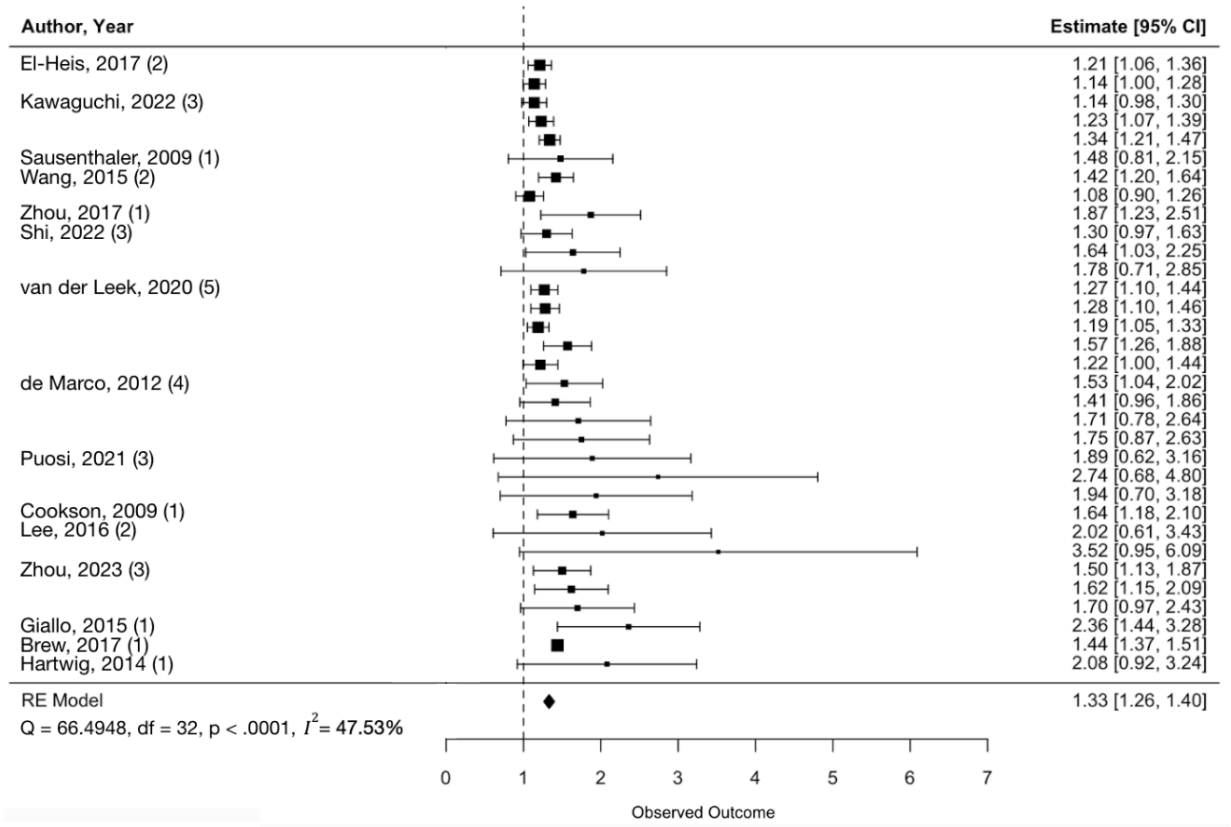

Figure 3. Forest plot illustrating the increased likelihood of developing atopic disease in those exposed to maternal distress compared to healthy dyads.

The funnel plot (Figure 5) showed asymmetry, indicating publication bias, which was confirmed by Egger's test ($z = 4.7794$, $p < .0001$). As the resulting funnel favors greater effect sizes, there is a possibility of overestimation in the meta-analytic model. An adjusted model was created using the trim-fill method, which did indeed show a lower effect size with a symmetrical funnel (OR = 1.29, 95% CI 1.23, 1.36).

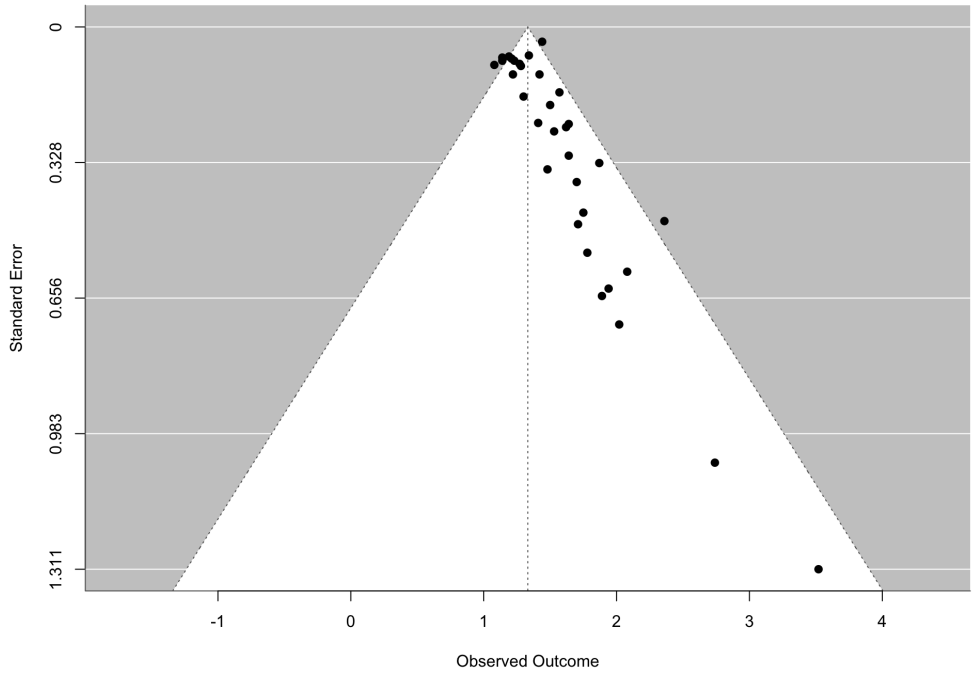

Figure 4. Publication bias was evident in selected studies (PSY).

Subgroup analyses were performed to determine the influence of stress based on time of exposure and type of allergy. The prenatal period was identified as a particularly sensitive window (prenatal OR = 1.38 95% CI 1.28, 1.49 compared to postnatal OR = 1.26, 95% CI 1.09, 1.35); however, regression did not show timing to be a significant moderator (p = 0.13). Compared to skin allergies (eczema and AD), respiratory allergies (asthma and AR) were impacted more by distress (respiratory OR = 1.48, 95% CI 1.37, 1.62 compared to skin OR = 1.24, 95% CI 1.18, 1.29, p <.0001). Regression by year was not significant (p = 0.31).

The influence test returned one influential study (Brew, 2017), so a leave-one-out (LOO) analysis was subsequently performed. The results showed that, excluding this study, the summary effect size would have been slightly lower (OR = 1.31, 95% CI 1.25, 1.38).

The Baujat plot showed one study (Giallo, 2015) with a notably high contribution to heterogeneity, labeling it as a potential outlier. The GOSH plot showed exclusion of that study to result in a lower effect size and slightly smaller value of I^2.

The QQnorm plot displayed a curve in the center, indicating non-normal distribution. This may be due to underrepresentation of effect sizes nearer either extreme, which may partially be a result of publication bias. The Shapiro-Wilk test confirmed the absence of normality (W = 0.82, p = 9.09e-5). This has minimal impact on the previous analyses, however, as an advantage of REML is that it does not assume normality.

Bootstrapping was performed using 2500 subsets to strengthen reliability of results. The summary effect sizes were similar to those of the original analysis (mean OR = 1.34, median OR

= 1.33, 95% CI 1.25, 1.44). By ensuring the validity of the results, the justification for their use in the program is strengthened.

Environmental pollution increases likelihood of atopy

The summary result is displayed in Figure 6. Exposure to air pollution, accounting for all pollutants and across all windows, was associated with increased risk of atopic disease (OR = 1.22, 95% CI 1.16, 1.27, p <.0001). These results also displayed statistical significance despite considerable heterogeneity (I^2 = 95.05%).

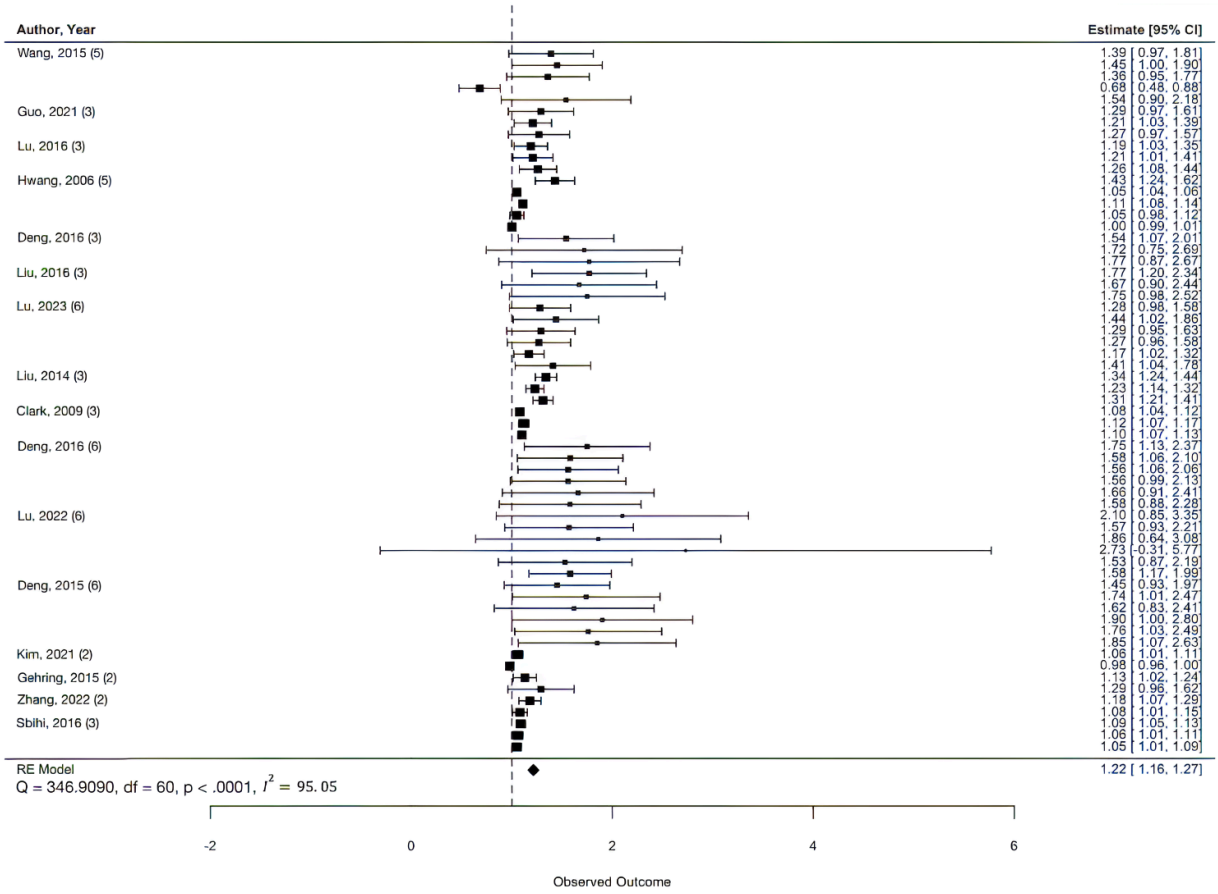

Figure 5. Forest plot illustrating the increased likelihood of developing atopic disease in those exposed to ambient air pollution compared to healthy dyads.

Again, the funnel plot showed asymmetry. Publication bias was confirmed by Egger's test (z = 8.7381, p <.0001). The resulting funnel also favors greater effect sizes, so there is a possibility of overestimation. The trim-fill model supported this proposal, showing a lower effect size (OR = 1.15, 95% CI 1.11, 1.20).

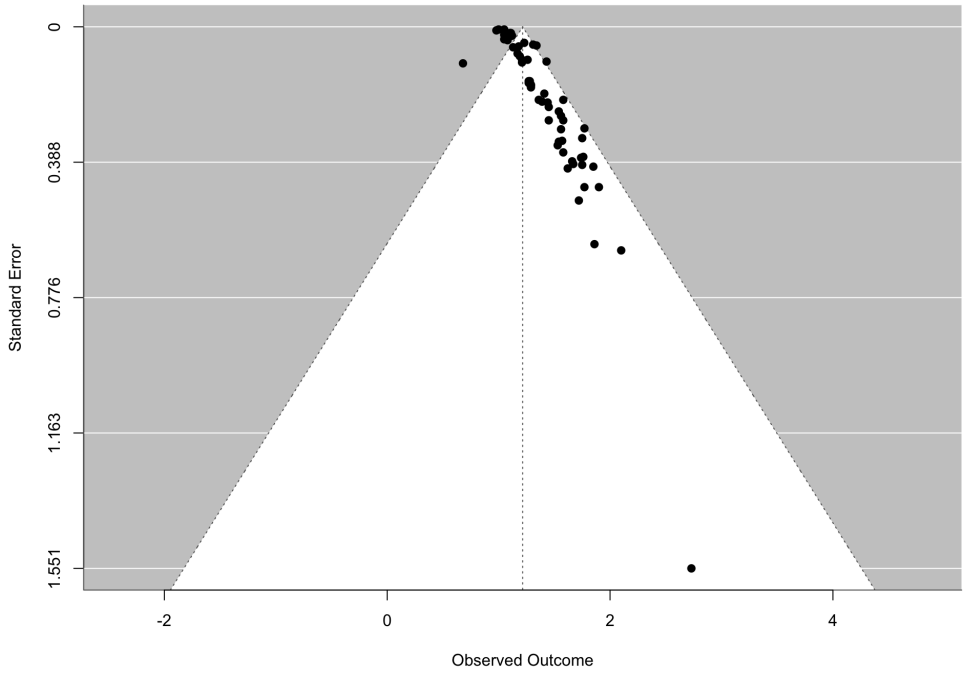

Figure 6. Publication bias was evident in selected studies (ENV).

Subgroup analyses were performed to determine the effects of pollution based on time of exposure and individual pollutant. Similar to PSY, the prenatal period was identified as a particularly sensitive window, a result supported by regression (prenatal OR = 1.29, 95% CI 1.20, 1.38 compared to postnatal OR = 1.17, 95% CI 1.06, 1.31, p = 0.02). Meta-regression by pollutant showed SO2 and PM2.5 to have the greatest effects in a prenatal and postnatal period, respectively; however, neither showed statistical significance. NO2 and SO2 were significant when analyzed across both periods (p = 0.03 for both). NO2 was also significant for a prenatal period only (p = 0.02). No individual pollutants were significant for a postnatal period. Collectively, these results indicate that the relationship between ambient air pollution and atopic disease does not depend heavily on the specific pollutants. Regression by year was not significant (p = 0.10).

No influential studies were detected, thus a LOO analysis was unnecessary. Again, one study (Wang, 2015) was visually detected to have a comparatively high contribution to heterogeneity, labeling it as a potential outlier. The GOSH plot showed exclusion of that study to result in a near-identical effect size and a slightly lower value of I^2.

The QQnorm plot again showed non-normal distribution; both tails were lower than expected and the middle curved up slightly. This may indicate an excess of more extreme values. The Shapiro-Wilk test again confirmed absence of normality (W = 0.93, p = 2.86e-3); however, the results were closer to a normal distribution compared to PSY.

Bootstrapping was performed again using 2500 subsets. The summary effect sizes (mean OR: 1.21, median OR: 1.21, 95% CI 1.15, 1.29) were similar to those of the original analysis. As with the first category, this closeness further justifies the use of these values in the program.

Microbial imbalances are correlated with atopy

As detailed in the Methodology section, the data was aggregated at the phylum and genus level. In general, the data showed perturbations at the genus level to be more consistent than those at the phylum level. This is logical as genera are more specific than phyla, so the aggregation makes a smaller assumption regarding the effects of each taxum. As such, to use dysbiosis as an indicator of atopy, narrower taxa should be compared to increase accuracy of prediction. Figure 7 below displays the changes in relative abundance of specific phyla and genera in atopic dyads.

Key:

Figure 7. Changes in microbiome composition of atopic dyads. a) Significant variation between studies was observed at the phylum level b) Slightly less variation was observed at the genus level

At the phylum level, atopic dyads exhibited decreased abundance of Actinobacteria and Bacteroidota, as well as increased abundance of Firmicutes and Proteobacteria. At the genus level, atopic dyads exhibited decreased abundance of Bacteroides, Bifidobacterium, and Faecalibacterium, as well as increased abundance of Clostridium and Ruminococcus.

One subgroup analysis was conducted to compare the changes at the phylum level in the maternal microbiome to those of the child microbiome. However, due to the severe imbalance in number of data points (3 maternal, 13 child), the results were almost identical to those of the

original phylum analysis and revealed no new insights. Any analyses conducted on each category individually would hardly be comparable, thus rendering the subgroup analysis irrelevant.

As displayed in Table 2, the PPVs in the genus category tended to be more accurate, which makes sense as they are more specific. Many of the categories showed PPVs near or even below 0.5, meaning that not all the categories are indicative of changes in odds of atopy. This also means that changes in microbial abundance should be used cautiously in tests. The amount of variance may be due to clinical diversity, as there are existing differences in microbiome composition along the lines of race or lifestyle differences.

	Mode	Positive	Negative	PPV	FDR
Phylum					
Actinobacteria	Decrease	6	3	67%	33%
Bacteroidota	Decrease	3	2	60%	40%
Firmicutes	Increase	4	6	40%	60%
Proteobacteria	Increase	4	2	60%	40%
Genus					
Bacteroides	Decrease	3	2	60%	50%
Bifidobacterium	Decrease	4	3	57%	43%
Clostridium	Increase	3	3	50%	50%
Faecalibacterium	Decrease	3	1	75%	25%
Ruminococcus	Increase	3	0	100%	0%

Table 2. PPV and FDR were calculated for each phylum and genus. These values give an indication of the accuracy of using a given category as a test for atopic disease.

V. Discussion, Conclusion, & Future Work

This research demonstrates that exposure to both psychological distress and environmental pollution have significant impacts on development of atopic disease, with varying effects depending on the time of exposure and type of allergy. Additionally, there are notable perturbations in the gut microbiome of atopic infants and mothers. Through identification of specifics, the results are applicable in a simple yet impactful way, as demonstrated by the program. The cumulative sample size and the diversity of location ensure that the results do not apply only to a small group.

The importance of this study lies in the communication of results to the general populace, especially regarding the impacts of distress and dysbiosis. The negative impacts of ambient air pollution have been long-established; while this research was able to identify sensitive windows and particularly harmful pollutants, it would likely be news to very few that air pollution is

damaging to the health of children. The impacts of the other two factors, however, are less widely known, likely due to inconsistency in existing literature. This study's results can be considered a significant reinforcement for the positive effect size proposed by the many existing studies. As a crucial advantage of meta-analysis lies in the size of its sample, the validity of this conclusion - that stress and dysbiosis are associated with childhood atopic disease - is strengthened by the combined study size. With this knowledge, the relationship between atopy and maternal distress or gut dysbiosis can more confidently be publicized. In addition, with the dramatic increase in global postpartum depression rates during the COVID-19 pandemic (Chen et al, 2022), it is important to monitor rates of allergic disease, as well as their likely causes, in the near future as the pandemic's effects recede.

The clear and critical disparities present in atopic disease further increase need of research into its causes. Allergic diseases, particularly asthma, are both more prevalent and more severe in minority and low-income communities. While genetic differences are likely to play a role, this disparity is also almost certainly a result of structural barriers. For instance, Guo et al (2022) found that low-income areas (i.e., residents living at below the 200% federal poverty level) are less likely to be in close proximity to healthcare facilities. This issue is exacerbated by the fact that such residents often lack transportation, whether it be public transit or a car. Air quality is another example; polluted areas tend to have higher percentages of non-white residents (Forno & Celedon, 2014). These instances are not recent developments; Clausing et al (2023) explained that many are the effects of historical racism (e.g., redlining leading to poor/minority communities being located in "undesirable" areas, often in close proximity to heavy traffic or polluting industries). Additionally, healthcare barriers and stigmatization often preventing women of color from seeking mental health treatment around pregnancy. Specifically, Kozhimannil (2013) showed that Black and Latina women were less likely to initiate, receive initial, or receive continued care postpartum. Cited reasons are often monetary, such as lack of time, no adequate childcare, and insufficient insurance coverage. These clearly indicate the relationship between maternal care and income level. From this, it can be understood that the link between socioeconomic status and prevalence of atopic disease may be causal rather than simply correlational.

This research is not without its limitations. First, the manual nature of the search leaves it prone to human error and bias, which could be corrected with the help of automation tools for literature review. Automation may also have enabled a more comprehensive and efficient search. Additionally, in this study, no demographic information was analyzed. In terms of quantitatively assessing disparities, no new insights are gained. The results are also prone to location bias, most notably in ENV as eleven of the sixteen studies analyzed took place in China. Thus ENV results may not be as generalizable to a larger and more diverse population, a limitation augmented by the homogeneity of the population of China.

These results also can provide insight into future therapies for atopic children. Examination of the home environment, mental health of parents, and air quality can give insight into places to address, and probiotics or antibiotics can be used as a potential treatment as well. Additionally, focusing on improving disparities in maternal healthcare, particularly paying attention to the impact that mental health can have on the child's physical health, can reduce gaps in allergy prevalence and severity. However, any potential treatments should be thoroughly discussed with health professionals, especially when considering antibiotics; their use in a developing gut microbiome has the potential to induce further dysbiosis.

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