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Research Article

The Hygiene Hypothesis: How Relevant

Kebret Kebede[1]* and Jeffrey Rollins[2]

[1]*Professor, Department of Physical and Life Sciences, Nevada State College, Henderson, Nevada, United States*

[2]*Department of Physical and Life Sciences, Nevada State College, Henderson, Nevada, United States*

***Corresponding Author**: Kebret Kebede, Professor, Department of Physical and Life Sciences, Nevada State College, Henderson, vada, United States.

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Abstract

The Hygiene Hypothesis was originally hypothesized by David Strachan in 1989 for an explanation in the increase in allergic diseases like asthma and hay fever [1]. Further evidence suggests that early childhood microbial exposure results in less frequent incidences of hypersensitivity reactions and autoimmune disorders. This lack of early childhood exposure to microorganisms increases the sensitivity to disease by weakening the natural development and normal function of the immune system. Due to the rise in modern living conditions in developed countries, lack of natural environmental exposure to these microorganisms leads to an increase in atopic diseases in the later stages of development.

Hygiene Hypothesis can be associated with more than just cleanliness and removal of microbes from your lifestyle. It can also be subject to what it is that we eat, or rather what we don't eat, as well as the drugs we take. Avoiding microbes is more than sanitizing the areas around us, but also the normal flora of our internal areas as well. Foods that destabilize the homeostasis of our gut microbiota can result in obesity. Ingestion of antibiotics at early stages of development can led to more frequent incidences of several autoimmune diseases.

A future study should intend to determine the factors that make females more susceptible to autoimmune diseases. Current literature maintains that females are more likely to develop auto-immune diseases than males. The correlation is due to the development of estrogen and how it may contribute to the pathogenesis of diseases like multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. Estrogen-related mechanism of action is most notable on the estrogen receptor alpha (ERα) [2]. The predominant number of female students enrolled at Nevada State College played an important role in the results.

Keywords: *Hygiene Hypothesis; Estrogen Receptor Alpha (ERα); Asthma*

Introduction

Since the 1980s, evidence shows a steady rise in atopic disease (including asthma, anaphylaxis, allergic rhinitis, food allergies) among the Millennial generation, most significantly in countries that are industrialized. It is also recognized to have a broader effect on chronic inflammatory diseases and immune-mediated diseases (including type 1 diabetes, inflammatory bowel disease (IBD), multiple sclerosis (MS), Crohn's disease and ulcerative colitis) [3]. These diseases result from tissue destruction mediated by chronic inflammatory processes which are brought about by white blood cells (lymphocytes) attacking organs or tissues inside of the body. In the short period of time from the 1980s to present, when the research pertaining to Hygiene Hypothesis was extensive, changes in sanitation and awareness of microbial spread necessitated frequent hand washing and focus on hygiene. This led to an exponential increase in the incidence of atopy and autoimmune diseases. Based on these findings several researchers were inclined to point to environmental factors as being the cause [4].

Irritable Bowel Disease (IBD) is chronic inflammation and irritation of the small and large intestine. Although cases of IBD existed before the emergence of modern sanitation, cases were uncommon [5]. With the introduction of industrialization in developed countries,

IBD has emerged quite more frequently over the last 40 years, and more than 1.6 million people are affected by IBD in the United States alone [6]. It is also more common with those who live in cities, rather than those who live in rural or agricultural settings. This combined information suggests that IBD is more likely to present in those who live in industrialized or developed countries [5].

Asthma is a condition in which airways narrow and restrict air flow due to chronic inflammation, oftentimes triggered by allergies. Like IBD, asthma has seen a notable increase in reported cases over the last 40 years. The majority of documented cases are located in large populated areas in developing countries. This information also suggests that asthma is more likely to be present or caused by living in cities of industrialized or developed countries [7].

Additionally, Multiple Sclerosis (MS) is an immune-mediated disease in which the body destroys neural pathways in the central nervous system. Just like asthma and IBD, MS shows the most prevalence in industrialized or developed countries. The occurrence of MS has increased dramatically over the last 40 years as sanitation has improved and the methods of sanitization became more commonplace [8].

The industrialized world has lesser incidences of contamination by disease-causing microbes through the process of pasteurization (the process of heat processing a liquid or food to kill pathogenic bacteria to make the food safe to eat), and frequent use of sanitizers (i.e. pocket hand sanitizing liquids, sanitizing wipes, household cleaning products). According to the hygiene hypothesis, the frequent use of these chemicals and the resulting cleanliness that ensues has reduced our exposure to primitive bacteria. With the extreme reduction in these exposures, the incidences of environmental allergies and autoimmune disease are on the rise (Rasoul., *et al*. 2015).

Studies have shown that in less industrialized areas, where children are exposed to infectious agents and parasites (Helminths) they have reduced risk factors of chronic inflammatory diseases like ulcerative colitis, or Crohn's due to suppression of autoimmunity (Rasoul., *et al.* 2015). In people who are infected with helminths, the infection has been shown to suppress autoimmune disease. Also, of note is that those who were infected with helminths earlier in development had a far less incidences of acquiring chronic inflammatory diseases and had increased immune health in adulthood [9].

Several studies conducted in the past few decades suggest that early administration and exposure to antibiotics can cause further problems in later stages of development. Children who were administered antibiotics within the first week of life are at a higher risk of acquiring allergic rhinitis by the time they reach the age of school attendance [10]. Further studies show that when a child in early development is exposed to antibiotics, there is a strong correlation to a higher chance of developing asthma and allergic disease [3].

The conclusive studies that demonstrate that antibiotics can cause problems emerging from early exposure support the theory of hygiene hypothesis from a different perspective. Early theories were focused on the association between natural environmental exposures of children, and how that correlated to diseases and disorders in later life. The new results corroborate with a more expanded perspective of the original theory, that overprotection and subduing children's exposure to the naturally present microbes by use of antibiotics and confined lifestyle, lends itself to more incidences of autoimmune disorders.

Diet plays an important role in the development and homeostasis of our bodies' metabolism and immune system. According to the World Health Organization, obesity and diabetes have continuously increased over the past 3 decades [11]. One study theorized the increase in obesity can be directly related to hygiene hypothesis. This study compares the gut microbiota composition in the regulatory process of energy homeostasis and fat storage. Their study determined that westernized diet played a key role in weight gain and metabolic response. They theorized that the improved sanitation and western diet increased susceptibility to metabolic diseases [12].

More than 75% of all autoimmune diseases have been described with a sex-linked susceptibility. The most prevalent risk factor is for women producing the sex hormone estrogen. Female sex hormone estrogen has shown a direct role in the development of T cell autoimmune response. "Deletion of estrogen receptor α (ERα) in T cells reduced disease burden in a mouse model of colitis. ERα-expressing T cells were more activated after stimulation, proliferated more, and expressed more proinflammatory cytokines than T cells lacking this receptor. Conversely, ERα-deficient T cells were more readily skewed to a regulatory T cell phenotype" [2]. This combined information shows the direct link between autoimmune response and the female sex hormone estrogen.

The data that we collected for this study was to scrutinize whether the hygiene hypothesis findings would continue to be relevant based on our demographically diverse sampling or if it would differ based on socio-economic backgrounds of the students who were enrolled in Microbiology at Nevada State College. Nevada State College has over 600 pre-nursing students attending each semester. Students at this institution are diverse in terms of race, gender, and socio-economic background. The student population at Nevada State College consists of students from different states across the nation. The exposure among the students would be varied and was essential for a randomized population pool.

The data collected was to be compared to the other studies and findings of similar nature, to determine if our sampling would result in the same conclusion. If our results differed from other studies and information, we would attempt to define the variable by completing a supplementary study to further assess the variation.

Our method of obtaining information was using a questionnaire. This was determined to be the most unambiguous and direct way to obtain the information required for the study. By choosing to employ direct questions, the survey was determined to be unbiased and with little to no room for error in data collection.

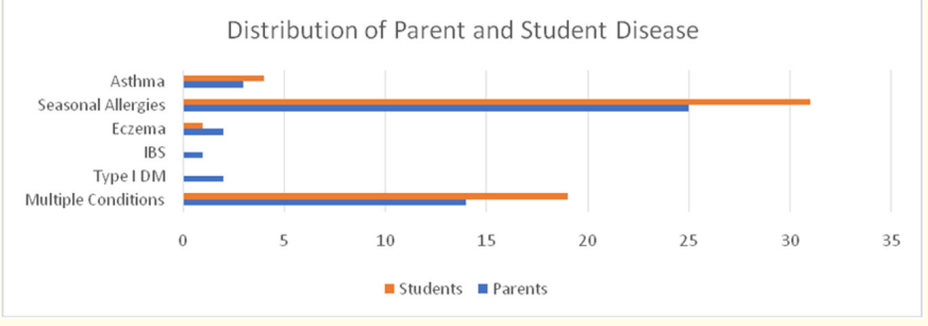
Materials and Methods

Our method of sampling was to survey both male and female students, of varying ages and demographically diverse backgrounds that are attending Nevada State College. We surveyed 89 undergraduate students who were enrolled in Microbiology. Participants ranged in age from 19 - 50 years (mean = 28.1, SD = 7.74). We addressed the significance of diversity by compiling a questionnaire that asked the individual's birthplace and family disease history. We ascertained early childhood exposure by asking questions relating to early preschool exposure and environmental exposures, this included agricultural and residential microbes that they may have been exposed to. In total there were 20 questions presented to the student in this study.

We surveyed both male and female students over 3 semesters. This time period extended from Fall 2016 to Spring 2017. The location of the study was on the campus of Nevada State College, in a classroom setting. All participants were volunteers and were not influenced to choose a specific answer. Out of the 89 students who were surveyed, 65 were female, 22 were male, and 2 identified as other. Due to the limited number of male students enrolled in Microbiology, more female students were surveyed for the study than males. We found associations between frequent occurrence of seasonal allergies and parent disease ($X^2 = 12.31$, $p = .031$), agricultural exposure ($X^2 = 4.185$, $p = .041$), and gender ($X^2 = 8.494$, $p = .014$).

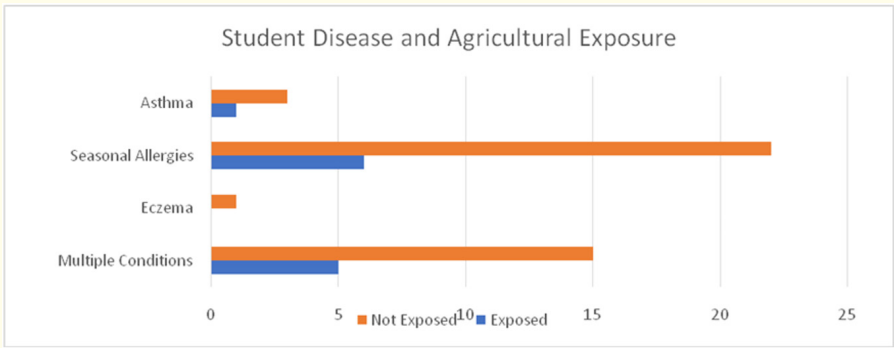
Results

Graph 1 shows that in our sampling, if a parent has an allergic disease, then the offspring were also very likely to have an allergic disease. Four parents had asthma, with three students also having asthma. Twenty-five parents were stated to have seasonal allergies, while thirty-one students presented with seasonal allergies. Two parents had eczema, while only one student had eczema. One parent had Irritable Bowel Disease and no student presented with this disorder. The same occurrence was exhibited with type 1 diabetes, two parents had the disease and no students presented with the disorder. This shows an association between hereditary factors or shared living conditions and the development of allergic diseases.



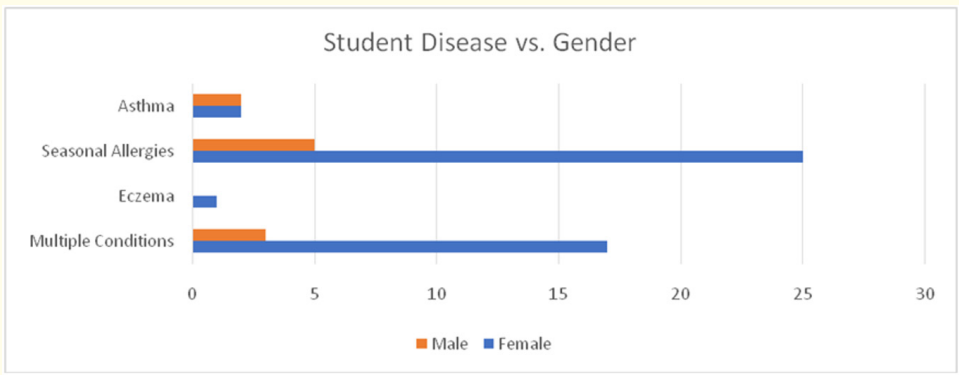
Graph 1: *Distribution of parent and student disease.*

Graph 2 shows the results of those individuals that were exposed to agricultural environments. Those students that were exposed to early agricultural and environmental exposures had a lower reporting of asthma, allergic disease, and autoimmune disease (included in multiple) greatly decreased incidences. While the incidence of autoimmune diseases in those students who did not report exposure was significantly higher. This is consistent with the hygiene hypothesis' original findings, and other subsequent studies [1,4].



Graph 2: *Student disease and agricultural exposure.*

Graph 3 indicates that our sample size was skewed towards females and that the incidence is different between genders. This could be an artifact of sample size. Age was not a significant factor in those who developed the diseases analyzed in this study. We also discovered that the earlier a participant attended pre-school and was exposed to a variety of nonfamilial microbes, the incidence of allergic disease was less common (not graphed).



Graph 3: *Student disease vs. gender.*

Discussion

From our survey, we can determine there is a strong correlation between early microbe exposure and fewer instances of environmental allergies, asthma, and autoimmune disease. The data provided answers to our testable hypothesis that our smaller sampling would have a similar outcome as the results of previous experiments. These findings are in support of the hygiene hypothesis but should continue to be tested as more information relating to the mutualistic, commensal, and parasitic relationship between humans and microbes are discovered.

Additional testing should be accomplished in the future with an even number of male and female students to determine the role sex-hormones play in the determining of autoimmune disease with those associated with environmental factors. Other factors to consider would be diet and obesity in the students who are part of the study.

As the world advancement in technology and science continues, so will the world population and its diverse health-related challenges. Understanding the hygiene hypothesis will be important as more individuals will be at risk for atopic and autoimmune disease. Further testing must be completed if we wish to discover a way to reduce or eliminate the instances of asthma, allergic, and autoimmune diseases. Data collection and research in this area is ongoing and corresponds with the research that is being conducted on the second human genome, or microbiome, which is increasing our understanding of microbes and their vast impact on human health and disease. Studies like the one we completed, although smaller in size, only add to the foundation of these experiments. The more data we can collect and interpret, the closer we are to finding a solution to many of the immune-related problems the world is facing [13-16].

Conclusion

Although the relevance of the hygiene hypothesis has been questioned in the last few years, our results corroborate with the hypothesis. We are fully cognizant of the fact that our sample size is limited and that we need to continue collecting data by conducting a broader survey.

It has been evident that children exposed to microorganisms during natural birth have fewer incidences of atopic diseases. In developing countries where the environment is not as sterile as that of industrialized communities, the exposure to microorganisms from mother to child, from siblings and playmates and relatives help the child to trigger and reinforce their immune mechanism. One general consensus is that as the modern environment changes fundamentally from the perspective of reduced bacterial exposure due to increased cleanliness using soaps and antibacterial agents, the incidence of atopic diseases and other more common conditions has not been correspondingly reduced. We should also consider genetic factors that equip certain groups and communities with special resistance to various diseases and conditions which in turn are characteristics developed thru early exposure to microorganisms.

As our modern world offers a much cleaner environment of living, the increased use of vaccinations, anti-microbial agents, antibiotics, hospital births, and a more urbanized life style, we cannot affirm that this has reduced the incidence of atopy and autoimmune conditions. To the contrary it has been shown that the incidence of diseases such as insulin-dependent diabetes mellitus that is on the rise has led to speculations that it may have some degree of association with microbial or viral exposure or lack of exposure.

It was evident that children that grow up in developing countries or rural environments leading to close contact with domestic farm animals, consumption of food that was not prepared in extreme hygienic conditions, drinking water from not so clean sources, and living in a not so sterile environment have a lesser incidence of Asthma and related airway diseases. The early exposure may have contributed to the functional activation of the immunological cells and their regulatory processes, by recognizing self and foreign antigens. This, obviously, does not preclude that they may be subjected to bacterial, viral and more frequently helminthic infections as they are growing up.

In conclusion, the relevance of the hygiene hypothesis or its biological plausibility does not seem to have been eroded. However, we may need to consider an expansion of the term or replacing it with a term specifically associated with exposure to microorganisms rather than the concept of the level of cleanliness.

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