Rates of Autoimmune Disease Increasing in Women

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An Integrative Literature Review

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Abstract

Autoimmune disorders (AD) are a group of highly disabling pathological conditions that are growing at an alarming rate affecting approximately 8% of the population. These disorders occur more frequently in women, as 78% of those diagnosed are women. Little conclusive research has been conducted as to determine why there is a tremendous sex disparity when looking at the rates. Due to the overall poor health that results from these disorders, there is an increase in the societal burden in terms of health care costs, loss of work productivity and reduced quality of life. The aim of this integrative literature review was to determine the reason for the sex disparity in autoimmune disorders and to determine the collective disease burden of these disorders on women. From this review, a determination will be made as to what education and preventative measure are being directed towards women in an attempt to decrease autoimmune rates. The literature search for the presented topic was found in the databases of CINAHL, ProQuest Nursing & Allied Health Sources and PubMed. The terms searched while researching this topic included: women, autoimmune, prevalence, and sex disparity. Results revealed that the sex disparity in autoimmunes are due to immunity interaction with female hormones, the presence of a double X chromosome, and immune response variation between males and females making their predisposition complex. With alteration of ICD codes to include contributing autoimmune disorders in death, the true burden of mortality that women face was revealed highlighting the need for further emphasis and research on this topic. Due to the limited research and knowledge, nurses need to be advocates for their female patients as they play a vital role in educating women on their risk and reducing their disease progression.

Keywords: women, autoimmune, prevalence, sex disparities, rise
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Chapter 1: Introduction

Background and Significance

In the past two decades, the rates of autoimmune diseases have expanded exponentially. Presently, they account for the third most common category of disease in the United States affecting approximately 5 to 8% of the total population (Fairweather & Rose, 2004). This type of diverse disease, first described by Ian Mackay and Macfarlane Burnet, is characterized by a dysfunction in the immune system causing a failure of an organism to tolerate its own cells resulting in an abnormal immune response by lymphocytes and/or antibodies (Ngo, Steyn & McCombe, 2014).

Autoimmunity results from an inflammatory state as the body attacks its own cells causing damage throughout the body's tissues and organs. In these diseases, the body literally invades itself, causing an inflammatory state while damaging its own tissues and organs at every site in the body (Fairweather & Rose, 2004). This response can either be classified as organ specific or systemic depending on the nature of the inflammatory process and cells that the body deems as “nons elf” (Ngo et al, 2014). This state causes its host homeostatic dysfunction resulting in debilitating symptoms for the individual (Mallampalli, Davies, Wood, Robertson, Polato, & Carter, 2013). In turn the individual is left with lifelong disabilities and a substantial health and financial burden due to the chronic nature of these diseases and associated comorbidities (Mallampalli et al, 2013).

The exact cause of autoimmune disorders has not yet been determined. Current research widely identifies that autoimmune dysfunction develops as a result of genetically susceptible individuals becoming exposed to environmental agents which trigger the onset of disease (Ngo et al, 2014). Each one of the nearly 80 identified autoimmune disorders have been shown to have
strong association with genetic variability in the human leukocyte antigen gene in combination with small effects on other genes contributing to the increased genetic susceptibility of certain individuals (Ngo et al, 2014). This genetic component can attribute to the incidents of autoimmune related diseases in families as a result of the interaction of common genes, accounting for an increase in an individual's genetic susceptibility (Ngo et al, 2014). Recent epidemiological trends in the incident rates also indicate a strong environmental cause, since large changes in rates over short periods of time cannot be explained by genetics alone (Mallampalli et al, 2013). The risk of specific autoimmune diseases such as systemic lupus erythematosus or Graves’ disease, have been linked to such environmental agents such as silica, pesticides and cigarette smoking (Mallampalli et al, 2013). The link between environmental exposure and autoimmune dysfunction has been proven in many studies yet, the exact mechanism of how this correlates is not fully understood (Mallampalli et al, 2013). Thus, it can be concluded that both genetic and environmental factors play a role in an individual's susceptibility in the development of one of these diseases.

But how does having two X chromosomes play a role? When examining incidence rates of autoimmune disease over a population, there is a profound sex disparity. 78% or 6.7 million of those diagnosed with autoimmune related disorders are women (Fairweather & Rose, 2004). Collectively, autoimmune diseases account for the fifth leading cause of death to women under the age of 65 (Mallampalli et al, 2013). Most notable are systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis and thyroid related diseases, which are diagnosed in women at a 9-10 times greater rate than men. As noted before, current research suggests that autoimmune diseases arise from the interplay between an individual's genetic susceptibility and environmental agents, yet neither of these causes can explain the role of sex and gender influence
of the mechanisms leading up to an autoimmune disorder (Mallampalli et al, 2013). While autoimmune related disorders have been rising in the last decades, the understanding of their prevalence and incidence is still unknown (Mallampalli et al, 2013).

**Problem Statement**

Despite researchers knowing of the female prevalence of autoimmune related disorders for the past 100 years, only recently has attention been paid as to why this occurs (Whitacre, 2001). When first discovered due to their rarity, autoimmune related disorders were looked at individually, as research tended to focus on questions pertaining to specific disease related mechanisms (Whitacre, 2001). With recognition that these disorders are collectively linked, the true extent of the sex disparity in autoimmunes was accepted. Presently, a knowledge gap still exists as to why there is a sex disparity in autoimmune related disorders. With the rates of autoimmune disorders rising in women, there is currently no conclusive research to suggest why this is. These diseases collectively result in a major public health problem due to their chronic nature which in turn increases societal burden in terms of healthcare costs, work productivity and reduced quality of life (Mallampalli et al, 2013). Due to this lack of research, the collective disease burden associated with autoimmunes on women is also unknown (Thomas, Griffiths, Smeeth, Rooney, & Hall, 2010). The proposed integrative review study has the potential to determine the nature of the sex disparity in autoimmunes and understand the collective burden of these disorders.

**Purpose of the Integrative Literature Review**

The purpose of this intended integrative literature review is first to determine the sex disparity between men and women in the development of autoimmune related disorders. This will help advance interventions and knowledge to decrease the likelihood of development of
such disease. The second purpose is to determine the collective burden that these disorders place on women. Research literature focusing on the specific aspects of the female sex in the role of autoimmunity will be analyzed and their findings will be reported. From this review, the interventions to reduce the prevalence of autoimmunes will be addressed as well as any need for further research and modification of research to reduce the prevalence of these diseases in women. The literature will allow women to be aware of their overall increased risk of autoimmune related disorders and specific factors that individually place them at an increased risk. The literature review also will provide information on the overall increased burden that autoimmune related disorders have on women.

**Research Questions**

1. What evidence has been collected to determine the sex disparity in autoimmune related disorders?
2. What is the burden that women face when diagnosed with an autoimmune related disorder?
3. What is being done to decrease the rates of autoimmune diseases in women?

**Conceptual Framework**

The lack of research and attention paid to the sex disparity difference between men and women’s rates of autoimmune disorders may be due to the lack of female specific health education, prevention and promotion in regards to these disorders. The conceptual framework used to demonstrate the possible lack of attention to this subject is best described through The Tannahill Model (Figure 1). The model created by Andrew Tannahill in 1980 consists of three overlapping spheres of activity health education, prevention and health protection (Tannahill, 2009). Health education is designed to change the knowledge, beliefs, attitudes, and behavior in
a way that facilitates health (Tannahill, 2009). Prevention aims at ways to decrease risk factors and minimize the consequences of disease and protection focuses on legal controls and policies aimed at preventing ill-health and enhancing well-being (Tannahill, 2009). In this review, the focus is on health education to change the knowledge of women’s risk of autoimmune related disorders as well as prevention to decrease the sex disparity and minimize the health burden placed on women when they are diagnosed with autoimmune related disorders. Thus, the model presented in figure 1 works best for the purposes of the literature review being conducted.

Figure 1: Conceptual Map Rates of Autoimmune Disease in Women

Chapter 2: Methods

Research Design

The design of the study presented here is an integrative literature review aimed to discover the evidence that has been collected to determine the sex disparity in autoimmune related disorders and to determine the burden that women face when they are diagnosed with an autoimmune disorder. In order to complete the integrative literature review, the researcher of this study will conduct a search of literature to find articles on studies that have been conducted that are appropriate for the criteria listed below. The integrative literature review will be conducted following the framework of Whittemore and Knaff (2005).

The review will include the stages of an integrative review including problem identification, literature search, data evaluation, data analysis and presentation. Themes from this analysis will be evaluated with current literature to support and confirm the current research regarding women and autoimmune disorders. The information from this review can be used to provide education to women in regards to their increased risk of autoimmune disorders and bring to light the collective burden related to a diagnosis.

Literature Search Strategies

For this integrative literature review, the DePaul and Rosalind Franklin University's search engines were utilized in order to access library databases. To gather sources for this integrative literature, review the following databases were searched: CINAHL, ProQuest Nursing & Allied Health Sources and PubMed. The keywords that were used to search the previously mentioned databases were “women” and “autoimmune” and “prevalence” which yielded eight sources. Other keywords that were used to search the databases to yield additional articles were
“sex disparity” and “autoimmune” which yielded another four sources. One article retrieved from PubMed, which was relevant to this literature review suggested several other studies the conducted research on the prevalence of autoimmune disorders in women that were useful for this literature review. When searching the terms, the majority of the research came from journals regarding women’s health and included a lot of significant information regarding the literature review.

**Literature Search Limitations and Inclusion/Exclusion Criteria**

The search for the integrative literature review was limited to journal articles published between 1995-2016. Initially, a search was generated using the keywords “women” and “autoimmune” and “prevalence” returning 9389 results. From this initial search the term “sex disparity” was added resulting in 564 results of which eight sources were yielded. Another search was conducted using the key terms “sex disparities” and “autoimmune” which yielded 883 results. When including the keyword “rise” 331 articles resulted in which four articles were picked. Several articles were also included that were suggested research based on the initial article included. Studies which did not focus on the link between women and autoimmune disorders and their collective burden, were excluded, limiting the relevant sources to 15 articles that discuss the cause of the rising rates of autoimmune disorders in women and their collective disease burden. See Figure 2 in appendix for diagram of review process.

**Data Analysis**

The studies that will be included will be organized into a table in which the articles will be under the following categories that discuss women and autoimmune diseases: author and year; design, sample and location, aim of study, outcome measures, study results, and study
conclusions. The various studies will be compared and contrasted based on their findings as to the link between autoimmune disorders and sex. Studies presented in the literature review will explore the sex disparity in autoimmune disorders, current methods of prevention and the collective burden of these disorders on women.
Chapter 3: Results

A synthesis across studies in the review of literature in relation to autoimmune disorders and sex disparities and the collective disease burden on women were analyzed. The chart matrix will be used in order to evaluate the studies that will be used in the systematic literature review and to close the knowledge gap which exists as to why there is a sex disparity related to autoimmune disorders. With the rise of autoimmune disorders, education and collective disease burden of these disorders need to be determined. As stated in the study by Quintero, et al (2011) women are at a 2.7 times greater risk of acquiring AD’s than men as they also tend to have a different age of onset related to reproductive ages coinciding when hormone levels begin to rise and different disease activity. Another study conducted revealed that with new research showed that in the UK, autoimmune disorders are a major cause of mortality among females appearing among the 10 most frequent underlying causes of death while also estimating the contribution of these disorders to mortality (Thomas et al, 2010). Furthermore, an overall trend in the articles proved that by grouping autoimmune disorders together helps identify the full extent of the sex disparity, promote research and identify common determinants for prevention strategies (Thomas et al, 2010).

Discussion

Hormones

The first theory as to why there is such a higher prevalence of AD’s in women began to form in 1978 when researchers targeted estrogen in mice as a possible factor that increased a woman’s susceptibility to these disorders (Squires, 1995). In their study, researchers removed the gonads in mice and then gave them either testosterone or estrogen exclusively (Squires, 1995). The results showed that mice who received testosterone were protected from AD’s, whereas the
mice who received estrogen developed AD’s at a higher rate (Squires, 1995). More recently, female sex hormones such as estrogen, prolactin, leptin and androgens (testosterone) have all been examined to determine the exact hormonal role into the development of AD’s due to their capacity of modulating the immune response via androgen and estrogen receptors (Quintero et al, 2011). In the case of estrogen, the hormone has been shown to direct the immune system to favor a more T-helper 1 (Th1) lymphocyte domination causing more B cell activation and antibody production (Quintero et al, 2011). In addition, estrogen acts as an immune-stimulator by affecting maturation and selection of autoreactive B cells and autoantibody secretion (Quintero et al, 2011). When administering estradiol into to animal models, the results show an increased the number of IgE production and induced specific anti-DNA antibody secretion (Moroni, 2012).

Estrogen also affects proinflammatory cytokine synthesis, as it is enhanced in the presence of the hormone (Whitacre, 2001). This can be seen in the example of systemic lupus erythematosus (SLE), which has a significant predominance in women (Quintero et al, 2011). In SLE, there is an imbalance between the hormone relationship resulting in lower immune-suppressive androgens and higher immune enhancing estrogens (Quintero et al, 2011). When estrogen levels are high such as in the case of pregnancy, SLE tends to worsen for women displaying the impact of estrogen on immunity (Quintero et al, 2011).

Other hormones that play a role in predisposing women to AD’s are prolactin and leptin. Like estrogen, prolactin acts as an immune stimulator affecting B cells and autoantibody secretion (Quintero et al, 2011). Prolactin reconstitutes humoral and cell mediated immune responses and are greater in females as a result of the effects of oestrogens (Da Silva, 1995). Prolactin has been shown to enhance autoimmunes worsening disease severity (Ngo et al, 2014). Leptin, in conjunction with estrogen has shown to also play a role in the development of
autoimmunity as it is a potent modulator of the immune response (Merrill, 2015). Specifically, leptin has been linked to the initiation of autoimmune thyroid disease as it has a direct effect on the thyroid through inflammatory molecules (Merrill, 2012). With an increased level of leptin, there is enhanced inflammation creating the foundation for thyroid autoimmunity (Merrill, 2012). These two hormones like estrogen that are increased in women, play a role in the enhancement of the overall immune response giving more opportunity for the development of an autoimmune response.

The last hormone affects the chances of autoimmune development are androgens. Androgens in contrast with the other hormones mentioned above are commonly associated with the development of masculine characteristics, as they are high in males and remain at a low level throughout a female's lifetime (Ngo et al, 2014). Like estrogen, androgens affect the immune system, such as testosterone which reduces the proliferation and differentiation of lymphocytes as well as inhibits the cytotoxic activity of NK cells (Ngo et al, 2014). These findings coupled with the reduced rates of autoimmunity in males show that androgens may play a protective role in autoimmunity (Da Silva, 1995). Despite the many hormonal influences that impact the immune system, the main female, estrogen and male, testosterone hormones have a large role in determining one’s predisposition to the development of an autoimmune.

**The X Factor**

The second mechanism proposed as to why AD’s are more prevalent in females traces back to the very reason that a human is female or male, the presence of XX or XY. Contrasting the Y chromosome, which has many fewer genes, the X chromosome contains over 1000 genes that are essential to cell development and viability (Quintero et al, 2012). During early female development, one of the x chromosomes and its genes, is inactivated to balance the amount of X
chromosomal genes in females (Dai & Ahmed, 2014). Despite this precision, this process is not always 100% accurate as 15% of the X chromosome linked genes escape, allowing expression on both copies of the X chromosomes to be present (Dai & Ahmed, 2014). Since many of the immune related genes are located on the X chromosome, the differential expression, overexpression, and/or mutation of these one or both of these genes contribute to the sex differences in immune response (Dai & Ahmed, 2014). For example, the gene Foxp3 is located on the arm of the X chromosome and is essential for T cell regulation (Moroni et al, 2012). A deficiency or mutation in this gene can lead to early onset, highly aggressive, and often fatal multiorgan AD’s (Moroni et al, 2012). Environmental agents that cause demyelination of the X chromosome can also contribute to a defective gene mutation causing T cell overexpression, autoreactivity and cytotoxic proinflammatory properties again leading to the development of AD’s (Mallampalli et al, 2013). An additional mechanism of skewed X chromosome inactivation during early development could also possibly lead to inactivation of genes that protect against autoimmunity or the overexpression of a susceptibility gene leading to an increase in AD predisposition (Quintero et al, 2012). These combined elements influencing the X chromosome and its gene expression result in the increased likelihood and predisposition that women have towards developing an autoimmune.

**Immune Differences**

The final key aspect in determining why there is such an increased rate of autoimmunes in women, emanates from the difference in immune response in the sexes. Overall, women respond to infection, vaccination, and trauma with increased antibody production, whereas in men, inflammation becomes more severe resulting in an increased mortality (Fairweather et al, 2008). Despite this increased antibody production, which protects women against infection, it is
a double-edged sword when it comes to the development of autoimmunity (Fairweather et al, 2008). With an increased antibody response, there is an increased risk of developing an autoimmune disorder as the number of autoantibodies present in an individual is a good predictor and escalates the risk of developing an AD (Fairweather et al, 2008). Additionally, with more antibody activation, T cell activation is more vigorous and women have a higher absolute number of CD4 lymphocytes (Fairweather et al, 2008). The number of antibodies, extreme T cell activation and higher number of CD4’s all are contributing factors to the increased immune response seen during an autoimmune disorder (Whitacre, 2001). This increased immune reactivity and greater immunocompetence found in women make them more prone to developing autoimmune disorders, which could account for the overall higher rates of the disorder (Ngo et al, 2014).

Finally, the role of miRNA also contributes to the difference in sex immunity. miRNA are a group of endogenously expressed, small, non-protein coding RNAs that regulate gene expression post transcriptionally and have different patterns of expression between males and females in the context of autoimmunes (Dai & Ahmed, 2014). This difference in expression of immune cells which regulate immune-linked genes, leads to the difference in disease susceptibility and severity between males and females (Dai & Ahmed, 2014). Environmental stimuli and pathological changes alter the expression of these miRNAs, for example, ionizing radiation, which can alter the downregulation of some miRNAs in women, but have no effect in males (Dai & Ahmed, 2014). The regulation of specific miRNAs on immune function is not fully understood despite several studies showing the differences of their expression between the sexes, thus more research needs to conducted to fully understand the role they play in autoimmunity (Dai & Ahmed, 2014). The combination of all these factors, antibodies, T cells, CD4 and
miRNA in women, cause a greater risk of developing autoimmunes based on the delicate balance and higher reactivity that the immune system must maintain.

**Collective Burden on Women**

Now that contributing factors behind the increased susceptibility of women to ADs have been determined, the collective burden that these increased rates have on them can be established. As mentioned before, the consequence of diagnosis of an autoimmune result in chronic ill health, poor quality of life and major health care costs (Thomas et al, 2010). These factors place an enormous burden on their hosts, which are predominantly women. In attempt to determine this collective burden, two separate studies examined death certificates, one from the US and one from the United Kingdom, to determine if alteration of ICD codes for underlying contributing autoimmune disorders would affect the ranking of the top official leading causes of death (Walsh & Rau, 1995). Current ICD classifications are limited and do not account for autoimmunes because disorders are listed under separate organ systems (Thomas et al, 2003). In 1995, US results showed that within two groupings of ADs, autoimmune related deaths exceeded the count for the 10th leading cause of death in all age groups younger than 65 (Walsh & Rau, 1995). Similar results were found in the UK from 2003, where autoimmunes were ranked as the 7th leading cause of death for women between the ages of 1-54 (Thomas et al, 2010). The limitation in classification of ICD codes have essentially hidden the combined burden of mortality for women due to autoimmunes due to their limited classification (Thomas et al, 2003). This is important because ICD rankings are the source of important information for health policymakers and those responsible for delivering health care, as well as highlight areas for further research on treatment and prevention on conditions (Thomas et al, 2003). Without recognition that ADs are a major leading cause of death for women, further research and
exploration in treatment and prevention will not be conducted and the burden of ADs on women as well as the healthcare system will rise (Thomas et al, 2003). Autoimmunes remain neglected in the ICD ranking lists and collective impact of autoimmune disorders on female health will continue to be masked (Thomas et al, 2003).

**Conclusion**

Based on the proposed literature review, it is apparent that the etiology behind the increased rates of autoimmunes in women is complex. There is not a definitive cause or contributing factor that predisposes women to this increased risk of their development, rather the inner workings of hormones, the double X chromosome, and the variation between immune response seen in women combined creates the ideal conditions for autoimmunity to develop. Based on multiple studies, researchers have determined that the interaction between hormones and the immune system is the most convincing theory to date to explain the sex difference in AD’s having a strong influence on predisposition based on the rates (Quintero et al, 2012). Although not discussed, genetics factors outside of the X chromosome and the environment can also trigger the onset of an autoimmune and further research is needed in order to determine their interaction with the elements discussed above (Quintero et al, 2012). Major understanding of the hormonal, genetic and epigenetic process related to sex differences in AD’s may gain further insight into answering the questions proposed as AD’s continue to be a leading cause of death among young and middle aged women (Quintero et al, 2012). By grouping AD’s together, rather than looking at each individually, emphasis will be placed on their shared pathogenesis bringing to light the true burden of these disorders on women and promote research needed to identify common determinants (Thomas et al, 2010). Finally, research is needed to explore the opposite conclusions, why are autoimmunes less prevalent in males and could there be a factor that is
protective to explain this phenomenon (Quintero et al, 2012).

**Future Directions and Nursing Limitations**

The current body of research regarding sex and autoimmunity is very limited and vague. More research is needed to understand the extent of the sex differences in AD’s and their etiology to begin to develop new treatments to suppress the progression of these disorders (Whitacre, 2001). New findings from researchers at Ohio State have suggested and began to test a new type of treatment known as oral tolerance therapy, which targets the destructive cell lines that turn off the destructive part of the immune system and reduce attacks on the brain tissue in MS patients (Squires, 2016). More emphasis on this type of research in sex differences and autoimmune treatments needed to be encouraged in order to gain advancements in this field to identify further prevention strategies (Thomas et al, 2010).

Regardless of the etiology of the development of an autoimmune, results from alteration of ICD codes show that AD’s constitute a major public health issue for women (Thomas et al, 2010). Nurses play a vital role in identifying and educating women who have an increased risk of the development of autoimmunes in order to reduce their chances of progression. Due to the limited research and knowledge that is available on these disorders, nurses need to be advocates for their female patients, encouraging them to seek the highest level and most appropriate care for treatment. This includes advocating for expert opinions on rare disorders in account of the burden of mortality that women face once diagnosed (Thomas et al, 2010). In addition to educating their patients, nursing as a profession needs to be educated regarding the disparity of autoimmunes between the sexes so that they can properly treat patients as well as help advocate for more research in this field. Since the 1970s when the difference in autoimmunity between the sexes was first identified, major progression in research has been made in identifying factors that
contribute to this discrepancy (Squires, 2016). More extensive studies are needed to identify treatment options that will reduce the effect of the identified factors which predispose women to developing autoimmunity.
References


Appendix

Figure 2: Diagram of Review Process

A diagram was created to display the process used to review the articles selected and studies that were included. This method enables readers to reproduce the search results and gain knowledge into the methods used to obtain information about this research topic. An initial diagram is depicted below in Figure 2.

Number of Studies Found Using Keywords

- CINAHL: N=135
- PUBMED: N=4364
- PROQUEST NURSING & ALLIED SOURCE: N=49

Number of Studies Meeting Inclusion Criteria

- CINAHL: 120
- PUBMED: 12
- PROQUEST NURSING & ALLIED SOURCE: 351

Number of Studies After Excluding Duplicates

- CINAHL: 23
- PUBMED: 10
- PROQUEST NURSING & ALLIED SOURCE: 128

Number of Studies After Using Exclusion Criteria and Background Articles

- CINAHL: 10
- PUBMED: 6
- PROQUEST NURSING & ALLIED SOURCE: 20

Number of Studies Selected Based on Total Content:

Figure 2: Diagram of Review Process and Study Selection.
### Table of Literature

<table>
<thead>
<tr>
<th>AUTHOR/ YEAR</th>
<th>DESIGN, SAMPLE, LOCATION</th>
<th>AIM OF STUDY</th>
<th>OUTCOME MEASURES</th>
<th>STUDY RESULTS</th>
<th>STUDY CONCLUSIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. Fairweather and N. Rose (2004)</td>
<td>Literature Review Johns Hopkins University Baltimore, Maryland</td>
<td>To determine the link between high incidences of autoimmunes in women and families with possible precursor inducing infectious agents.</td>
<td>Studying the early differences in cytokine response to CB3 infection in susceptible or resistant mice to determine if this could provide clues to the progression to autoimmunity.</td>
<td>Sex hormones increase myocarditis in female and male mice by increasing interleukin and tumor necrosis factor levels in the heart. The myocarditis virus can trigger autoimmune disease in susceptible mice by immune-mediated mechanisms.</td>
<td>The precise interaction between hormones and the innate immune response after infection is poorly understood. Vitro studies of immune cells cultured in the presence of hormones have shown that estrogen significantly increases proinflammatory cytokine production. The elevated immune response in women may further amplify the adjuvant effect if infection thereby increasing the chronic autoimmune likelihood in women.</td>
</tr>
<tr>
<td>C. Whitacre (2001)</td>
<td>Commentary The Ohio State University, Columbus Ohio</td>
<td>To understand the biology of the sex difference in autoimmune disorders as well as opportunities for focused research on priorities in sex differences.</td>
<td>To examine the history behind the increasing focus in the sex differences in autoimmune rates and to determine where research should follow.</td>
<td>More research is required in the basic immune response and the sex differences that play a role in autoimmunity.</td>
<td>Differences between the stimulation of male and female innate immune response by pathogens must be studies as well as more clarification as to the male versus female differences in the adaptive immune response.</td>
</tr>
</tbody>
</table>
### Thomas, S., Griffiths, C. et al. (2010)

**Analysis of 1993-2003 death certificates that listed autoimmune conditions as underlying or contributory causes of death.**

Peer Reviewed

There is a lack of population based studies based on autoimmune disorders and little is known about the collective disease burden associated.

To determine the collective disease burden of mortality from autoimmune diseases among females in the UK.

In 2003, autoimmunes were the 6-7th leading most frequent underlying cause of death among females in all age groups 75 or below. The proportions of females dying with an autoimmune remained constant and deaths were underestimated during this time.

Autoimmune diseases are a leading cause of death among females in England and Wales, but their collective impact remains hidden in current disease classification systems. Grouping these together may help promote research needed to identify common determinants and future prevention strategies.

### S. Walsh and L. Rau (2000)

**Counts of 24 autoimmune disorders were compared with the frequencies of 10 “official” leading causes of death in women in the US in 1995.**

To determine if autoimmune diseases cause sufficient mortality among women to constitute a leading cause of death.

Measured the number of autoimmune disorders that fell into each age category and compare these counts to the 10 leading causes of death.

Autoimmune deaths exceeded the frequency of the 10th leading cause of death in every age category for women less than 65 and exceeded the that for the 8th leading cause in 15-24 and 25-44.

Autoimmune diseases constitute a leading cause of death among young and middle aged women.

### M. Mallampalli et al. (2013)

**Report George Washington University, District of Columbia**

To address the issues of the limited research on autoimmune environmental research and limited research regarding the role of sex in

The roundtable discussion resulted in the conclusions as to why there is this gap in the research and how the community can fix this knowledge gap.

Sex differences, epigenetics, and the environment all interact with each other in playing a role in developing an AD although

While progress had been made, it has been slow and preliminary limited to a few autoimmune disorders. Further identification of environmental agents and studies on their interaction...
| S.T. Ngo, F.J. Steyn, and P.A. McCombe (2014) | Literature Review, University of Queensland Centre for Clinical Research, Herston, Queensland, Australia | Summarize human data to provide an overview of the prevalence in males and females in common autoimmune diseases in countries commonly surveyed. Then discuss the possible mechanisms for sex specific differences. | Examination of possible mechanisms for sex specific differences including gender differences in immune response, organ vulnerability, reproductive capacity with pregnancy, sex hormones, genetic predisposition, parental inheritance and epigenetics. | Evidence demonstrates that gender and sex have a significant influence on the development of an autoimmune disease. | Considerations of gender should be at the forefront of all studies that attempt to define mechanisms the underpin autoimmune disorders. |
| L. Moroni, I. Bianchi, and A. Lleo (2012) | Literature Review, Survey of Geological Area, IRCCS Instituto Clinico Humanitas, Razzano, Italy | Describe geoepidemiological aspects related to the study of autoimmune conditions and its female prevalence. To attempt to focus on the critical issues of the lack of knowledge of the mechanism of influence. | Studying the distribution of autoimmunes across various global regions and ethnic groups by means of geoepidemiology to provide data and advance the understanding of their pathogenesis. | Females overall have higher rates of autoimmunes due to environmental factors, sex hormones and the presence of the extra X chromosome. | The study of sex differences in autoimmunity will help towards better definition of the mechanisms leading to the widely different autoimmune clinical features, allowing a clear definition of the cases more likely to progress or to present major complications and to develop novel therapeutic approaches. |
### S. Squires (1995)
**Review**
The Washington Post

**Authors:** S. Squires

**Main Points:**
- Doctors have long known that women suffer disproportionately from autoimmune disorder but why is this?
- Examine the latest research to determine if factors other than estrogen could be the cause of these higher rates of autoimmunes in women.
- Pregnancy may protect women against getting autoimmune disorders as pregnancy can be somewhat protective where the body is more lenient on detecting foreign invaders.

### D. Fairweather, S. Frisaancho-Kiss, and N. Rose (2008)
**Review**
Johns Hopkins Medical Institutions, Baltimore Maryland

**Authors:** D. Fairweather, S. Frisaancho-Kiss, and N. Rose

**Main Points:**
- Discusses the distribution of autoimmune disease based on sex and age showing the autoimmune disease progress from an acute pathology associated with an inflammatory immune response to a chronic pathology.
- Examine the distinction between acute and chronic pathology as it impacts the understanding of sex differences in autoimmune diseases.
- There is a difference between acute and chronic phases of disease are regulated differently in males females, distinguishing these two pathological phases in animal models and patients could lead to more effective treatments.

### O. Quintero, M. Amador-Patarroyo, G. Montoya-Ortiz, and A. Rojas-Villarraga
**Literature Review**
Universidad del Rosario, Bogotá, Colombia

**Authors:** O. Quintero, M. Amador-Patarroyo, G. Montoya-Ortiz, and A. Rojas-Villarraga

**Main Points:**
- To determine the exact causes in the differences in autoimmune trends seen between men and women.
- Examine the exact differences in hormonal influence on the immune system as well as how specific female hormones influence autoimmune.
- Autoimmunes are complex and multifactorial entities which genetic, epigenetics and hormonal differences strongly affect.
- The more frequent the autoimmune is and later it shows up the more women are affected. Additional efforts need to explore why AD’s are prevalent in males and if there is a group of...
RATES OF AUTOIMMUNE DISEASE IN WOMEN

| (2012) | severity. | influence the predisposition of women. | protective factors that could explain this. |