

Sex and Gender in Rheumatoid Arthritis: Considering a Risk Factor Hierarchy

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Abstract

Is sex or gender a greater risk factor for Rheumatoid Arthritis (RA)? Identifying how gender and sex mediate RA is important because women and females make up the majority of RA patients. Additionally, rheumatoid arthritis is a serious immune disease that greatly affects an individual's quality of life. The reason behind the difference in RA diagnosis by gender and sex is important to guide how the difference can be mitigated. In this study, it is hypothesized that susceptibility to RA is mediated more by factors associated with sex, rather than behavioral and environmental factors associated with gender. Females are more susceptible to autoimmune diseases due to the skewed inactivation that can occur when half of the x-chromosome genetic material, which plays a role in the immune response, is silenced. During skewed inactivation, maternal and paternal x-chromosomes are not silenced in the same proportions, leading to two different self-antigens that cause a stronger immune response and can react to each other, which can produce an auto immunological response, such as RA. A secondary data analysis was performed using the National Library of Medicine database to search for genetic, behavioral, and environmental risk factors that were measured using an odds ratio. The behavioral and environmental risk factor odds ratio was compared to the skewed x-linked odds ratio to compare the effects of sex and gender. It was determined that there are greater odds that RA will be mediated by skewed x-linked chromosomal inactivation than any individual aspect of gender, however there is room for uncertainty regarding whether if either sex or gender definitively has a greater impact on RA diagnosis.

Introduction

Rheumatoid Arthritis (RA) is the most commonly diagnosed systemic inflammatory disease (Wasserman, 2018). When a person has RA, the body attacks joint tissues, produces antibodies, and causes the joint to swell (Wasserman, 2018). As the disease progresses, the joint tissue can be completely destroyed, leading to inflammation, bone erosion, misshapen or fused joints all of which limit physical abilities and cause pain. This is considered a chronic disease, but long-term remission is available and is more successful in the earlier stages of the disease (Wasserman, 2018). The inequality present in RA is described by literature as “disease patterns vary between sexes; the condition is more commonly seen in women (3 women for every one man), who exhibit a more aggressive disease and poorer long-term outcome” (Da Silva and Hall, 1992). It is surprising that the article claims that there is a difference in disease patterns between sexes, but puts the scale of the difference in terms of gender. This prompts interests as to which

category, sex or gender, has a greater effect on mediating RA.

The exploration of the gender and sex disparity in RA is just starting to be uncovered. In the 1930's researchers implicated sex hormones to be contributing to RA due to the temporary remission that occurred during pregnancy (Lampner, 2018). Then at the start of the 2000's the disparity was thought to exist due to less intensive prescriptions for women, however, this assumption was proven to be incorrect by a national committee that confirmed that women and men receive similar proportions of prescription treatments (Lampner, 2018). Rheumatologists have noticed greater disease activity and disability scores in women, which they attribute to women being more vocal about their symptoms which they suggest alter the scores generated from disease activity and disability tests (Lampner, 2018). Several studies have come to the same conclusion that men and women do not differ in disease activity score, with a few caveats, that men more often meet criteria for remission, and that RA disease scores between men and women

only differ in subjective measures (women experiencing higher scores), not in objective measures (Lampner, 2018). This has led to disagreement in the field, some believing that gender and sex-based treatment is not needed and others thinking it should be available due to physiological changes during pregnancy and lactation and the greater likelihood of comorbidities in women and differences in coping strategies (Lampner, 2018).

It is hypothesized that the susceptibility to RA is mediated more by factors associated with sex, rather than behavioral and environmental factors associated with gender. This hypothesis is based on the higher prevalence of all immune diseases in females compared to males. It is suspected that this is due to skewed inactivation that can occur during x-chromosome inactivation in females. Half of the x-chromosome genetic material must be silenced because females have two x-chromosomes. However, not all females have equal proportions of cells with the paternal or maternal x-chromosome activated (Shvetsova et al., 2018). The x-chromosome that cells receive is randomly distributed, therefore females have what is considered a mosaic expression (Shvetsova et al., 2018). The mosaic expression leads females to have two populations of dendritic cells that either express maternal or paternal x-linked self-antigens for negative regulation (Libert et al., 2018). The expression of both types of dendritic cells allows for a stronger immune response, but the presence of two types of antigens may cause the breakdown of self-tolerance, where the immune system begins to respond to self-produced antigens (Shvetsova et al., 2018). The breakdown of self-tolerance in individuals with skewed x-linked inactivation can lead to autoimmune diseases, where the body attacks and destroys its own tissues, like RA. This hypothesis was supported by the secondary data analysis, which found that RA has greater odds of being mediated by skewed x-linked inactivation, a proxy for sex-related risk factors, than any single gender-related risk factor.

Methodology

A quantitative systematic literature review was performed using the National Library of Medicine database to search for genetic, behavioral, and environmental risk factors that had been measured in the last twenty years using an odds ratio or provided raw data

allowing for the odds ratio to be calculated. An odds ratio is a measure of association between exposure and outcome, the outcome of interest being RA diagnosis. Using the odds ratios collected from the primary literature studies, a forest plot was constructed to display the average odds of a behavioral or environmental risk factor being associated with RA. The behavioral and environmental risk factor odds ratios were compared to the skewed x-linked odds ratio to compare the effects of sex and gender. Sex is a biological category, that can be defined using the X-Y determination system. Skewed x-link inactivation was used as the risk factor for sex because it can only occur in females. Gender is a social category, so it takes into account how the person interacts with their environment and the behaviors they are expected to perform. The behavioral and environmental risk factors range from substance use, nutrition, social networks, socioeconomic status, and pollution. A forest plot was utilized to display this information, so the individual and average odds of environmental and behavioral factors associated with RA can be visualized.

Results

The odds ratio of behavioral and environmental factors being associated with RA is 2.07, 95% CI (1.26, 3.52) (Table I). The odds ratio of skewed x-linked inactivation being associated with RA is 4.13, 95% CI (2.11, 8.10) (Chabchoub et al., 2009) (Table II). The odds ratio and 95% confidence intervals of individual behavioral and environmental factors are listed in Table I and displayed in a forest plot in Figure I. The odds ratio and 95% confidence interval for skewed x-linked inactivation are in Table II.

Substance use-related Risk Factors Results

Smoking is the most well-supported risk factor for RA; the odds ratio was calculated by comparing those that have zero pack-years to those who have 10 pack-years (one pack-year is equivalent to smoking twenty cigarettes a day for a year) (Pederson et al., 2006). The reason behind the connection between smoking and RA occurs via oxidative stress, inflammation, auto-antibody formation, and epigenetic changes (Chang et al., 2014). The alcohol consumption odds ratio was calculated by comparing those who do not consume alcohol at all to those who drink one to five drinks a week

Table I. Odds Ratio and Confidence Intervals for Behavioral and Environmental Risk Factors. The behavioral and environmental risk factors serve as a proxy for gender since gender identity reflects the manner individuals behave and interact with their environment. The behavioral and environmental risk factors used fall under the broader categories of substance use, nutrition, social networks, socioeconomic status, and pollution.

Behavioral or Environmental Risk Factors	Provided Odds Ratio	95% Confidence Interval	Source
Smoking Tobacco	1.65	1.03, 2.64	(Pederson et al., 2006).
Alcohol Consumption	1.98	1.22, 3.19	(Pederson et al., 2006).
Remaining Unmarried	1.71	1.14, 2.58	(Pederson et al., 2006).
Coffee Consumption	2.18	1.07, 4.42	(Pederson et al., 2006).
Inadequate Vitamin D Consumption	2.46	1.14, 5.32	(Lee and Bae, 2016)
Consumption of Sugar-sweetened Beverages	2.65	1.56, 4.46	(Alpizar-Rodríguez et al., 2017)
Occupational Exposure to Dust	2.80	1.60, 5.20	(Alpizar-Rodríguez et al., 2017)
Low Educational Level	2.43	1.31, 4.16	(Pederson et al., 2006)
Ground Level Ozone at Residence	1.26	1.18, 1.36	(DeRoos et al., 2014)
Reside in Low Socioeconomic Status (SES) Neighborhoods	1.73	1.23, 2.44	(DeRoos et al., 2014)
Residential Proximity to Highway	1.39	1.16, 1.68	(Xu and Lin, 2017)
Living in Poverty	2.96	1.77, 4.65	(Philippou and Nikiphorou, 2018)
Consumption of Red Meat	2.30	1.10, 4.90	(Philippou and Nikiphorou, 2018)
High Sodium Intake	1.50	1.10, 2.20	(Philippou and Nikiphorou, 2018)

Table II. Odds Ratio and Confidence Interval for Innate Biological Risk Factors. Skewed x-linked inactivation was used as the risk factor for sex because it can only occur in females and is the only known innate biological risk factor associated solely with sex.

Risk Factor	Calculated Odds Ratio	95 % Confidence Interval	Source
Skewed X-linked Inactivation	4.13	2.11, 8.10	(Chabchoub et al., 2009)

(Pederson et al., 2006). The relationship of alcohol to RA is unexpected since alcohol is an immunosuppressant (since RA occurs with an overactive immune system), however, it is thought that because alcohol use is positively correlated with smoking, the effect of alcohol on RA diagnosis is skewed by the effect of smoking on RA diagnosis. (Pederson et al., 2006).

Socioeconomic Status-related Risk Factor Results

Poverty was measured using the Family Monthly Poverty Level Index and those that lived with less than 300% of the poverty level were counted as living in poverty and compared to those who lived with greater than 300% of the poverty level (Xu and Lin, 2017). Living in

poverty may decrease access to healthy foods, increase substance use as a coping mechanism and increase exposure to polluted environments that are typically less expensive to live in, all of which are risk factors for RA. The education odds ratio was formed by comparing those with no education to those with over four years of advanced schooling. This study was performed in Denmark, where there is universal health care, so health insurance status and wealth are unlikely to mediate this relationship (Pederson et al., 2006). Education plays a role in mediating RA because educated individuals are more likely to seek medical advice at an earlier stage in the disease than less educated people (Pederson et al., 2006). The neighborhood socioeconomic status (SES)

Odds Ratio for Behavioral and Environmental Factors

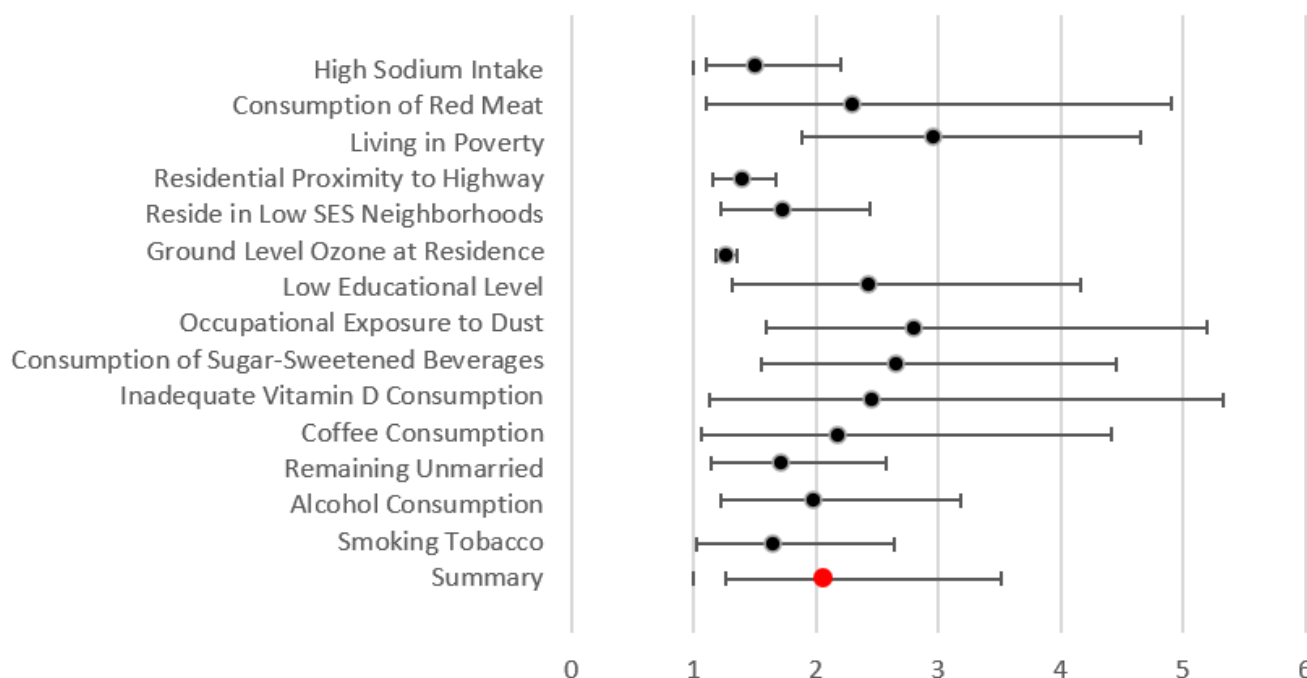


Figure I. Forest Plot of the Odds Ratio for Behavioral and Environmental Factors. The forest plot displays the odds the exposure to a given risk factor will lead to RA diagnosis. The summary point and confidence interval in the figure displays the average odds and confidence interval of an individual behavioral and environmental risk factor leading to RA diagnosis. The summary point does not reflect the average risk of gender, as it does not account for exposures to multiple risk factors for RA.

odds ratio was made by comparing the lowest two quintiles of SES neighborhoods to the highest three quintiles of SES neighborhoods (DeRoos et al., 2014). The low SES neighborhoods may have a higher odds ratio of being diagnosed with RA due to the prevalence of smoking and second-hand smoke (DeRoos et al., 2014).

Pollution- related Risk Factor Results

Ground-level ozone was measured in $\mu\text{g}/\text{m}^3$ and compared the highest quintile to the lowest quintile (DeRoos et al., 2014). Ozone is proposed to lead to RA via oxidation of biomolecules, causing DNA methylation, and altering the DNA protein binding sites (DeRoos et al., 2014). The biological changes can trigger the generation of autoantigens that lead to autoimmune logical conditions, like RA (DeRoos et al., 2014). Interestingly, ozone was found in the highest concentrations within suburban and higher SES neighborhoods (DeRoos et al., 2014). The parameters for occupational exposure to dust are not specified. Occupational exposure to dust impacting RA is said to be caused by silica, silica particles can trigger the innate immune system, causing inflammatory cytokine release (Alpízar-Rodríguez et al.,

2017). Residential proximity to a highway was defined as those who live less than or equal to 50 meters from a highway, which was compared to those who lived greater than 150 meters away from a highway (DeRoos et al., 2014). However, the reasoning behind the relationship between the proximity to a highway and RA remains unclear because noise levels and vehicle-related pollutants were shown to not be responsible for this relationship (DeRoos et al., 2014).

Nutrition-related Risk Factors Results

Both high sodium intake and consumption of red meat are considered to trigger RA and exacerbate inflammation (Philippou and Nikiphorou, 2018). This is thought to occur via the enhancement of the autoimmune cascade response through the production of inflammatory cytokines and chemokines that destroy joint tissues like synovial membranes and cartilage. Increased red meat consumption was considered to be greater than 88 g/day and was compared to less than 49 g/day to generate the odds ratio. The fat, nitrates, and iron from meat are also suspected to contribute to the inflammation. Specifically, the consumption of red meat is a concern

because it may be taking the place of protective food in a meal, such as omega-3 rich fish. The parameters for what was considered high consumption of sodium were not included in the study. Sugar-sweetened beverages were also shown to affect the odds of being diagnosed with RA, however, the parameters of the odds ratio were also not provided (Alpizar-Rodríguez et al., 2017). The mechanism of sugar sweetened-beverages mediating RA is likely due to excess sugar in the vascular system, which activates the pathway for reactive oxidative species, which produces similar effects as ozone. Vitamin D was measured in serum, however, the parameters for what was considered a vitamin D deficiency were also not included (Lee and Bae, 2016). Vitamin D plays a role in mediating RA because it is an immunosuppressant and it inhibits immune cell proliferation, therefore without vitamin D the immune system will not receive negative feedback and the immune system's self-tolerance is decreased (Lee and Bae, 2016). The coffee consumption odds ratio was calculated by comparing those that consume no coffee to those who consume over ten cups of coffee, but the connection of coffee consumption to RA is not well understood (Pederson et al., 2006).

Social network-related Risk Factor Results

The odds ratio for remaining unmarried was calculated by comparing those that are married or cohabiting with their partner to those who are unmarried, widowed, or divorced (Pederson et al., 2006). The reason for not being married affecting RA diagnosis may be due to decreased access to social capital, which leads to poorer health outcomes.

Discussion

Interpretation of Result

When comparing the odds ratios collected in this study, there are greater odds that RA will be mediated by skewed x-linked chromosomal inactivation than an individual behavioral or environmental factor. The association made between the factors (x-linked chromosomal inactivation, behavioral, and environmental factors) measured and the purpose of this research lead to the conclusion that sex as an individual risk factor puts a person at a greater risk for RA than any individual risk factor related to gender. However, there is room for uncertainty since there is no certainty as to how many

behavioral and environmental risk factors an individual may experience, if any at all. In addition, a limitation of this study is that it is not known what effect the compounding of several risk factors could have. For example, an individual may have a high sodium intake, consume alcohol, and live in a low SES neighborhood. This brings into perspective the idea that there is no definitive gender experience, so the effect size of gender becomes more unclear. It seems like both sex and gender play a role in mediating RA and determining which plays a greater role would require determining an average definitive gender experience. Determining an average gender experience could have serious implications, for example marginalizing non-average gender experiences, like those of gender minorities.

Aside from the focus on gender and sex, in this study there was also a focus on risk factors for RA, but not on protective factors. While there is a gender and a sex that have a greater prevalence of RA, there may be protective factors that females and women may have, and exploring those may be important so they can be emphasized in the prevention of RA.

Additionally, in the realm of risk factors, they are framed in a binary manner, not in terms of a spectrum (i.e. drinks a day), so these may misconstrue the odds ratio. While there was data that did separate factors into brackets of exposure or a spectrum, not all data had this separation. Adding several categories of the same risk factor (i.e. smoking) would then lead to the average behavioral and environmental risk factors to be more greatly influenced by that risk factor, and lead the odds ratio to not be as representative of the average behavioral and environmental risk factor.

Challenges

There were some challenges of using a systematic review as the research method, including finding data in similar terms (for comparison) and the limitation of using already published data. Information on risk factors of RA was not hard to find, however finding all the risk factors measured using an odds ratio was difficult. As a result, there are many more environmental and behavioral risk factors that show an association with RA, but could not be included in this study, for example, stress. Another limitation was the uncertain effects of estrogen since no studies have studied the serum levels of endog-

enous estrogen, only the effect of exogenous estrogen, used for hormone replacement therapy or birth control. These forms of estrogen may not be a great way to study the effect of higher levels of endogenous estrogen in females, since they may be influenced by confounding factors, like age, environmental factors, and access to healthcare. While there were challenges due to research design, there were also limitations due to the topic being studied. It was challenging to select risk factors that were strictly related to sex or gender. One major risk factor that was excluded as a consequence was excluding other medical conditions as risk factors. For example, obesity is a major risk factor for RA, but there are environmental (obesogenic environments), behavioral (overeating), and sex-related factors (distribution of body fat), that all play into this condition. Despite these challenges, it was determined there was sufficient data to analyze the effects of gender and sex on RA.

Sources

The critiques of the sources used are mostly based on their stance in terms of the disparity at hand, rather than the validity of their data. “The X Chromosome in Immune Functions: When a Chromosome Makes the Difference” by Libert, Dejager, and Pinhero, presents ideas in an androcentric manner. For example, they consider the female immune system to be hyperresponsive in comparison to the male immune system, however, the male immune system could have been framed as having a dull response, instead of being the norm. Androcentrism was also present in “Sex-based Differences in Rheumatoid Arthritis: Clinical Implications and Patient Management” as well as gender stereotypes in the case where professionals were interviewed and claimed women to be more vocal in reporting symptoms (rather than men under-reporting symptoms in an attempt to maintain the hegemonic masculinity). Although women are more likely to care for their health, accusing them of over-reporting is a rash accusation, because the measures used to gauge the disease progression of RA objectively are most likely based on disease patterns of men, so women are most likely not over-reporting, they are just not reporting what is expected based on the androcentric standard. Then in “Are We Really What We Eat? Nutrition and its Role in the Onset of Rheumatoid Arthritis,” it is surprising to see that instead of making policy recommendations, the authors claim that they trust that elucidating the impact of nutrition on RA will

encourage the involvement of registered dieticians in RA management. The authors seem too ambitious in their prediction that this will occur on its own, without considering structural factors that may prohibit registered dietician involvement, for example, doctors will need to facilitate the referral to the dieticians and patients will need to also value the importance of a dietician, so it seems that educational programs that cover current research for both medical professionals and patients are necessary to increase the involvement of registered dietitians. Their suggestion to decrease the intake of meat, without providing replacements or addressing why meat is eaten in large quantities appears unlikely to persuade the target demographic to change their behavior. I would urge the authors to provide a reasonable manner of making this dietary change and to take into consideration any structural reasons, for example, food deserts, that may lead people to consume meat over fresh produce.

Conclusion

The hypothesis of this study was centered on finding a definitive ranking for the effects of gender and health, but the research performed was not sufficient to draw these conclusions. However, the research did provide insight into the many risk factors of RA both gender and sex mediate as well as implications for policy and future research.

Implications on Policy

In consideration that skewed x-linked inactivation is the single greatest risk factor for RA, the genetic screening of skewed x-linked inactivation should be performed as part of female preventative medical visits. This should be implemented early on in life since the earlier RA is detected, the greater likelihood there is of achieving remission and the less damage to joint tissues the patient will incur. This is particularly important as females may report symptoms of RA, like diffuse joint aches, and be ignored due to the stereotype that women are more vocal and tend to complain. Instead, if there is a previously-noted genetic susceptibility to RA, then a diagnosis of this condition is more likely to occur, and management of the condition is likely to occur earlier. To address the role of gender via health policy, environmental and behavioral risk factors that an individual faces should be tracked via electronic medical records,

so physicians can take these into account when making a differential diagnosis. In terms of addressing the risk factors directly, large-scale policy changes would have to be implemented, like addressing poverty, so individuals can afford healthy foods, choose to live and work in safer environments, and afford an education.

Future Research

To elucidate the effects of gender and sex on RA, research should be directed towards the outcomes of those skewed linked x-activation to the behavioral and environmental factors differ from those without skewed linked x-activation, to investigate if skewed x-linked inactivation has a causal relationship with RA, not only a correlational relationship. Additionally, it would be interesting to see how male and female odds ratios of being diagnosed with RA differ with exposure to the same risk factors since this could bring to light any epigenetic mechanisms at play in the RA disease activity.

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