The Effect of Epigenetic Modifications Due to Violence on the Chronic Health of Refugees and Possible Mechanisms

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Writer's Comment: The refugee population has been a continuous, growing presence, especially in the world that I have grown up in. In the past 20 years that I have lived, I have seen only a growth in violence and situations that create more refugees. As a Genetics major and someone who is aspiring to become a healthcare professional, the only method I know to possibly help is with science and medicine. This research paper was assigned in our UWP 104F class to look into healthcare related questions that interest you and have not necessarily been answered yet. I knew that this project, for me, would need to address the healthcare needs of the refugee population that are not being met. I especially wanted to look at health issues that may uniquely be caused by the experiences of refugees.With such a large and growing population of refugees resettling in new places all over the globe, I hope that they become better served by healthcare professionals.

Instructor's Comment: I admire Hufssa's commitment to researching and writing about health issues of refugees around the world. For this research project in our UWP 104F class during Spring 2020, the task was to write a preliminary research paper which would inform a grant proposal for a larger project. To qualify for the grant, the research proposal would need to satisfy the following criteria informed by actual NIH grants: 1) the question has not been fully answered by previous research, 2) it would help specific groups in society live better lives, 3) it would promote diversity in or new approaches to health science, and 4) it would lead to meeting an unmet need by patients or health professionals. Hufssa's paper satisfies all four of these criteria. When she searched academic databases, Hufssa realized a lack of existing research into her topic, possibly due to the newness of epigenetics. Instead of abandoning her question, Hufssa researched what is known about

health conditions due to trauma, abuse, and violence in non-refugee populations as well. By linking the types of health conditions and the known epigenetic modifications of those health issues to survivors of trauma and violence, of which refugees are a subgroup, as well as what is known specifically about refugee populations, Hufssa discusses critical refugee health information. She further reports on the possible physiological mechanisms for the changes in gene expression. In this research paper, Hufssa reveals a significant data gap in healthcare research for some of the world's most disenfranchised and disadvantaged communities. Through the power of evidence, inference, and argumentation, she offers knowledge in answer to her unique question and unequivocally advocates on behalf of our world's refugees.

—Agnes Stark, University Writing Program

Abstract

Increased war and refugee populations give rise to the issue of treatment and healthcare for refugees in the countries they resettle. The violence and trauma that many refugees have likely experienced affect their mental and physical health through multiple pathways. This study looks at the epigenetic modifications that come about from violent experiences of refugees and result in chronic physical health issues and possible mechanisms that link the two. Data was obtained by searching databases for studies within 10 years and related to keywords such as refugee, epigenetic(s), genocide, violence, and chronic health. Cardiovascular, respiratory, and musculoskeletal disease that are prevalent in refugee populations overlap with the prevalent health issues in people who have experienced violence and trauma. Multiple studies show that experiencing violence or genocide can result in epigenetic aging, increased methylation of NR3C1, and decreased methylation of BDNF and CLPX. The differential expression resulting from these epigenetic modifications can be directly linked to the health issues in refugees through the proposed mechanisms.

Introduction

Due to global political turmoil, statistics show that the number of refugees and displaced people has reached a record 70.8 million

(UNHCR, 2019). Refugees flee their homes for a multitude of reasons; however the majority are indeed fleeing from war and violence (UNHCR, 2019). It is well known that exposure to violence and trauma can have lasting impacts on a population, well into the future. These impacts are not just cultural or psychological, but can be passed on epigenetically. The experiences of people affected by these horrific situations are likely to change their epigenetic makeup, and possibly be passed on to their children and grandchildren in the future. The effects of these epigenetic changes could very well show up in children who do not go through the same experiences as their parents or grandparents.

Epigenetics is a relatively new field in the world of genetics and genomics. It refers to heritable changes in gene expression that do not change the sequence of DNA. These heritable changes present as a number of different types or combinations of modifications that can amplify or suppress the expression levels of a gene. The types of modifications include methylation, acetylation, and phosphorylation. Methylation alone is often associated with gene suppression, while acetylation is generally associated with increased gene expression. Epigenetic modifications can change chromatin structure. If a gene is to be more expressed, the modification can make the DNA sequence of the gene physically more accessible to transcription machinery. On the other hand, modifications that suppress the expression of a gene can cause the DNA sequence to more tightly bind to the nucleosome, blocking the gene from being physically accessible to transcriptional machinery.

Given the worldwide increase in displaced refugees fleeing violence in their home countries, doctors will likely have a significant increase in patients who are refugees, or children of refugees. There are around 3.5 million asylum seekers in the world currently and around 25.9 million refugees that have already resettled in new countries (UNHCR, 2019). Every continent houses refugees from around the world, mainly Asia, Africa, and Central America. All these refugees are more likely to have health issues in general, but less likely to have access to secondary and tertiary health care which deals with chronic and non-communicable diseases (Amara and Aljunid, 2014).

This study looks at the common chronic health issues resulting from epigenetic changes in refugees who have experienced violence and trauma that doctors should be prepared for. Refugees are not a monolith, and likely have very different experiences and health problems depending

on their respective home nations. This study focuses on individuals who have experienced violence and the most common non-communicable disorders across the board that may result from epigenetic changes. This study also attempts to look at the likely epigenetic changes, and suggest a possible mechanism to connect these changes to the resulting common diseases. Since there is also a difference between refugees who have not seen much violence, this study focuses on those individuals who have experienced higher trauma situations.

Methods

Data was found from studies using PubMed and JSTOR databases, the UC Davis Catalog and Course Reserves, and all UC libraries (Melvyl). The key search words were the words epigenetic(s), refugee, violence, genocide and chronic health. Search results were narrowed by keeping the studies within 10 years of 2020. Once narrowed, I scanned the titles to look for studies involving the identification of specific health effects of epigenetic changes that did not exclusively involve PTSD or other mental health disorders. While mental health is a commonly investigated point of concern among refugees, this study focuses on other physical health effects. The results were narrowed by reading the abstracts and determining the relevance to the question of this study. Gaps in data from these results were filled in by pulling articles from the references of the studies obtained from the databases. Studies pulled from the References sections were put through the same process of elimination, resulting in some studies that are older than 2010.

Results

Health Issues Most Prevalent in Individuals Who Experienced Trauma, Abuse, and Violence (Keeshin, B., Cronholm, P., & Strawn, J. 2012)	*Health Issues Most Prevalent in Refugee Populations* (Amara, A.H. and Aljunid, S.M., 2014)
Chronic Pain and Somatic disorders: These include musculoskeletal pain, chronic fatigue, gastrointestinal pain, and chronic head pain (e.g., headaches). *Respiratory disorders*: These include asthma, COPD, reduced lung function, and lung disease. *Obesity*: This becomes a risk factor for developing hypertension, CVD, and diabetes. Obesity is often seen in those who experienced sexual abuse. *Cardiovascular disease (CVD)/ Hypertension*: Violence does correlate with an increased risk of developing CVD, even when taking factors like hypertension, smoking, etc. into account. Hypertension (constitutively high blood pressure) was observed in individuals exposed to violence and trauma. *Cancer*: Experiencing violence as a child has been linked to a 2x increase in developing cancer of any kind. Increased cancer development is also a secondary health effect of the previous health issues such as obesity.	*Hypertension/Cardiovascular disease*: Prevalence of hypertension was especially high in Iraqi, Palestinian, Somali and Burmese refugees. The numbers ranged from 18% to 33% of the populations having hypertension, and correlated with high CVD prevalence. *Musculoskeletal diseases*: These were especially prevalent in Asian refugee populations. This included general chronic pain as well as joint pain and arthritis as well as other somatic disorders. In the populations in which this was most prevalent the numbers went up to 15%. *Respiratory diseases*: These were very common in refugees, especially in refugees settled in Africa and Iran, where the numbers went up to 11% and 7%, respectively. These diseases include asthma and COPD. *Diabetes* was prevalent. *Renal disease* was prevalent in certain Asian refugees. *Gastrointestinal diseases* were common in North Korean refugees. *Cancer* was often found in young Afghan refugees.

Figure 1. This table compares the similarities between physiological health issues that are prevalent in individuals who have experienced violence and abuse (left column) and the health issues most prevalent in refugee populations (right column). The information in the left column was obtained from the 2012 study by Keeshin, et. al, "Physiologic Changes Associated With Violence and Abuse Exposure: An Examination of Related Medical Conditions." The information in the right column was obtained from the 2014 study by Amara and Aljunid, "Noncommunicable diseases among urban refugees and asylum-seekers in developing countries: a neglected health care need."

Epigenetic Modification from Exposure to Violence/Trauma	*Function of Modification*	*Diseases from Figure 1, Most Related to Modification*
Increased epigenetic aging found in children who experienced violence (Jovanovic, et al., 2017).	Increased epigenetic aging was shown to result in children having the physiological responses of adults in response to stressors. Children who experienced violence had the oldest epigenetic age. Children who only witnessed violence had an older epigenetic age but not to the extent of those who experienced violence. (Jovanovic, et al., 2017)	Musculoskeletal Disease Cardiovascular disease/ Hypertension
Increased methylation in the promotor region of NR3C1 was found in survivors of genocide and their children (Perroud, et al., 2014).	NR3C1 is a gene involved in the translation of glucocorticoid receptors. Increased methylation resulted in lower plasma cortisol levels as well as lower glucocorticoid receptor levels (Perroud, et. al., 2014). According to Perroud, et. al., increased mineralocorticoid levels were seen as an attempt to compensate for the low GR levels (2014).	Respiratory Disease Cardiovascular disease

Decreased methylation of an upstream regulatory region of BDNF was found in people who were exposed to community violence. This change was more prevalent in youth (Serpeloni, et al., 2020).	Dysregulation of BDNF has been linked to psychotic and mental illnesses in this paper. It is also linked to age related illnesses (Serpeloni, et al., 2020). It could be related to other diseases through more complex mechanisms.	Musculoskeletal Disease
Decreased methylation in CLPX was found in people exposed to community violence (Serpeloni, et al., 2020).	CLPX dysregulation results in changes of mitochondrial function that can negatively affect cell processes (Serpeloni, et al., 2020).	N/A

Figure 2. This table compiles several specific epigenetic modifications identified in individuals who have experienced trauma and violence, either by their community or through genocide (left column). The specific effects of the epigenetic modifications identified are compiled in the center column. The possible diseases connected to the identified epigenetic modifications are compiled in the right column. These diseases are only listed if they have been proven to occur with high prevalence in refugee populations as well as in individuals who have experienced abuse, trauma, and violence.

Discussion

Prevalence of Non-Communicable Diseases between Two Populations

Refugees that resettle in new countries are primarily screened and treated for infectious diseases due to the possible threat to the existing population (Amara and Aljunid, 2014). However, recent studies show that infectious diseases are not a large concern among these populations. One screen performed on newly arrived Syrian refugees found a less than 10% incidence of infectious diseases compared to a nearly 30% incidence of chronic diseases (Maldari, et al., 2019). Another study found a higher incidence of hypertension in refugee children when compared to immigrant children, despite both facing similar challenges in adjusting to living in a new environment (Lane, et al., 2019). The most chronic conditions that affect refugee populations appear to be musculoskeletal disease, respiratory diseases, cardiovascular disease, and hypertension (Amara and Aljunid, 2014) which overlap with the prevalent health issues that have been linked to individuals that experienced violence, abuse, and trauma (Keeshin, et al., 2012). Violence is proven to have lifelong, serious health impacts on individuals who experienced it (Keeshin, et al., 2012). Being that many of today's refugee populations are fleeing war and genocide, it is likely that the correlation between the health issues of the two populations indicates possible causation as well.

The most prevalent health issue in refugees is hypertension, which is a large risk factor for cardiovascular disease. Increased hypertension is suggested to correlate with higher levels of trauma in refugees (Kinzie, et al., 2008). The refugee populations with the highest levels of hypertension were Iraqi, Palestinian, and Burmese refugees (Amara and Aljunid, 2014). These specific refugees have fled situations that are known to be incredibly cruel and traumatic, for example the Iraq war, the genocide of Rohingya Muslims, and Palestinian apartheid. In addition, cardiovascular disease is also directly related to experiencing abuse even after controlling for other risk factors such as hypertension (Keeshin, et al., 2012).

Musculoskeletal pain is among the most prevalent chronic diseases after hypertension, affecting up to 15% of a given refugee population, especially Asian refugees (Amara and Aljunid, 2014). While a number of environmental reasons can directly contribute to the increase of these issues, experiencing violence has been linked to these health issues that include muscle and joint pain, arthritis, chronic headaches, and

chronic fatigue (Keeshin, et al., 2012). In addition, respiratory disease has an increased prevalence in refugee populations, which includes a prevalence of issues such as asthma and COPD (Amara and Aljunid, 2014). Reduced lung function and respiratory disease are also linked directly to experiencing abuse and trauma (Keeshin, et al., 2012). Both musculoskeletal and respiratory diseases can be linked to possible environmental and lifestyle causes, although further research is needed to confirm such factors. However, the obvious overlap of these conditions and the fact that they are not necessarily specific to ethnic groups strongly suggests that epigenetic modifications are worth looking into in refugees.

The studies that have focused on the prevalence of these chronic conditions in children (Lane, et al., 2019) suggest a possible hereditary factor of these conditions in refugee populations. If this is true, then these issues would stay prevalent in future generations of the current refugee populations. However, the major overlap of health issues between the refugee population and individuals who lived through abuse, trauma, and violence suggests a link between the violence and trauma that refugees have experienced and their resulting health issues.

Premature Epigenetic Aging

Children who have experienced violence are shown to have epigenetic ages that are older than their biological age (Jovanovic, et. al., 2017). This increased aging is directly correlated to the extent of exposure to violence, showing that increased and more direct exposure to violence, such as being the target of violence as opposed to witnessing it, resulted in higher epigenetic ages in children (Jovanovic, et al., 2017). Increased epigenetic age resulted in adult-like physiological responses to stress in children, such as lower heart rates (Jovanovic, et al., 2017). This is likely due to the fact that an increased epigenetic age means that genome-wide gene regulation resembles adults more than children, which Jovanovic, et. al., suggested could be an adaptive measure of the body to better deal with the constant stress of witnessed or experienced violence and trauma (2017).

The increased epigenetic age could be a short-term adaptive measure for stress, but may have deleterious long-term effects such as an increased susceptibility to age-related illnesses at younger ages. Age related illnesses include increased musculoskeletal diseases such as chronic muscle and joint pain or arthritis. Cardiovascular diseases are also more prevalent

in aging populations (King, 2015). Individuals who have experienced violence and trauma are proven to be more susceptible to these illnesses (Keeshin, et al., 2012). The prevalence of these illnesses in refugee populations, despite the fact that many refugee populations are younger, on average (Maldari, et al., 2019) could be a result of increased epigenetic aging in the population.

Long-term studies are needed to confirm if the increased epigenetic age in victims of abuse and violence maintains its difference from the individual's biological age, or if the epigenetic age and biological age eventually begin to correlate again. It is likely that the result is a combination of the two possibilities in that the epigenetic regulation of many parts of the genome begins to more closely correlate with the individual's biological age, while some specific genes maintain their differential regulation in comparison to the biological age. BDNF seems to be a gene whose differential regulation is apparent in younger generations, but is no longer statistically significant in older individuals (Serpeloni, et al., 2020). The expression in younger generations can contribute to age-related diseases at younger ages, that eventually match the expression expected when the individual reaches the age at which the diseases become prevalent.

NR3C1

The gene NR3C1 is directly involved in production of glucocorticoid receptors (GR) (Perroud, et al., 2014). The lower levels of GR in the Tutsi women who survived genocide strongly suggests that the increased DNA methylation of the NR3C1 in these women suppresses NR3C1 gene expression (Perroud, et al., 2014). Glucocorticoids are steroid hormones that regulate immune responses (Kino, 2017) and help maintain the baseline status of the HPA (Hypothalamic-Pituitary-Adrenal) axis and cortisol levels, which are the stress responders of the body (Nicolaides, et al., 2018). GR are the receptor proteins that regulate glucocorticoid transport in and out of nuclei (Kino, 2017). Once a glucocorticoid protein and a GR come in contact, they form a complex with the help of other proteins, and the GR transports the glucocorticoid near its gene targets on the DNA (Nicolaides, et al., 2018). These gene targets are generally involved with inflammatory response and the glucocorticoid activates the anti-inflammatory genes while repressing pro-inflammatory genes (Nicolaides, et al., 2018).

Increased methylation of the NR3C1 resulting in lower levels of GR means that glucocorticoids are less able to enter cell nuclei and respond to inflammation. These women are likely to be more prone to longer durations of inflammation as immune responses and difficulty in reducing said inflammation. Respiratory diseases, the most common among refugees being asthma and COPD (Amara and Aljunid, 2014), are both caused by excessive lung inflammation. Multiple different inflammatory cytokines, including increased signaling of TNF-alpha, IL-8b, and IL 6, cause the inflammation in asthma (Junchao, et al., 2016) as well as COPD (King, 2015). Glucocorticoids and GR work to repress the expression of these three inflammatory agents, among others, to reduce inflammation (Junchao, et al., 2016).

Increased inflammatory signaling has been found to contribute to cardiovascular diseases in conjunction with asthma (Xu, et al., 2017) and COPD (King, 2015). Although the exact mechanisms are unknown, frequent increases of inflammation, measured by the presence of IL 6, were associated with increased arterial stiffness (King, 2015). The inflammatory cytokine expression controlled by glucocorticoids and GR primarily affects inflammation of the body, but can also affect other functions of the body that can lead more directly to a chronic decline in cardiovascular health. Increased inflammatory cytokine signaling associated with asthma and COPD also lead to constriction of blood vessels and more uptake of LDL cholesterol (King, 2015), both of which contribute heavily to the onset of coronary health issues, such as hypertension and atherosclerosis.

Studies testing the epigenetic status of NR3C1 in refugees are needed to take steps to confirm the link between this epigenetic change and the prevalence of these respiratory and cardiovascular diseases. However, the current evidence gives a coherent mechanism by which it is possible that the violence and trauma experienced by refugees could result in suppressed immune response to inflammation.

BDNF

BDNF is a neurotrophic factor that acts mainly in the central and peripheral nervous systems and promotes the creation of neuronal pathways, often responding to environmental stimuli (Binder and Scharfman, 2004). One function of BDNF is to increase pain sensitivity after injury by way of increased nociceptive (pain receptor) signaling

(Binder and Scharfman, 2004), which can also be linked to chronic pain when BDNF is dysregulated or overexpressed (Stack, et al., 2020). Studies of individuals who experience community violence have found decreased methylation of BDNF (Serpeloni, et al., 2020), indicating a likely increase in BDNF signaling in those individuals.

Increased BDNF signaling results in longer, chronic nociceptive sensitivity, which has been linked to chronic joint pain and spinal degeneration, leading to severe back pain (Stack, et al., 2020). Back pain was among the most common complaints in refugees who were reported to have musculoskeletal health issues (Amara and Aljunid, 2014). BDNF acts to weaken the inhibitory response of hyperpolarizing nociceptors which stops continued signaling of pain (Caumo, et al., 2016). It is possible that this epigenetic modification is a result of an adaptive measure of the body in response to the continuous threat of violence. More research is needed to conclusively connect BDNF signaling to chronic pain and musculoskeletal diseases as well as the likelihood of the presence of this mechanism in refugees. This epigenetic modification is also suggested to be linked to age-related diseases (Serpeloni, et al., 2020), of which musculoskeletal diseases and chronic pain are the most likely. The prevalence of chronic musculoskeletal diseases in the refugee population can come from possible environmental factors, but it is worth looking into the possibility of these epigenetic changes that can affect the health of refugees even after lifestyle changes.

CLPX

Serpeloni, et al., also found differential epigenetic regulation of CLPX (2020). The decreased methylation of CLPX in individuals who have experienced violence (Serpeloni, et al., 2020) suggests an increased transcription of the CLPX protein. The CLPX protein is a protease that degrades a large number of tagged proteins, but does not have a specific affinity to degrading any one protein or protein type (Baker and Sauer, 2012). An increased translation of this protease could result in increased indiscriminate degradation of proteins not tagged to be degraded. There are likely detrimental health effects to increased CLPX signaling. The original paper suggests that this epigenetic modification is likely related to age-related illnesses as well (Serpeloni, et al., 2020). More research is needed to determine the actual health effects of increased CLPX signaling and to determine the prevalence of this epigenetic modification

in refugees.

Conclusion

In summary, violence and trauma result in epigenetic changes that likely affect many refugees and contribute heavily to the resulting prevalent non-communicable diseases in the refugee populations. More research is required that specifically studies refugee populations in order to determine the actual rates of these epigenetic changes. There needs to be more recent studies focused on the health status of refugees living in Asia and Africa rather than only on those who have immigrated to Europe or western nations. Research is also needed to specifically link the epigenetic changes to resulting health issues. Lastly, given the environmental causes of the epigenetic changes discussed in this paper, it is likely that treatment can include reversing these epigenetic changes through environmental means. Future research in treating refugees, but also individuals who have experienced trauma and abuse, can involve measuring the effectiveness of certain therapies by comparing the epigenetic status of patients to that of control groups.

References

Amara, A.H., Aljunid, S.M. (2014). Noncommunicable diseases among urban refugees and asylum-seekers in developing countries: a neglected health care need. *Global Health* 10-24. https://doi.org/10.1186/1744-8603-10-24

Baker, T. A., Sauer, R. T. (2012). ClpXP, an ATP-powered unfolding and protein-degradation machine. *Biochimica et biophysica acta*, 1823(1), 15–28 https://doi.org/10.1016/j.bbamcr.2011.06.007

Binder, D. K., Scharfman, H. E. (2004). Brain-derived neurotrophic factor. *Growth factors (Chur, Switzerland)*, 22(3), 123–131. https://doi.org/10.1080/08977190410001723308

Caumo W., et. al. (2016) Motor Cortex Excitability and BDNF Levels in Chronic Musculoskeletal Pain According to Structural Pathology. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2016.00357

Jovanovic T, et al. (2017). Exposure to Violence Accelerates Epigenetic Aging in Children. *Sci Rep*. 7(1):8962. https://doi.org/10.1038/s41598-017-09235-9

Junchao, Y., et al. (2017). Anti- trachea inflammatory effects of diosgenin from Dioscorea nipponica through interactions with glucocorticoid receptor α. *The Journal ofinternational medical research*, 45(1), 101–113. https://doi.org/10.1177/0300060516676724

Keeshin, B., et al. (2012). Physiologic Changes Associated With Violence and Abuse Exposure: An Examination of Related Medical Conditions. *Trauma, Violence & Abuse*, 13(1), 41-56. https://doi.org/10.2307/26631743

King P. T. (2015). Inflammation in chronic obstructive pulmonary disease and its role in cardiovascular disease and lung cancer. *Clinical and translational medicine*, 4(1), 68. https://doi.org/10.1186/s40169-015-0068-z

Kino T. (2017). Glucocorticoid Receptor. In *Endotext*. Retrieved from: NCBI library https://www.ncbi.nlm.nih.gov/books/NBK279171/

Kinzie JD, et al. (2008). High prevalence rates of diabetes and hypertension among refugee psychiatric patients. *J Nerv Ment Dis*. 196(2):108-112. https://doi.org/10.1097/NMD.0b013e318162aa51

Lane G, et al. (2019) Chronic health disparities among refugee and immigrant children in Canada. *Appl Physiol Nutr Metab*. 43(10):1043-1058. https://doi.org/10.1139/apnm-2017-0407

Maldari T, et al. (2019). The health status of newly arrived Syrian refugees at the Refugee Health Service, South Australia. *Aust J Gen Pract*. 48(7):480-486. https://doi.org/10.31128/AJGP-09-18-4696

Nicolaides N.C., et al. (Ed). (2017). Glucocorticoid Therapy and Adrenal Suppression. In *Endotext*. Retrieved from: NCBI library https://www.ncbi.nlm.nih.gov/books/NBK279156/

Perroud N, et al. (2014). The Tutsi genocide and transgenerational transmission of maternal stress: epigenetics and biology of the HPA axis. *World J Biol Psychiatry*. 15(4):334-345. https://doi.org/10.3109/15622975.2013.86669

Serpeloni F, et al. (2020). Experiencing community and domestic violence is associated with epigenetic changes in DNA methylation

of BDNF and CLPX in adolescents. *Psychophysiology*. 57(1):e13382. https://doi.org/10.1111/psyp.13382

Stack E., et al., (2020) *In vitro* affinity optimization of an anti-BDNF monoclonal antibody translates to improved potency in targeting chronic pain states in vivo, https://doi.org/10.1080/19420862.2020.1755000

Stenz L, et al. (2018). Intergenerational Transmission of DNA Methylation Signatures Associated with Early Life Stress. *Curr Genomics*. 19(8):665-675. https://doi.org/10.2174/1389202919666171229145656

United Nation High Commissioner for Refugees. (2019). Refugee Statistics | USA for UNHCR. Retrieved from https://www.unrefugees.org/refugee-facts/statistics/

Xu, M, et al. (2017). Asthma and risk of cardiovascular disease or all-cause mortality: a meta-analysis. *Annals of Saudi Medicine*. https://doi.org/10.5144/0256-4947.2017.99