Migraines and Myocardial Infarction in Women

Haley Moak

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Abstract

Background: Heart disease is the number 1 cause of death for U.S. women, myocardial infarction (MI) included. It has been established that ischemic stroke has a positive correlation with those who experience migraines, but there were no definitive studies saying that migraines cause all other cardiovascular related diseases, even though there is a common consensus that migraines are a vascular phenomenon. This systematic review focuses on the correlation between migraines and myocardial infarction particularly in women.

Methods: An exhaustive search of available medical literature was conducted using MEDLINE-Ovid, Web of Science, and CINAHL databases. The following terms were searched as keywords: migraine, myocardial infarction, and women or female. Studies applicable to the topic of the association of migraines and myocardial infarction in women were included as long as they were in English, on human subjects, and prospective cohort studies. The quality of relevant articles was evaluated via the GRADE Working Group guidelines.

Results: The initial search yielded 193 articles that were narrowed down to 3 prospective cohort studies by applying the eligibility criteria. Each study yielded odds ratios of having a MI in women with migraines compared to women without migraines. The Kurth et al, WHS, resulted in the hazard ratios of 1.94 (95% CI 1.27 to 2.95, P value 0.002) for active migraine with aura. The Kurth et al, NHS II, had an age adjusted hazard ratio of 1.79 (95% CI 1.52 to 2.10, P value

Conclusion: Women who have migraines, especially those with aura, are at an increased risk of myocardial infarction compared to those without migraines. Providers should consider migraines in women as a positive risk factor for myocardial infarction. These findings should prompt research on the biological process of migraines and whether the treatments we use now can protect women from the increased risk.

Keywords: Migraine, myocardial infarction, heart attack, women, female, and risk.

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Migraines and Myocardial Infarction in Women

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
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Faculty Advisor: Elizabeth Crawford
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Haley Moak is an Oregon native, raised on a ranch in Baker City. She majored in Medical Sciences at Washington State University. During this time she taught human anatomy lab, was active in her church, and was an avid ultimate frisbee player. Additionally, she worked as a medicine aide; caring for residents at an assisted living community. After completion of her undergraduate degree, she married a fellow WSU alumni, traveled, and was gratefully admitted into Pacific University’s School of Physician Assistant Studies.
Abstract

Background: Heart disease is the number 1 cause of death for U.S. women, myocardial infarction (MI) included. It has been established that ischemic stroke has a positive correlation with those who experience migraines, but there were no definitive studies saying that migraines cause all other cardiovascular related diseases, even though there is a common consensus that migraines are a vascular phenomenon. This systematic review focuses on the correlation between migraines and myocardial infarction particularly in women.

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Results: The initial search yielded 193 articles that were narrowed down to 3 prospective cohort studies by applying the eligibility criteria. Each study yielded odds ratios of having a MI in women with migraines compared to women without migraines. The Kurth et al, WHS, resulted in the hazard ratios of 1.94 (95% CI 1.27 to 2.95, P value <0.002) for active migraine with aura. The Kurth et al, NHS II, had an age adjusted hazard ratio of 1.79 (95% CI 1.52 to 2.10, P value <0.01) for overall migraineurs. And the Bigal et al, AMPP, had odds ratios of 2.32 (95% CI 1.63–3.31, P value <0.01) for migraines overall, 3.52 (95% CI 2.38–5.19, P value <0.01) for MA, and 1.75 (95% CI 1.19–2.58, P value <0.01) for MO.

Conclusion: Women who have migraines, especially those with aura, are at an increased risk of myocardial infarction compared to those without migraines. Providers should consider migraines in women as a positive risk factor for myocardial infarction. These findings should prompt research on the biological process of migraines and whether the treatments we use now can protect women from the increased risk.

Keywords: Migraine, myocardial infarction, heart attack, women, female, and risk.
Acknowledgements

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Table 1:  Quality Assessment of Reviewed Studies
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List of Abbreviations

AMPP  American Migraine Prevalence and Prevention study
CI     Confidence Interval
FRS    Framingham risk score
HR     Hazard Ratio
MI     Myocardial Infarction
MA     Migraine with Aura
MO     Migraine without Aura
NHS II Nurse’s Health Study II
OR     Odds Ratio
WHS    Women’s Health Study
Migraines and Myocardial Infarction in Women

BACKGROUND

Migraines are a common disorder that affects 18% of U.S. women.¹ Migraines present as a severe, usually unilateral headache often with the associated symptoms of nausea, vomiting, dizziness, sensitivity to light, sound, touch, and smell. The headaches usually last between 4 to 72 hours. Migraines can also have a perceptual disturbance called an aura that precedes the headache. The aura can come in many forms: visual disturbances (flashing lights, blind spots, difficulty focusing), auditory disturbances (fullness in the ear, tinnitus, pressure), weakness or tingling of the face or limbs, or coordination problems.

Migraines have previously been established to be an increased risk factor for ischemic stroke.² Migraines have also been speculated to be a risk factor for overall cardiovascular disease including myocardial infarction (MI), also known as a heart attack. The pathophysiology of migraines is not fully understood, but there is a common consensus that it is a vascular phenomenon. Many studies³-⁵ have researched the association of migraines with major cardiovascular disease risk only within some cardiovascular risk groups or for certain vascular events. This review specifically looks at women and their risk for myocardial infarction in association with migraines.

Because heart disease is the leading cause of female deaths in the U.S.⁶ it would be beneficial for providers to know whether women with migraines are having more MIs than those without migraines. Providers could use this
information when calculating a female patient’s risk for heart disease and predicting future heart attacks. This knowledge may drive providers to treat patients they may have otherwise overlooked and could save a life.

METHODS

A comprehensive literature search using MEDLINE-Ovid, Web of Science, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) was conducted. The following search terms were used: “migraine,” “myocardial infarction,” and “women or female.” The bibliographies from relevant background articles were used and eligibility criteria were applied. The quality of relevant articles was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group guidelines.7

Inclusion Criteria

Included were studies conducted on women who had migraines compared to a control group of women who did not experience migraines. Additionally, these studies had to have compared the specific cardiovascular event of myocardial infarction in their data set. Other inclusion criteria required human studies and studies published in the English language.

Exclusion Criteria

Studies were excluded if researchers did not dissect out myocardial infarction from other cardiovascular events such as stroke and claudication. Studies that related specific migraine pharmacology treatment to myocardial infarction were excluded as well. In addition, case series and case control studies
were omitted due to their inherently low quality results for a prognosis question. Lastly, only the primary study from a data set was included while all secondary studies were excluded from the search.

RESULTS

The initial search yielded 193 articles for review. After eliminating duplicates and screening these results for relevancy to the search terms there were 39 articles to further analyze. Using the eligibility criteria, there were 3 articles that answered the clinical question. All 3 articles⁸,¹⁰,¹¹ are prospective cohort studies. (See Table 1.)

Kurth et al, WHS

This is an article on a prospective cohort study called the Women’s Health Study (WHS)⁸ conducted by Harvard Medical School and Brigham and Women’s Hospital. The women in this study were US female health professionals, ≥45 years old. Baseline information was collected by self-reported questionnaires that were mailed to the participants. The follow-up information was also collected via mailed questionnaires twice in the first year, 1993, and yearly thereafter through March 2007. The questionnaires asked about cardiovascular risk factors, personal characteristics, medical history, and health habits. At the start, there were 27 519 women participants all free of cardiovascular disease at baseline, with a 97% follow-up of the cohort.⁸

Assessment of migraine was based off the baseline questionnaire. The WHS had reported good agreement of self-reported migraine compared to the
1988 International Headache Society criteria for migraine. The results of the questionnaires categorized women into “no migraine” (n=22,445), “prior migraines” (n=1,497), “active migraines with aura” (n=1,418), and “active migraines without aura” (n=2,159). The distinction of prior migraines and active migraines was whether the participant had a migraine within the previous year before the initial questionnaire.\textsuperscript{8} 

The primary outcome of the WHS was major cardiovascular disease events measured by myocardial infarction, ischemic stroke, and death via cardiovascular events. The WHS also categorized their data according to the well-known Framingham risk score.\textsuperscript{9} The result reviewed for this study was the secondary outcome of myocardial infarction. The results of myocardial infarction were obtained via medical records, specifically the record of abnormal cardiac enzymes or abnormal electrocardiographic results indicative of an MI. The study resulted in the hazard ratios of 1.94 (95% CI 1.27–2.95, P value 0.002) for active migraine with aura, 0.95 (95% CI 0.58–1.56, P value 0.85) for active migraine without aura, and 1.20 (95% CI 0.76–1.89, P value 0.44) for prior migraines. These are the overall results of the women studied. The only significant result of the Framingham risk groups was those with active migraine with aura and a Framingham risk score ≥10%; resulting in a hazard ratio of 3.34 (95% CI 1.50–7.46, P value 0.003).\textsuperscript{8,9} 

Kurth et al, NHS II 

This was a prospective cohort study from the Nurses’ Health Study II\textsuperscript{10} conducted by Brigham and Women’s Hospital, Harvard Medical School, and
Harvard T.H. Chan School of Public Health. This was a cohort of women from the ages 25-42 years old at baseline who were followed from 1989 through June 2011. The NHS II began with a baseline questionnaire and follow-up questionnaires every two years through 2011. The participants were all female nurses in the United States that were free of angina or any other cardiovascular disease at the start.\textsuperscript{10}

The study began with 115,541 women and had more than a 90% follow-up rate. There were 17,531 women in the study who reported physician-diagnosed migraine at baseline in 1989 and an extra 6,389 women reported a new, physician-diagnosed migraine during the study time frame; only the women with a migraine diagnosis at baseline were included in the statistical analysis.\textsuperscript{10}

The primary outcome of the study was major cardiovascular disease that was measured as a cumulative endpoint of myocardial infarction, stroke, and fatal cardiovascular disease. Only the measured secondary endpoint of myocardial infarction was investigated. During the follow-up, 678 myocardial infarctions occurred. Compared with women without migraines, those with self-reported physician-diagnosed migraines had an age adjusted hazard ratio of 1.79 (95\% CI 1.52–2.10, P value <0.01) for experiencing a myocardial infarction.\textsuperscript{10}

**Bigal et al, AMPP**

Bigal et al\textsuperscript{11} is an article on the prospective cohort study called the American Migraine Prevalence and Prevention (AMPP) study conducted by the National Headache Foundation. Participants were 18-69 years old and were categorized by sex, 10 year increments of age, and race. The study began in 2004
with a randomization of 120,000 U.S. households. The participants were given the validated self-administered questionnaire used by the WHS (same questionnaire discussed in Kurth et al, WHS). Five years later a cohort of 24,000 migraine sufferers and 10,000 controls without headaches were resurveyed for the primary outcomes of myocardial infarction, stroke, and claudication. All outcomes were verified by medical record, including myocardial infarction.\textsuperscript{11}

The migraineurs were counted overall as well as into the categories of migraine with aura (MA) and migraines without aura (MO). Odds of having an MI compared to those without migraines, women with any type of migraine have the odds ratios of 2.32 (95% CI 1.63–3.31, P value <0.01), with MA 3.52 (95% CI 2.38–5.19, P value <0.01), and with MO 1.75 (95% CI 1.19–2.58, P value <0.01).\textsuperscript{11}

The follow-up rates were 67% for migraineurs and 52.4% for controls. The study states responders and non-responders did not vary significantly by demographics.\textsuperscript{11}

**DISCUSSION**

**Clinical Relevance**

Heart disease is the number one killer of women across the United States. Of that, coronary heart disease, including myocardial infarction, is the greatest.\textsuperscript{6} If there was a way that could better predict and prophylactically treat the risk factors for heart disease, specifically myocardial infarction it should be utilized. This is already being done in many ways by treating the known risk factors of hypertension, diabetes, obesity, hypercholesterolemia, and smoking. What if
migraines were also on that list of risk factors for women? Would this encourage clinicians to monitor cardiovascular risks in women with migraines? Would this urge practitioners to prophylactically treat migraines more aggressively? Additionally would it prompt researchers to further study the mechanism of migraines and discover whether the treatments used today are sufficient to reduce the risk of MIs?

This systematic review was able to uncover three studies\(^8,10,11\) that look at the effect of migraines on the occurrence of MIs in women. In synthesizing the results from the three prospective cohort studies, the consensus was that women with migraines do show an increase in the occurrence of myocardial infarction. This was true for all data sets with statistical significance and could potentially be more than double the risk for an MI, especially in those women with aura associated to their migraine.

As seen in Table 2, the Kurth et al, NHS II,\(^10\) represented the lowest association with an age-adjusted OR of 1.79 (1.52 to 2.10) for MIs compared to women without migraines. The highest overall association was in the Bigal et al, AMPP,\(^11\) with an OR of 2.32 (1.63 to 3.31) for MIs compared to women without migraines. The Kurth et al, WHS,\(^8\) fell between these two with an OR for MA of 1.94 (1.27 to 2.95) for MIs. In collaborating these studies, it is apparent that there is an increase correlation between MIs and female migraineurs.

Further dissecting these studies, the Kurth et al, WHS,\(^8\) categorized their data into Framingham risk score groups.\(^9\) The only Framingham risk score\(^9\) group that had statistical significance was the group of women with a risk score
≥10% and active migraines with aura. This group’s OR was even higher than any of the figures discussed earlier, with an OR of 3.34 (1.50 to 7.46). This may indicate that women with a higher 10-year cardiovascular disease risk are impacted even more so by a history of migraines.

The Bigal et al, AMPP,\textsuperscript{11} additionally sub-categorized their data into MA and MO, as did Kurth et al, WHS.\textsuperscript{8} The Kurth et al, WHS,\textsuperscript{8} had data without statistical significance (P value >0.05) for MO and “prior migraines.” This lack of statistical significance is not surprising since the study only had 24 participants who experienced an MI. The values from the category of “active migraine with aura” was statistical significant represented by the P value of 0.002. As far as Bigal et al, AMPP,\textsuperscript{11} the participants with MA had an OR of 3.52 (2.38 to 5.19) while those with MO had the OR of 1.75 (1.19 to 2.58). This may suggest that women with MA represent a greater MI risk than those with MO.

The odds ratios shown here are between 1.75 and 3.52, representing a positive correlation between migraines and MIs in women. Looking at the big picture, 2.6 million U.S. women have MIs in their lifetime and about 18% of U.S. women have migraines.\textsuperscript{12} This would implicate that thousands if not 10s of thousands of women with migraines could experience an associated myocardial infarction in the US alone.

**Limitations of Study**

These studies were evaluated using the GRADE method\textsuperscript{7} and results can be seen in Table 1. The major limitation of all three studies is that they are observational studies. Observational studies do not allow for as much control of
other factors that may play into the correlation between migraines and MIs, therefore it is not possible to draw a cause-effect relationship, merely just a correlation.

Another limitation is within the Bigal et al, AMPP study.\textsuperscript{11} This study had incomplete follow-up with a response rate of 67\% in the migraines group and 52.4\% in the control group; however, the article states that the demographics between the responders and non-responders “did not significantly differ”.\textsuperscript{11} The original article shows that response rate was higher in white participants that were greater than 50 years old. The older age of responders may have caused a change of incidence due to age rather than migraine history.

The Kurth et al, WHS,\textsuperscript{8} and the Kurth et al, NHS II,\textsuperscript{10} obviously have the same primary author; who is also a secondary author on the Bigal et al, AMPP, article.\textsuperscript{11} This may represent a bias in the display of information although each of the studies had many additional authors and are based off separate cohort/data sets.

Further research should address whether or not migraine history warrants screening and managing other cardiovascular risk factors. More information regarding migraine pathology would help to inform clinicians and researchers of possible shared mechanisms with myocardial infarctions and result in strategies for interventions. Lastly, it is unknown if migraine prophylaxis will reduce the patient’s risk for myocardial infarction.
CONCLUSION

The leading cause of death of women in the United States is cardiovascular disease, including myocardial infarction. This systematic review resulted in a positive correlation between migraines and myocardial infarction in women. The review of three prospective cohort studies in total representing women from 18 to 69 years old across the US exhibited a potential doubling of the occurrence of myocardial infarctions compared to women without migraines, especially those with an aura.

The implication for practice is whether migraines should be a risk factor considered in the prophylactic management of cardiovascular disease in women. Furthermore, continuous research would be helpful to know whether the current migraine management prescribed is protective against the risk of myocardial infarction, and whether this treatment should be used more aggressively. Research on a more in-depth pathophysiologic understanding of migraines would be beneficial to potentially develop a protective treatment if the current treatment is not protective.
References


Table 1: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurth et al (WHS)</td>
<td>Prospective Cohort</td>
<td>Not serious, Not serious, Not serious, Not serious</td>
<td>Unlikely</td>
<td>None</td>
</tr>
<tr>
<td>Kurth et al (NHS II)</td>
<td>Prospective Cohort</td>
<td>Not Serious</td>
<td>Unlikely</td>
<td>None</td>
</tr>
<tr>
<td>Bigal et al (AMPP)</td>
<td>Prospective Cohort</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Large Magnitude of effect&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Very low</td>
</tr>
</tbody>
</table>

<sup>a</sup> Bigal et al study only had a follow-up of 67% in the target group and 52.4% in the control group

<sup>b</sup> Bigal et al had an odds ratio greater than 2
Table 2. Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Migraineurs with MI n (%)</th>
<th>Migraine overall with MI ORa (95% CI)</th>
<th>Migraine with aura with MI ORa (95% CI)</th>
<th>Migraine with aura and FRS of ≥10% with MI ORa (95% CI)</th>
<th>Migraine without aura with MI ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurth et al (WHS)</td>
<td>24 (1.69)</td>
<td>---------</td>
<td>1.94 (1.27 – 2.95)</td>
<td>3.34 (1.50 – 7.46)</td>
<td>---------</td>
</tr>
<tr>
<td>Kurth et al (NHS II)</td>
<td>678 (3.87)</td>
<td>1.79 (1.52 – 2.10)</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Bigal et al (AMPP)</td>
<td>314 (6.40)</td>
<td>2.32 (1.63 – 3.31)</td>
<td>3.52 (2.38 – 5.19)</td>
<td>---------</td>
<td>1.75 (1.19 – 2.58)</td>
</tr>
</tbody>
</table>

Abbreviations: CI – confidence interval, OR – odds ratio
All P values are ≤0.05
aAll ORs are vs control (women without migraines)