Review

To what extent do biological sex and gender affect women's symptoms and therefore mortality from acute coronary syndrome?

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Abbreviations

ACS – acute coronary syndrome
MI – myocardial infarction
UA – unstable angina
NSTEMI - non-ST-segment-elevation myocardial infarction
STEMI - ST-segment-elevation myocardial infarction
SCAD – spontaneous coronary artery dissection
ED – emergency department
RCT – randomised controlled trial
AMI – acute myocardial infarction
MAPMISS - McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey

Abstract

Acute Coronary Syndrome (ACS) is a highly prevalent fatal disease. It encompasses conditions like myocardial infarction (MI), which are due to a sudden reduction of blood flow to the heart, usually by a blood clot. Women are more likely than men to die from this, despite a lower prevalence. This disparity creates a health inequality. This review aims to investigate why there is a difference between in-hospital mortality for women hospitalised with ACS compared to men, by understanding whether there is a dimorphism between symptom presentation, and patient perception of symptoms, as two possible causes. Studies show symptom presentation differs between men and women, due to physiological differences, which are not widely recognised. In women, these differing symptoms appear to be perceived incorrectly, as 'atypical' symptoms, which in turn contributes to their statistically significant increased mortality. Studies should aim to quantify the extent of sex and gender interplay in symptomatology and mortality.

Introduction

Acute Coronary Syndrome (ACS) encompasses conditions including unstable angina (UA), non-ST-segment-elevation myocardial infarction (NSTEMI) and ST-segment-elevation myocardial infarction (STEMI), caused by sudden reduced blood flow to the heart, commonly due to a blood clot within a coronary artery.[1] Other causes include plaque rupture, coronary vasospasm and spontaneous coronary artery dissection (SCAD).[2] Currently, 2.3 million people in the UK are affected, with 66,000 deaths a year.[3–5] Although disease prevalence is higher in men, women are more than twice as likely to die from ACS.[6] This disparity creates a fundamental health inequality between men and women.

The difference exists due to many factors. There are differences in ACS pathophysiology, varying with subclassification; STEMI occurs due to a blocked coronary artery or branch of supplying the heart, causing heart muscle death. Blood flow is reduced in UA and NSTEMI, but there is no muscle death.[1] The distinguishing feature between UA and NSTEMI is elevated cardiac markers in NSTEMI, like troponin, implying myocardial damage.[7] The most frequent diagnosis among

women presenting to the emergency department (ED) with suspected ACS is NSTEMI and UA.[8]

Sex is a biological variable, determined by genetic complement and chromosomes, which influences physiology and pathophysiology.[9] Specific to cardiovascular physiology, women have smaller epicardial coronary arteries and lower plaque burden than men. These may contribute to sex-based pathophysiological differences, such as more diffuse and non-obstructive coronary artery disease, twice the prevalence of microvascular dysfunction,[10–13] and having more plaque erosion and coronary vasospasm.[13]

These pathophysiological differences in turn cause differences in symptomatology and disease presentation and affect how women experience the disease.[14] Such differences are poorly understood and not widely realised due to a fundamental problem, which is cardiovascular research bias. Most studies do not report on sex, or they have mostly male participants and extrapolate results to women.[15,16] Consequently, the disease model has been built towards male physiology.[17] This has led to disease patterns and phenotypes causing symptoms more common to women being classed as 'atypical' compared to the traditional male model.[18] One study defines typical symptoms as chest pressure/heaviness/tightness/pain, sweating, shortness of breath, arm pain, jaw/neck pain. It defines atypical symptoms as chest numbness/tingling/pricking/stabbing, palpitation, nausea/vomiting, dizziness or syncope, fatigue, and indigestion.[19] Typically, chest pain is the most common symptom of ACS, however, this is more common in men than in women.[19]

The deficiency of research and awareness surrounding these differences in women leads to incorrect symptom perception, from both patient and provider sides. Focusing on patient perception, many women are unable to recognise their symptoms, as often they are not exclusively chest pain. Patient perception is influenced by gender not sex. Gender is a social construct, affecting access to healthcare and health-seeking behaviour, as well as perception of risk.[18] The effects of gender are determined by socio-cultural factors like gender representation, education and it affects knowledge of pathologies additionally.[10] This, in addition to different pain manifestations, aggravates this sexual dimorphism.[10] Due to the possibility of different symptom presentation, it can be harder for women to interpret their symptoms correctly and seek timely and appropriate medical diagnosis and intervention.

Lack of timely intervention, in this case from delayed symptom recognition, contributes to treatment delay, infarct expansion, and worse prognosis,[20] all contributing to higher mortality in women than men. Mortality is used as an outcome, due to the definitive nature of this endpoint being objective not subjective. It relates to the number of deaths caused by the health event under investigation,[21] in this case ACS. This review aims to investigate why there is a difference in in-hospital mortality for women hospitalised with ACS compared to men, by understanding whether there is a difference between symptom presentation and perception, as two possible causes.

Methods

Medline (PubMed), Cochrane Library and Trip Database were searched, using the search string ("symptomatology" OR "symptom" OR "symptom presentation") AND ("gender" OR "sex") AND ("diagnosis") AND ("mortality") AND ("women") AND ("AMI" OR "ACS"). Randomised controlled trials (RCTs), clinical trials and meta-analyses were included. Non-English papers were excluded. No arbitrary cut-off date was used, however papers published in the last 20 years were used, to remain up to date with the latest definition of MI.

Out of 189 results, six primary studies were selected, after screening for relevance and proper stratification by sex. Other information was retrieved using reputable websites, systematic reviews, and forwards and backwards citations. **Figure 1** illustrates the process of primary evidence synthesis.[22]

Results and Discussion

Symptom presentation

Examining the relationship between sex and symptom presentation, a US study by Canto et al[23] MI reported 42.0% (95% CI; 41.8-42.1) women and 30.7% (95% CI; 30.6-30.8) men, P<0.001 presented without chest pain/discomfort. This suggests significantly more women than men presented without chest pain/discomfort. The VIRGO study[24] investigated the role of gender on outcomes for young acute MI (AMI) patients, and reported 13.0% women and 10.5% men presented without chest pain, pressure or tightness. Women over 45 had 1.39 (95% CI 1.01-1.92) times the odds of presenting without chest pain compared to men, suggesting women are more likely than men to present without chest pain. Non-chest pain symptoms contribute to delayed help-seeking and access to care and treatment.[25]

Women in VIRGO also presented with more additional non-chest pain symptoms compared to men. Women experienced a mean number of symptoms of 3.4±2.0, and men 3.0±1.9, P<0.0001. The very small p-value suggests a significant difference between the two groups. Asgar Pour et al also looked at this, reporting women with ACS had a mean of 2.94±1.78 typical and atypical symptoms, whereas men had 2.75±1.36.[19] However, despite their more diverse symptom profile, women with atypical symptoms are significantly less likely to be diagnosed with ACS, than with typical symptoms. Despite no direct statistical comparison in mean symptoms, the results seem to agree with the former study, suggesting women present with more symptoms than men.

Canto et al had the largest sample size of 1,143,513, increasing the generalisability to a larger population. VIRGO had a smaller sample size of 2985, so is less generalisable than the first study, however, it spanned 103 US hospitals in geographically diverse locations, thus may be more representative of a broader demographic. Asgar Pour et al's is the smallest, with 438 participants from across eight hospitals and is the least generalisable. The first study is the most favourable in this regard, as due to large sample size, anomalous participants have less skew on results.

Despite its large sample size, in all categories, most of each group in Canto et al's were of White race/ethnicity, with the lowest being 73.1%, therefore is not representative of all MI patients in the US. VIRGO similarly, had a majority of 76% participants being White, decreasing representation of a varied society. This is a limitation, due to 42.2% of the US population being non-White,[26] inaccurately reflecting the US demographic, so cannot be generalised to the entire US population, or allow conclusions to be drawn regarding differences in presentation with ethnicity.

Furthermore, Canto et al had no cohort without MI to compare to, hence findings cannot be generalised to all patients with suspected ACS. However, Asgar Pour et al's study combats this, by comparing between those with and without ACS, stratified by gender and diagnosis, therefore is more applicable to a wider group.

The inclusion and exclusion criteria differ between these two studies, with Canto et al's missing certain data on age, sex and symptoms, and excluding those with a secondary diagnosis of MI or transferred patients, whereas VIRGO included those aged 18-55 hospitalised with AMI. Participant age may contribute to differences; the mean age of women was 73.9, and the second study excluded those above 55, due to the differences in pre- and post-menopausal women, particularly the lack of oestrogenic protection in the latter.[11,27]

Despite the limitations, the data supports each other's findings, suggesting more women than men present without chest pain, with a higher number of women experiencing more additional non-chest pain symptoms. These women are less likely to be diagnosed with ACS.

Symptom perception

Symptom perception was explored by An et al, investigating the gender differences in Chinese patients' ACS attribution of symptoms.[28] They reported 50.9% women and 37.2% men correctly identified their symptoms, although statistical significance is unreported. Contrarily, a Swedish study by Sederholm Lawesson et al reported 59.5% of women and 69.4% men, p=0.04 interpreted their symptoms as of cardiac origin.[29] Concordantly, The VIRGO study reported 54.7% women did not perceive their symptoms to be heart related vs 52.3% men, p=0.379, and were significantly more likely to attribute symptoms to stress or anxiety. However, with such a large p-value, evidence of a significant difference is quite weak. Despite this, 7.4% more women sought medical care before being hospitalised than men, however, significantly more women than men reported that their provider thought symptoms were unrelated.

All three studies used surveys, questionnaires or interviews, which rely upon episodic memory. Consequently, relying upon this being the same across all genders and all participants introduces recall bias, decreasing internal validity due to confounders. This is most prevalent within An et al's study, in which data was obtained 3-6 days post admission. Comparatively, data was collected within 24 hours in the study by Sederholm Lawesson et al, minimising recall bias.

Despite primary data limitations, the alternative is to collect observations from medical records, as demonstrated by Canto et al using secondary data. This was reliant upon subjective interpretation, and lacked standardisation, both in collecting and recording data. In contrast, use of patient interviews in VIRGO was standardised and administered by trained personnel, therefore this primary data may be more reliable, despite its recall bias.

Differences surrounding awareness of ACS symptoms in women may contribute to differing results between the studies. It has been previously identified that there are lower levels of symptom awareness in mainland China, with suboptimal attitudes and beliefs towards ACS, although this has limited capacity for extrapolation and may be outdated.[30] This contradicts the findings from An et al, and may be due to small sample size. Awareness of atypical symptoms, thus the ability to recognise and seek medical help, either directly by recognising their own symptoms, or indirectly by others recognising symptoms, is a predictor of delay in seeking medical attention.[30] In addition to such awareness, other confounders such as international and gender disparities in education, cultural norms, socioeconomic status and healthcare systems may affect health-seeking behaviours.[31] The confounding effect of these behaviours may be reduced in Sederholm Lawesson et al's study, as Sweden is one of the most gender equal countries and has complete healthcare coverage for all citizens, with studies reporting only small gender disparities found in health-seeking behaviour.[31]

Both the studies by An et al and Sederholm Lawesson et al used surveys or questionnaires to obtain data, which have limitations. An et al used the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS), which was translated from English to Mandarin. Despite efforts of four experts, translation and interpretation errors may remain, reducing internal validity. Language barriers also affected Sederholm Lawesson et al's study.[29] To ensure high internal validity, individuals with difficulties reading and speaking Swedish were excluded. This minimised the effect of literacy as a confounding variable. However, by excluding this group, firm conclusions could not be drawn about certain immigrant and refugee groups in particular,[29] but also differing educational levels and learning difficulties could act as confounders, reducing generalisability.

An et al's study observed all individuals with ACS, however, Sederholm Lawesson et al's study only observes those with STEMI, so participants make up a subset of those with ACS. Symptomatology may differ by ACS subclassification, due to differences in pathophysiology, and Sederholm Lawesson et al's findings cannot be generalised to all ACS patients.

The incongruence of results and lack of statistical significance suggests no firm conclusions can be drawn on gender differences in symptom perception.

Mortality

Canto et al also investigated the relationship between sex, symptom presentation and hospital mortality for patients with MI. They reported an in-hospital mortality for women of 14.6%, and for men 10.3%. This aligns with an Australian study by Mnatzaganian et al[32] evaluating sex differences in in-hospital mortality following a first AMI. They reported despite adjusting for age, women still had significantly higher crude death rates than males. Both studies share congruence, suggesting women have a higher in-hospital mortality from MI than men.

Changes in the universal definition of MI shortly after Canto et al's study, and diagnostic methods and treatment, means participant inclusion may differ if the study had been conducted more recently, yielding different results. This may affect the reproducibility and applicability of older findings.

With all studies, survival bias contributed largely. All participants who died before hospital admission were excluded, so results may be lower than actuality.

Due to the nature of the variables being measured, observational studies were deemed the most suitable format to record data: observation is the only way to observe natural occurrences. Since no intervention or exposure is being measured in these studies, RCTs would have been unsuitable for data collection.

In-hospital mortality was used as an endpoint to reduce the effect of confounding variables such as quality of follow-up care and recurrence of cardiac episodes.

Limitations

Increased mortality causes are multifactorial, aside from symptom presentation and perception. These include biological differences (genetic, epigenetic and hormonal) and gender differences, affecting both biological and social factors like stress and nutrition, and behaviour.[10] Additionally, factors like time taken from symptom onset to presentation to ED (onset-to-door time), and time taken from patient arrival at ED to percutaneous coronary intervention PCI (door-to-balloon time), provider bias resulting in misdiagnosis, appropriate intervention, follow-up care, co-morbidities, and risk factors such as age, further affect prognosis. This review focuses on exploring symptom presentation and perception as two possible contributors to mortality, not exclusively causing it.

Conclusion

Studies show women are significantly more likely to present without chest pain and experience more symptoms than men. Asgar Pour et al elaborated on this by correlating typical symptom presentation, such as chest pain, and likelihood of diagnosis, suggesting that since fewer women than men experience chest pain, these women are less likely to be diagnosed correctly.

Both Sederholm Lawesson et al's study and VIRGO agree women less often interpret symptoms as heart related than men. However, the study by An et al contradicts these findings. This may be due to awareness differences with gender disparity. Despite the congruence of the former two studies, neither is statistically significant, so no reliable conclusions can be drawn.

Both studies demonstrate a higher in-hospital mortality post-MI for women, although change in outdated diagnostic protocols must be considered and may not be comparable to more recent studies such as from Mnatzaganian et al. Furthermore, due to survival bias particularly affecting mortality rates, these figures may be substantially higher. However, this in addition to potential confounders, does not provide convincing evidence of no difference in mortality between men and women.

The interaction of biological sex and gender with symptom presentation and perception of ACS is significant and does contribute to the dimorphism in mortality. However, there is a dearth of research on the relationship between atypical symptom presentation and incorrect patient perception, and the extent of their contribution to increased mortality in women. There is also no link between the extent of the interaction of sex and gender, and the quantitative effect on outcomes. Consequently, studies should aim to quantify the extent to which sex and gender interplay in symptomatology and mortality and the links between, by ACS subtype. Future sex-specific studies on women should be conducted in cardiovascular research, to ascertain nuanced differences between sexes. Furthermore, it would be beneficial to have accessible information on atypical symptom recognition in GP and community settings and public health campaigns to ameliorate public health awareness. Additionally, using results to inform clinical protocols would greatly increase the prognosis of women, particularly by promoting urgent medial intervention.

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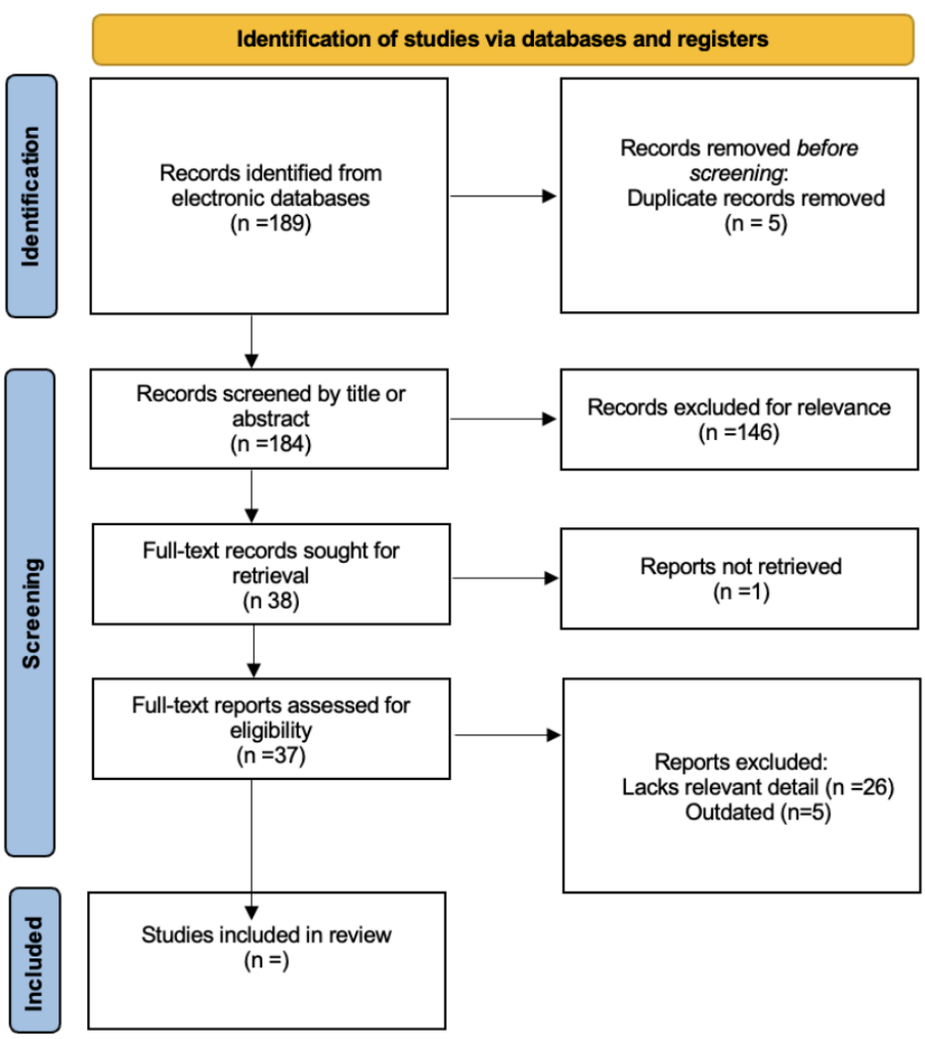

Figure 1. PRISMA diagram outlining primary evidence synthesis of literature for this review. This PRISMA diagram has been adapted from the BMJ Prisma 2020 Statement.[22]