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DIFFERENTIAL RISK OF ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION BETWEEN MALE AND FEMALE SMOKERS

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Condensed Abstract

Smoking increases STEMI risk. This study is the first to differentiate the risk between genders and age groups. STEMI rates per population group were created using retrospective admission and general population data over a 5 year period. Compared to their non-smoking counterparts, smoking females and a greater risk of STEMI risk than male smokers. This difference was present across all ages, but the difference was greatest in the 50 to 64 age range. Female smokers in the less than 50 age group had the greatest increased STEMI risk. This study quantifies smoking risk in an approachable format to encourage patients in smoking cessation.

Abstract

Background: Smoking is a well documented cause of STEMI. The differential effect between genders has yet to be quantified.

Objectives: To differentiate the impact of smoking on increased risk of ST-segment elevation myocardial infarction (STEMI), between genders.

Methods: A retrospective ecological cohort study. All patients at a UK tertiary cardiothoracic centre who presented between 2009 to 2014 with acute STEMI were combined with population data to generate incidence rates of STEMI. Age-standardised incidence rate ratios (IRR) using the Poisson distribution were calculated comparing STEMI rates between smokers and non-smokers stratified by gender and three age groups (18-49, 50-64, >65 years).

Results: 3,343 patients presented over 5,639,328 person-years. Peak STEMI rate for current smokers was in the 70-79 age range for females (235/100,000 pt/yrs) and 50-59 (425/100,000 pt/yrs) in males. Smoking was associated with a significantly greater increase in STEMI rate for females than males (IRR 6.62, CI: 5.98 to 7.31 vs 4.40, CI: 4.15 to 4.67). The greatest increased risk was in females aged 18-49 (13.22, CI: 10.33 to 16.66 vs 8.60, CI: 7.70 to 9.59 in males). The greatest risk difference was in the 50-64 year group with IRR of 9.66 (CI: 8.30 to 11.18) in females and 4.47 (CI: 4.10 to 4.86) in males.

Conclusions: This study quantifies the differential impact of smoking between genders, with females having a significantly increased risk of STEMI than males. This information encourages continued efforts to prevent smoking uptake and promote cessation.

Keywords: Gender, Smoking, Incidence, STEMI

List of abbreviations:

CHD – Coronary heart disease

CI – Confidence interval

IHS – Integrated Household Survey

IRR – Incidence rate ratio

LAD – Left anterior descending

LMS – Left main stem

ONS – Office for National Statistics

PCI – Percutaneous coronary intervention

RCA – Right coronary artery

STEMI – ST-segment elevation myocardial infarction

Introduction

Cardiovascular disease remains the leading cause of mortality worldwide, with an increasing prevalence. In 2000, this mortality was recorded at 28%, whereas in 2015 this had increased to 31%.(1,2) Heart disease also accounts for over one-quarter of all deaths in the USA.(3) Acute STEMI is amongst the most life-threatening manifestations of cardiovascular disease, affecting all age groups, resulting in death within 30 days in 5.7-11.0% of cases.(4-6)

In 2015, it was estimated that there were 933.1 million smokers worldwide, with 82.3% of these being male.(7) In contrast, of the UK's 7.6 million smokers there is a much narrower gender divide:(8) In 2016, 17.7% of the male population and 14.1% of the female population were smoking, the lowest recorded values since 2010.(8) The comparative similarity of smoking prevalence between genders in the UK makes the effects of smoking easier to compare. Studies assessing gender-differentiated risk of ischaemic heart disease attributable to smoking have yielded varying results. A Danish study found that smoking was a greater risk factor for all acute coronary syndromes in women, compared to men.(9) A study of a large Swedish registry has identified smoking as a more significant risk for STEMI for women than men, under the age of 65.(10) Older studies have either suggested an increased risk of myocardial infarction for women compared to men,(11,12) no difference in risk (Framingham),(13) or less risk than men.(14)

Although the magnitude of risk of acute STEMI attributable to smoking has been studied (15), none have quantified and compared the incidence of STEMI associated with smoking between genders and within different age groups. This study aims to assess smoking as an independent risk factor for STEMI, and determine differences in risk between age and gender groups.

Methods

In this retrospective ecological cohort study, data were compiled for all patients presenting with acute STEMI managed by primary PCI, in the South Yorkshire region over a five year period, between 4th January 2009 and 31st July 2014.

Employing a departmental database mandated by national audit processes, patients were identified and their individual patient case-notes examined. Data collected included patient age, gender, smoking status, other key cardiovascular risk factors, and cardio-protective drugs taken

prior to STEMI onset. Culprit artery of STEMI was also recorded. Ex-smokers were described as being abstinent for a minimum of 28 days prior to STEMI, although duration of smoking cessation was omitted from patient case notes in 38% of cases of ex-smoker.

Statistical Methods

Differences in the normally distributed continuous variables of ages within genders were compared using independent samples T tests. Differences between genders in categorical variables, other STEMI risk factors and pre-STEMI cardiac medications and the percentage of cases attributed to culprit arteries were compared using chi-squared tests.

STEMI incidence rates by age and gender were calculated, stratified by smoking status. These were derived by comparing the raw STEMI numbers, to the entire population served by the South Yorkshire Cardiothoracic centre, with data obtained from the Integrated Household Survey (IHS), from the United Kingdom Office for National Statistics (ONS).

The second dataset was derived from responses from South Yorkshire residents ≥aged 18 years participating in the Office for National Statistics Integrated Household Survey (ONS-IHS) between April 2009 and March 2012. The ONS-IHS asks randomly sampled respondents a range of topics using telephone or face-to-face interviews and is the biggest pool of UK social data after the census. It does not contain medical diagnoses due to the self-reported nature of the questionnaire. Respondents were asked both if they had ever smoked and if they currently smoked. Regional and/or national estimates of population responses are generated using a multi-stage population weighting procedure which accounts for probability of selection and adjusts for non-response, and have reported similar estimates to other social surveys. The weighted responses from the local authorities served by the cardiac centre were used to estimate population age and smoking status strata.

$$\text{Incidence rate} = \frac{\text{Number of acute STEMI events within study period for patient group}}{\text{Total corresponding person years at risk during the study period}}$$

95% confidence intervals were obtained from the Poisson distribution.

Incidence rate ratios (IRR) and their confidence intervals, indirectly standardised to account for age differences between the genders were calculated, and directly compared to assess differences in the impact of smoking on STEMI risk, between genders. Incidence rate ratios were calculated by age group by the formula:

$$\text{IRR} = \frac{\text{Incidence rate of STEMI in current smokers (exposed)}}{\text{Incidence rate of STEMI in ex} - \text{smokers and never smokers (unexposed)}}$$

Relative risk of smoking associated STEMI was then compared between the genders, across the age groups by dividing the IRRs through each other.

Ethics

Permission for this study was gained from the Sheffield Teaching Hospitals Research and Development Department, using previously collected data from hospital records, extracted and anonymised to preserve patient confidentiality and abide with the Data Protection Act. At the study's conception, approval was not required from the NHS Research Ethics Committee for retrospective studies of this sort.

Results

3,343 STEMIs were recorded within our five-year study period. Of these, 27.3% occurred in females whose mean presentation of age was 5.8 years older than males (66.6 vs 60.8, p=0.011). The prevalence of most risk factors and all pre-STEMI cardiac medications were similar (Table 1). However, hypertension, diabetes and history of cerebrovascular accident were significantly more common in females, whereas a previous history of myocardial infarction was more prevalent in males (Table 1). The proportion of STEMI patients who were current smokers were similar between genders (46.8% of female patients vs 47.6% of male patients).

The distribution of culprit artery for STEMI was impacted by gender, age group and smoking status (Table 2). STEMI in females were more likely to involve the RCA (right coronary artery), and less likely to involve the circumflex. The RCA was involved less in the cases of the 18-49 year old age group. Current smokers were more likely to have the RCA as their culprit lesion, and less likely to involve the LAD (left anterior descending) artery.

In smokers, the highest rate of STEMI was in the 50-59 year age group, at 286.3 (262.1 - 312.2) per 100,000, whereas in non-smokers, the highest rate was in the 70-79 year old group, at 95.1 (82.7 - 108.9) per 100,000. An incidence rate graph displaying the raw STEMI figures versus the general population demonstrated a similar risk between ex- and never-smokers for STEMI incidence, with confidence intervals overlapping between the groups at every 10 year age group

(Figure 1). Figures 2 and 3 demonstrate the incidence rates of acute STEMI for different smoking groups at each 10 year age group, differentiated for gender (female and male, respectively), with similarity between non-smoking groups confirmed. These figures justified the combination of the ex-smoker and never-smoker groups for further comparison of the effect of smoking vs not smoking, by looking at age-standardised IRRs (Figure 4).

Compared to their non-smoking counterparts, the STEMI risk was 6.62 times higher (CI: 5.98-7.31) in female and 4.40 (CI: 4.15-4.67) in male smokers. Female smokers under 50 years ran the highest relative risk of acute STEMI, 13.22 (CI: 10.35-16.66) times greater than their non-smoking counterparts. This was significantly higher than males of the same age group, with a smoking associated risk of 8.60 (7.70-9.59).

The largest relative risk difference in smoking-associated STEMI was found in the middle-aged (50-64), with female smokers being 9.66 (CI: 8.30-11.18) times increased risk of STEMI vs 4.47 (CI: 4.10-4.86) for males, indicating smoking is a more severe risk factor for women of this age group compared to men, by a factor of 2.16. Figure 5 demonstrates the relative risk of smoking associated STEMI for female smokers, compared to male smokers.

Discussion

Smoking is an established reversible risk factor for CHD. Our group has previously identified smoking as the causative agent for STEMI in nearly 50% of all cases,(16) and have highlighted that smoking poses the greatest risk in the young (under 50 years).(15) Despite this, there is no significantly increased mortality risk post STEMI according to smoking status.(17) Expanding from these previous studies, the established prevalence of risk factors at baseline have remained very similar.

We have found that smoking increases STEMI risk in all patients, regardless of age or gender. However, this is the first study to quantify this risk and its differential effect according to gender, and its variation within age groups. Smoking increases STEMI risk in females more than males by a significant degree at all ages, with the largest risk difference present in the middle aged (50-64 years) group. However, the highest risk increase for both genders was in the youngest patients (18-49 years). This study emphasises the differential effect of smoking on STEMI risk between younger and older smokers. This is most striking in young females, in

whom smoking increases STEMI risk by over 13 times, with young male smokers at 8.6 times increased risk.

The protective effects of endogenous oestrogens have long been known, due to their effects on serum lipid concentrations, and their effects on vessel walls, notably vasodilation and inhibiting response to injury, thus preventing the development of atherosclerosis.(18) It has been observed that oestrogen activity or production is inhibited by cigarette smoke.(19) This has been supported by studies finding statistically lower levels of serum oestrogen and increased failure rates of in-vitro fertilisation in smoking females compared to their age-matched counterparts.(19,20) Therefore, smoking poses a double risk to pre-menopausal women, with its causality to atherosclerosis as well as its disturbance on oestrogen levels.

Men have also been found to have larger calibre coronary arteries than women in a large study, regardless of body habitus or left ventricular mass.(21) The pathological effect of smoking on STEMI is multifactorial and is attributable to thrombosis, endothelial dysfunction and inflammation. Whereas artherogenic change and a hypercoagulable state will have similar effects regardless of arterial lumen diameter, chronic inflammation may lead to a greater degree of arterial narrowing in women than men, due to the already reduced calibre vessel.(22-24) This could result in female smokers having further reduced coronary artery diameter than men, compared to non-smokers. Furthermore, it has been suggested that the aetiology of female STEMI may differ from males. Whilst atherosclerotic change is the main culprit for both genders, other mechanisms have been recognised as more prevalent in female STEMI patients: vasospasm, vasculitis, fibromuscular dysplasia, spontaneous coronary artery dissection and plaque erosion (as opposed to plaque rupture).(25) It is highly likely that cigarette smoking perpetuates some of these extra-atherosclerotic events, thus imposing a greater increase in STEMI risk for women. For example nicotine, a key component of cigarette smoke induces vasospasm, a mechanism of STEMI known to be more common in females.(22,25)

STEMI patients present later and receive less standardised treatment if they are female, resulting in greater mortality.(25) This discrepancy in outcomes is mirrored at all stages of risk prevention for CHD. In a study of 172 physicians, the “attitude study”, found that physicians perceived coronary artery disease in males as being more important than in females. Despite identical demographics, laboratory results and degree of atherosclerotic disease, preventative therapy was prescribed significantly more often in male than female patients.(26) Whilst this study did not evaluate differences in smoking cessation advice between genders, others have,

and we may speculate that smoking is considered less of a cardiac risk for females than for males, and therefore advice may differ between genders.(27,28)

The similarity in STEMI risk for ex- and never-smokers has been identified in this study. This suggests marked reversibility in STEMI risk by cessation, possibly in as little as a few weeks or months. Whilst chronic atherosclerotic change is unlikely to be affected, it is plausible that risk of acute events, including thrombosis and vasospasm quickly regress with cessation.(29,30) This interesting observation carries a strong public health message to encourage smoking abstinence. Exploring the reversibility of harm from smoking for cardiovascular risk is a potential avenue for future research.

As a cohort study, this ensured all patient groups were equally and fully represented from the South Yorkshire region, with a reduction in the risk of group under-representation. The population data gained from the ONS provided accurate denominators to create genuine STEMI rates, that could be applied both to the statistics of the study, as well as to clinical advice, within the study region.

Study Limitations

This study categorised people as current, ex-, or never-smokers. However this study did not provide information about volume of smoking or length of smoking cessation in ex-smokers.

The retrospective nature of data collection may have resulted in variable accuracy of detail within some patients' past medical history from the case notes. However, attempts were also made to complete missing data from other database sources. This has potential to create error if a certain patient group was more at risk of not having paper records still on file, but was an unfortunate necessity of the study.

This study includes only those presenting with STEMI as a candidate for PCI. It does not include those that died in the community prior to admission. Smoking may contribute to death before hospital admission, and this is therefore a potential source of bias. This study does not include other subtypes of acute coronary syndrome.

Conclusion

This study is the first to quantify the differential effect of cigarette smoking between genders on STEMI risk. It has provided strong evidence that smoking incurs a greater STEMI risk to all female patients, compared to male. The differential effect of smoking was most significant in the middle-aged, by two-fold. However, the highest increased STEMI risk attributable to smoking was in young females (18-49), at over 13 times greater than non-smokers.

This study also demonstrates that smoking cessation, regardless of age or gender, reduces STEMI risk to that of a never smoker, possibly within a month. Patients who smoke merit encouragement to give up their habit, and this study adds quantitative evidence to the benefits of doing so. The results shown here may also be used to demonstrate the negative effects of smoking to those who may otherwise seek to start, in particular young, otherwise healthy adults.

Clinical Perspectives

Competency in Patient Safety: Cigarette smoking increases the risk of acute myocardial infarction in all, but to a greater degree in young women. This information encourages continued efforts to prevent smoking uptake and promote cessation.

Translational outlook: Incidence rates demonstrate that ex-smokers have similar risk of STEMI as never-smokers. Further investigation into the reversibility of risk is warranted, and could lead to more compelling smoking cessation strategies.

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Legend

Figure 1. Incidence rate of STEMI in South Yorkshire (male and female), per 100,000 years of patient risk by smoking status.

The incidence rate of STEMI across the total population of South Yorkshire during the study period, with 95% CI, within 10-year age groups and by smoking status. Presenting cases were compared to population data regarding age, smoking status and gender to provide STEMI rates per 10-year age group. Current smokers had an incidence rate of STEMI great than ex or never smokers in all age groups, peaking at 50-59 years old. Ex and never smokers had similar incidence rates across all ages, with incidence peaking later in life than current smokers, at 70-79 years old.

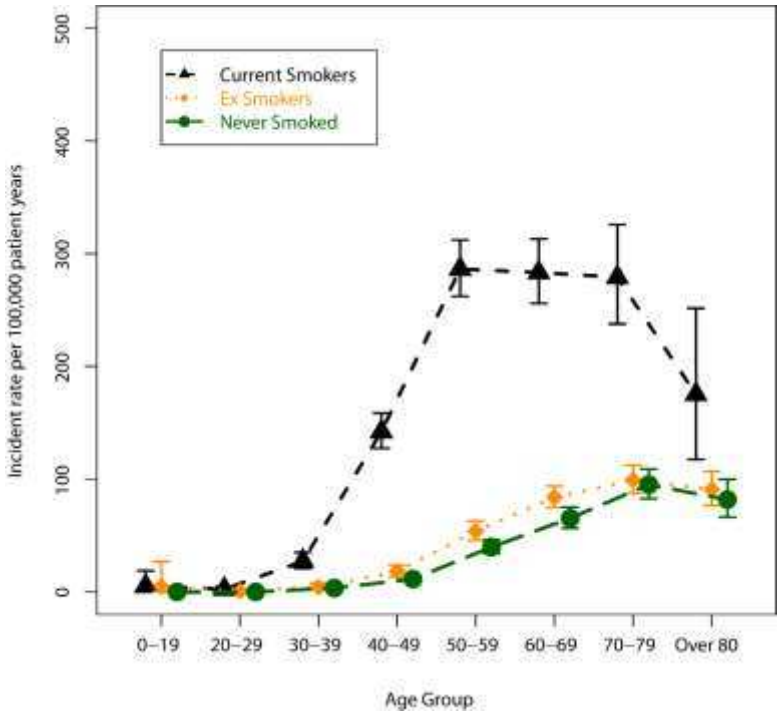


Figure 2. Incidence rate of STEMI in South Yorkshire (female), per 100,000 years of patient risk by smoking status

The incidence rate of STEMI across the female population of South Yorkshire during the study period, with 95% CI, within 10-year age groups and by smoking status. Presenting cases were compared to population data regarding age, smoking status and gender to provide STEMI rates per 10-year age group. Female current smokers had a higher incidence rate of STEMI than ex or non-smoking females in all ages, with the peak incidence rate in the 70-79 years old group. The rates of STEMI for ex and never smokers were similar throughout, and noticeably smaller than the rates for male ex and never smokers shown in Figure 3.

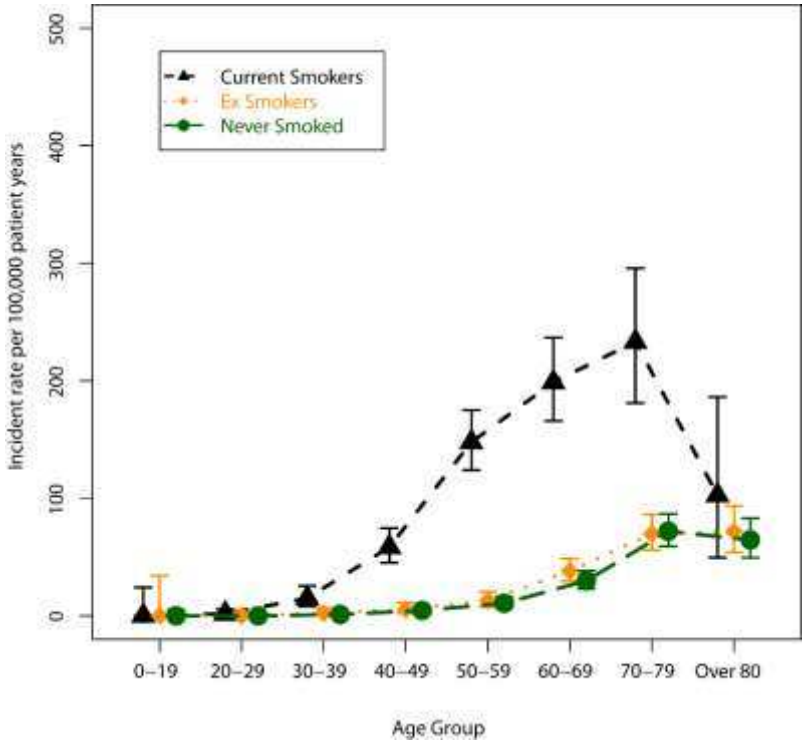


Figure 3. Incidence rate of STEMI in South Yorkshire (male), per 100,000 years of patient risk by smoking status

The incidence rate of STEMI across the male population of South Yorkshire during the study period, with 95% CI, within 10-year age groups and by smoking status. Presenting cases were compared to population data regarding age, smoking status and gender to provide STEMI rates per 10-year age group. Male current smokers had a greater incidence rate of STEMI than ex or never smokers across all ages, peaking in the 50-59 years old group. The rates of STEMI for ex and never smokers were similar throughout, and noticeably greater than the rates for female ex and never smokers shown in Figure 2.

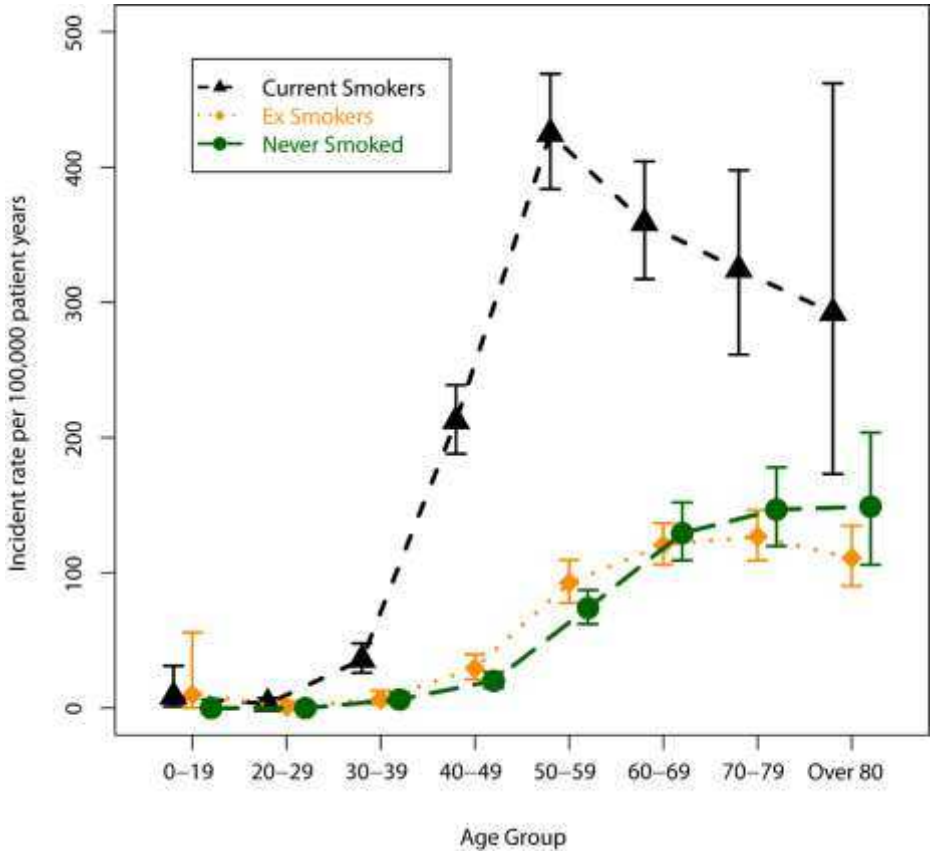


Figure 4. Age standardised incidence rate ratios and 95% confidence intervals in current smokers

The incidence rate ratios and 95% CI comparing the rate of STEMI between current and non-smokers, which have been indirectly standardised to account for age differences between the genders. As demonstrated in Figures 1-3, incidence rates for STEMI in ex and never smokers were similar, and so were combined to compare current and non-smokers in Figure 4. Compared side by side, the incidence rate ratio is significantly greater for females than it is for males at all ages. This difference is most marked in the 50-64 years old age group. The greatest incidence rate ratio is found with female smokers in the 18-49 year old age group. At all ages, smoking increases the incidence rate of STEMI in females at a greater magnitude than it does in males.

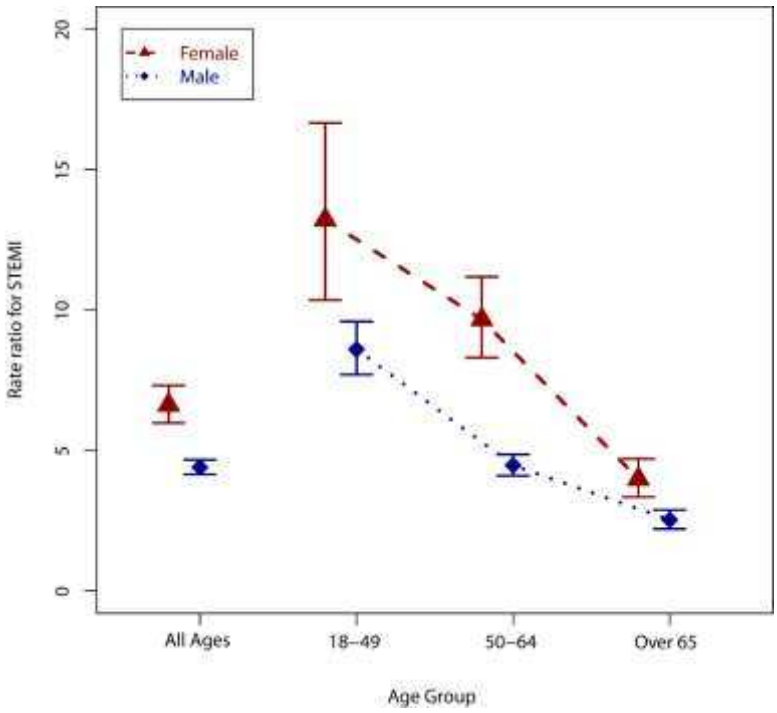


Figure 5. Relative risk of acute STEMI in female smokers compared with male smokers

The increased relative risk of STEMI that smoking incurred to female patients compared to males. By dividing female incidence rate ratios by male incidence rate ratios, the relative risk of female smokers suffering a STEMI is greater than 1.0 and therefore significant compared to male smokers.

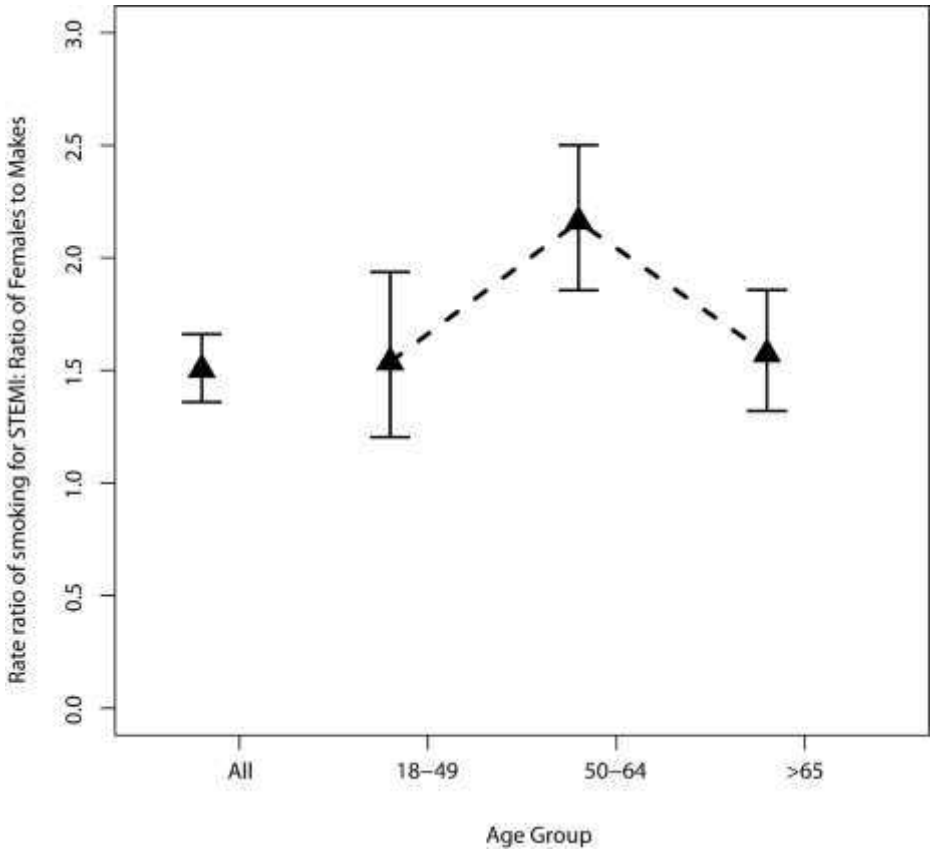


Table 1. Comparison of cardiovascular risk factors and pre-STEMI drugs between genders

The prevalence of cardiovascular risk factors and cardiac medications being taken by the presenting cases prior to STEMI, compared by gender. P-values are calculated with Chi-squared tests. Female patients were more likely to have hypertension, diabetes and cerebrovascular disease. Male patients were more likely to have suffered a previous MI. Other risk factors and use of all cardiac medications were similar between the genders.

Table 2. Comparison of the culprit artery for STEMI cases by gender, age and smoking status

The culprit artery of all STEMI cases in the study. These are separated by gender, age group and smoking status respectively, and are displayed by value and percentage of cases. P-values were calculated using Chi-squared tests. Female patients were significantly more likely to have a lesion affecting the RCA and male patients had greater chance of affecting the circumflex artery. Patients in the 18-49 year were significantly less likely to have a lesion of the RCA. Current smokers were significantly more likely to have a lesion affecting the RCA. Never smokers were significantly less likely to have the circumflex as their culprit artery, but were much more likely to have a lesion of the LAD artery. Very few cases were attributed to the LMS.

Table 1: Comparison of cardiovascular risk factors and pre-STEMI drugs between genders				
Risk factor	**All Patients (%)**	**Male patients (%)**	**Female patients (%)**	**P-value**
Hypertension	38.9	36.3	45.6	<0.001
Family history of IHD	39.4	39.9	38.0	0.321
Diabetes	14.5	13.7	16.6	0.041
Dyslipidaemia	34.9	35.4	33.6	0.349
South Asian origin	2.5	2.7	1.8	0.131
Previous MI	19.5	20.5	17.0	0.024
Chronic kidney disease	1.2	1.1	1.5	0.377
Congestive heart failure	0.2	0.3	0.1	0.691
Cerebrovascular disease	5.4	4.8	6.8	0.025
Peripheral vascular disease	4.2	4.1	4.5	0.562
Aspirin	15.7	16.1	15.0	0.446
P2Y12 inhibitor	3.6	3.8	2.9	0.178
Statin	21.4	22.5	19.3	0.050
ACEi / ARB	16.6	16.4	17.6	0.425
Beta blocker	11.8	11.9	11.9	0.956

Footnote:

p-values are derived from chi-squared tests.

MI = Myocardial infarction

IHD = Ischaemic heart disease

ACEi = Angiotensin converting enzyme inhibitor

ARB = Angiotensin receptor blocker

The prevalence of cardiovascular risk factors and cardiac medications being taken by the presenting cases prior to STEMI, compared by gender. P-values are calculated with Chi-squared tests. Female patients were more likely to have hypertension, diabetes and cerebrovascular disease. Male patients were more likely to have suffered a previous MI. Other risk factors and use of all cardiac medications were similar between the genders.

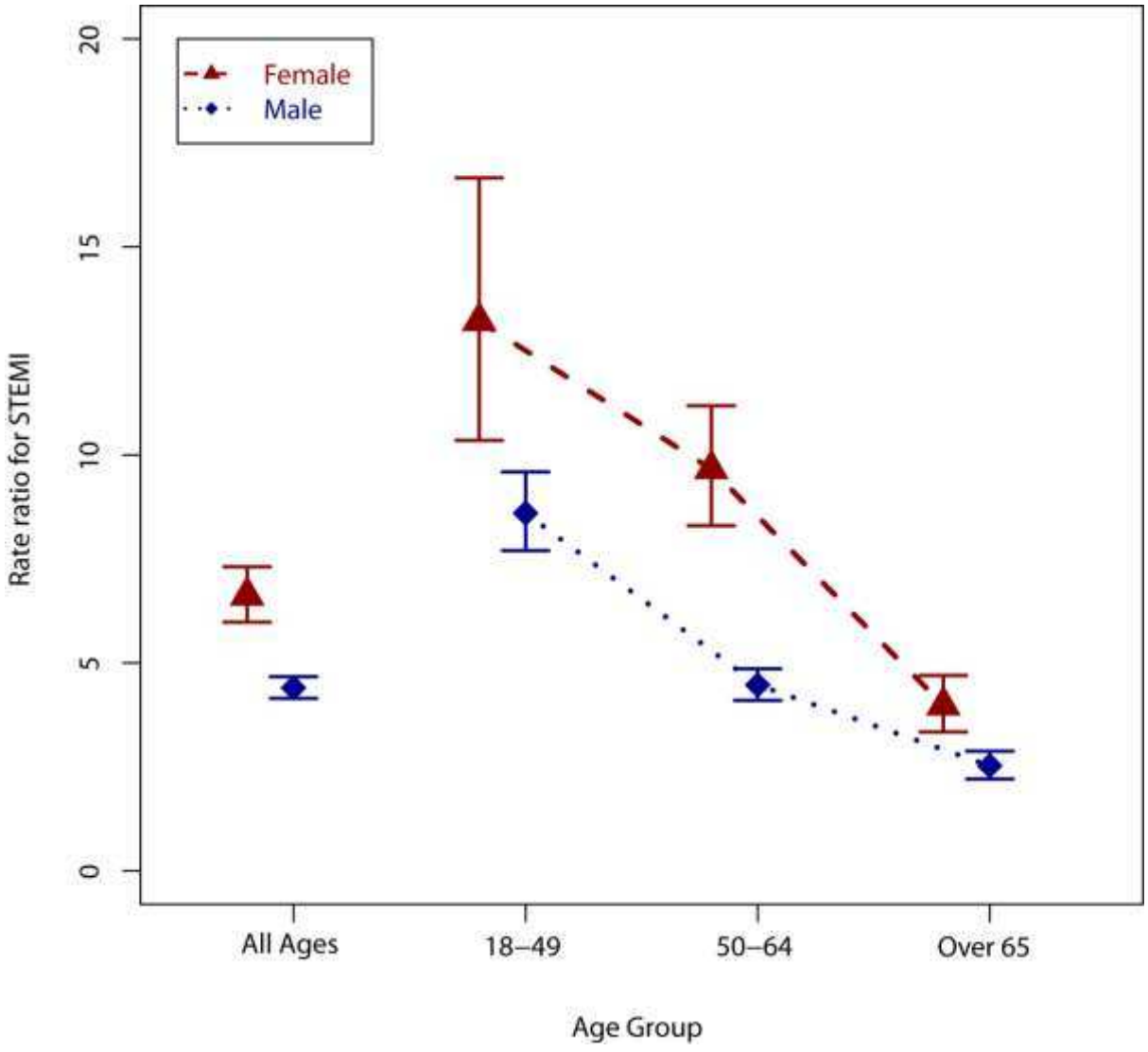
Table 2: Comparison of the culprit artery for STEMI cases by gender, age and smoking status					
Variables		**Culprit Artery**			
		Left Main Stem (%)	**Left Anterior Descending (%)**	**Circumflex (%)**	**Right Coronary (%)**
Gender	**Female**	1.3	39.9	10.6	50.5
	Male	1.8	42.3	14.4	45.1
	P-value	0.377	0.238	0.005	0.007
Age group	**18-49**	0.9	45.5	12.0	41.4
	50-64	1.7	40.9	14.7	47.2
	Over 64	1.9	40.8	12.7	47.9
	P-value	0.318	0.144	0.187	0.031
Smoking Status	**Current smoker**	1.5	37.4	14.1	49.7
	Ex smoker	2.2	41.3	15.1	44.8
	Never smoker	1.4	50.7	9.8	42.1
	P-value	0.329	0.000	0.004	0.002

The culprit artery of all STEMI cases in the study. These are separated by gender, age group and smoking status respectively, and are displayed by value and percentage of cases. P-values were calculated using chi-squared tests. Female patients were significantly more likely to have a lesion affecting the right coronary artery and male patients had greater chance of affecting the circumflex artery. Patients in the 18-49 year were significantly less likely to have a lesion of the right coronary artery. Current smokers were significantly more likely to have a lesion

affecting the right coronary artery. Never smokers were significantly less likely to have the circumflex as their culprit artery, but were much more likely to have a lesion of the left anterior descending artery. Very few cases were attributed to the left main stem.

Central Illustration

The objective of this study was to determine differences in the risk of STEMI that smoking confers on men and women. A comparison of smokers with non-smokers by gender using age-standardised incidence rate ratios (IRR) and their confidence intervals, showed that. smoking increased the risk of STEMI by a greater degree in females than in males, across all ages. Moreover, the greatest incidence rate ratio was in female smokers under 50 years of age, with a relative risk of STEMI 13.22 (CI: 10.35-16.66) times greater than that of their non-smoking female counterparts. The largest gender difference was in the 50-64 year old age group. This provides strong evidence to help encourage cessation in young smokers, particularly females.



Age standardised incidence rate ratios and 95% confidence intervals in current smokers.

Box presentation

- Smoking increases risk of STEMI in females more than it does in males.
- The greatest increased risk of STEMI is in the female smokers under the age of 50.
- Rates of STEMI in ex-smokers are similar to those of never smokers.
- Smoking cessation must be encouraged in all, but particularly in the young and in women. Although their cardiovascular event risk is often perceived as low, these groups have the highest increased STEMI risk.