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Lloyd, A., Steele, L., Fotheringham, J. et al. (4 more authors) (2016) Pronounced increase in risk of acute ST-segment elevation myocardial infarction in younger smokers. *Heart*. ISSN 1355-6037

<https://doi.org/10.1136/heartjnl-2016-309595>

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MARKED INCREASE IN RISK OF ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION IN YOUNGER SMOKERS.

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Word Count: 3087

Abstract Word Count: 255

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Abstract

Objectives: Previous studies have shown that smokers presented with ST-segment elevation myocardial infarction (STEMI) a decade earlier than non-smokers. However no account has been made for population smoking trends; an important deficit addressed by this study.

Methods: The combination of admission data on patients with acute STEMI undergoing PCI and demographic data supplied by the Office for National Statistics for the South Yorkshire population between 2009-2012 were analysed to generate incidence rates and rate ratios (RR) to quantify the relative risk of STEMI from smoking, overall and by age group.

Results: There were 1,795 STEMI patients included of which 72.9% were male. 68 patients were excluded as they had no smoking status recorded leaving 48.5% of the remaining population as current smokers, 27.2% ex-smokers and 24.3% never smokers. Smokers were over-represented with overall smoking prevalence in South Yorkshire calculated at 22.4%. The incidence of STEMI in smokers aged under 50, 50-65 and over 65 years was 59.7, 316.9 and 331.0 per 100,000 patient years at risk compared to 7.0, 60.9 and 106.8 for the combined group of ex- and never smokers. This gave smokers under the age of 50 an 8.47 (95% CI: 6.804-10.542) increase in rate compared to non-smokers of the same age, with 50-65 and greater than 65s having RR of 5.20 (95% CI: 4.761-5.689) and 3.10 (95% CI: 2.669-3.599) respectively.

Conclusions: Smoking was associated with an eight fold increased risk of acute STEMI in younger smokers, when compared to ex- and never smokers. Further efforts to reduce smoking in the youngest are needed.

Keywords: Smoking, acute ST-segment elevation myocardial infarction, risk factor, prevention.

What is already known about this subject?

Smoking is a recognised and important cardiovascular risk factor that as of yet has not been quantified using incidence rate ratio analysis in different age groups.

What does this study add?

This study specifically looks at incidence rate ratios of acute STEMI and shows that smoking is associated with an increased incidence in acute STEMI for all ages, but this is greatest in the youngest smokers compared to their age-matched non-smoking counterparts.

How might this impact on clinical practice?

The cause of the differing risks from cigarette smoking on younger and older smokers remains unclear. All current smokers must be encouraged into smoking cessation therapy to reduce their risk of acute STEMI, with a focus on the youngest smokers whose increased risk is often unrecognised.

INTRODUCTION

Cigarette smoking was first identified as a risk factor for cardiovascular disease with the Framingham Heart Study of the 1950s (1, 2). This landmark project was one of the first, alongside Doll and Hill (3, 4) to publicise the ill-effects of smoking. Large epidemiological studies have since demonstrated the link between tobacco smoking and acute myocardial infarction (AMI) and have established that smokers present at an earlier age than non-smokers. In particular the National Registry of Myocardial Infarction 2 (NRM12) found that smokers presenting with AMI were on average 14 years younger than non-smokers (5) and the Multinational Monitoring of trends and determinants in cardiovascular disease (MONICA) trials showed that prevalence of smokers was up to 81% in young patients aged 35-39 with AMI (6).

However, there remains uncertainty as to the magnitude of the effect of tobacco smoking on the younger smoker. No study has compared the incidence of STEMI within young smokers and young non-smokers by using local population data as a denominator. This is likely due to a lack of comparative analysis of local population data with the population suffering a STEMI. This study was carried out to provide a clear incidence analysis and to quantify the risk of acute STEMI in the South Yorkshire region of the United Kingdom.

METHODS

Participants

To calculate incidence analysis of STEMI in South Yorkshire, this study analysed two populations. The first was the case data of all South Yorkshire patients over the age of 18

who underwent percutaneous coronary intervention (PCI) for acute STEMI at the South Yorkshire Cardiothoracic Centre, Sheffield, United Kingdom. A continuous population between 1/1/2009 and 6/4/2012 of patients aged 18 and over were studied. The second data set was derived from responses from South Yorkshire residents aged 18 and over participating in the Office for National Statistics Integrated Household Survey (ONS-IHS) between April 2009 and March 2012 (7).

Procedures

Each patient included in the STEMI cohort had full demographic, risk-factor and procedural information collected from the individual hospital case records and the hospital database. Smoking status was recorded as “current smoker”, “ex-smoker” or “never smoker”. An ex-smoker did not have a minimum duration of cessation needed to fit into this category, although when data was available, duration of cessation was recorded. This was due to difficulties in obtaining the smoking cessation duration, as this was not routinely recorded in admission documentation. In a small number of cases there was insufficient record keeping of the smoking status, and these were excluded from the rate ratio incidence analysis.

Previous medical history of ischaemic heart disease, hypertension, diabetes, dyslipidaemia, transient ischaemic attack/stroke, peripheral vascular disease, and family history of ischaemic heart disease (IHD) were recorded.

The ONS-IHS uses a multi-stage population weighting procedure which accounts for probability of selection and adjusts for non-response, enabling responses from South Yorkshire ONS-IHS to be weighted to represent the entire South Yorkshire population (7). As this weighting is specific to the period the ONS-IHS data is collected it also accounts for

people entering or leaving the population. Therefore, this data was presented as patient year at risk to most accurately reflect the open and changing population.

Statistical methods

Univariate categorical analysis of risk factors across smoking status within the STEMI cohort was performed using the Chi-Squared test, with multivariate adjustment for age using logistic regression.

The incidence rate of STEMI in South Yorkshire was calculated using the STEMI and ONS-IHS populations using the following equation. “Person-time at risk” is measured in patient-years, and represents the true time that each patient spent in this at risk population. For example, a person who moved into the geographical area served by the South Yorkshire Cardiothoracic service part way through the study would have fewer person-time at risk, compared to a person who always lived in the catchment area.

$$\text{Incidence Rate} = \frac{\text{Number of acute STEMI cases with disease in time period}}{\text{Total person – time at risk during that time period}}$$

Rate ratios were used to compare incidence rates of STEMI between different groups (e.g. smokers and non-smokers).

$$\text{Rate ratio} = \frac{\text{Incidence rate in smokers}}{\text{Incidence rate for ex – smokers and never smokers}}$$

Analyses were performed with Stata 12.1 (STATA Corp, Texas) and SPSS software 23 (IBM).

RESULTS

A total of 1,795 patients were included in the STEMI data. In 68 (3.8%) patients, the smoking status was unobtainable and was excluded from incidence analysis. The mean age of patient was 63.0 years (95% CI 62.38-63.56) and 72.9% of the population was male.

Just under half of the population with known smoking status were current smokers (48.5%). At presentation, the mean age of the current smokers was 57.4 years (95% CI 56.63-58.13) which was around 10-11 years less than ex- and never smokers (ex-smokers: 68.5 years, 95% CI=67.48-69.61 and never smokers: 66.7 years, 95% CI=65.50-67.84.)

ONS-IHS data allowed calculation of smoking prevalence rates for the South Yorkshire area, as shown by age group in figure 1. With this population, the highest prevalence of current smoking was found in those under the age of 50 (27.3%). However, this was much higher in those under the age of 50 who had suffered an acute STEMI (74.8%).

Risk factor profiles of current, ex- and never smokers

Logistic regression analysis allowed further study of the likelihood of risk factors being present in those who were current or ex-smokers compared to those patients who have never been exposed to cigarette smoking (table 1). Current smokers presenting with STEMI requiring PCI were less likely to have hypertension or diabetes, but more likely to have a family history of IHD ($p < 0.05$ for all three). However, after adjusting for age, the differences in the odds of these risk factors were not statistically significant. Ex-smokers and current smokers were more likely than never smokers to have a previous history of IHD, including after adjustment for age OR=2.37, 95% CI 1.69-3.31, $p < 0.001$ and OR=1.45, 95% CI= 1.03-2.05, $p < 0.05$ respectively). Lastly, current smokers were three times more likely than never smokers to suffer with peripheral vascular disease (OR=3.44, 95% CI 1.56-7.59, $p < 0.005$).

Table 1 - Unadjusted and age-adjusted odds ratios for risk factors across smoking groups

| Risk Factor | Age unadjusted risk factor prevalence | | | | Age-adjusted risk factor prevalence (odds ratio) | | |
|-----------------------------|---------------------------------------|----------------|----------------|--------|--|---------------------------------|--------------|
| | Current Smoker | Ex Smoker | Never Smoker | P | Current Smoker | Ex Smoker | Never Smoker |
| | n=838 | n=470 | n=419 | | | | |
| Hypertension | 285 (34.0%) | 209 (44.5%) | 178 (42.5%) | <0.001 | 0.88 (0.69-1.14) p=0.337 | 1.03 (0.79-1.36) p=0.803 | 1 |
| Previous history of IHD | 139 (16.6%) | 138 (29.4%) | 61 (14.6%) | <0.001 | 1.45 (1.03-2.05) p=0.035 | 2.37 (1.69-3.32) p<0.001 | 1 |
| Diabetes | 87 (10.4%) | 74 (15.7%) | 60 (14.3%) | 0.012 | 0.72 (0.50-1.04) p=0.080 | 1.11 (0.77-1.61) p= 0.580 | 1 |
| Dyslipidemia | 316 (37.7%) | 209 (44.5%) | 163 (38.9%) | 0.051 | 0.90 (0.70-1.16) p=0.431 | 1.27 (0.97-1.66) p=0.080 | 1 |
| Family History of IHD | 382 (45.6%) | 184 (39.1%) | 166 (39.6%) | 0.033 | 0.87 (0.68-1.13) p=0.306 | 1.06 (0.81-1.40) p=0.664 | 1 |
| Previous TIA/Stroke | 45 (5.4%) | 35 (7.4%) | 22 (5.9%) | 0.251 | 1.59 (0.91-2.77) p=0.106 | 1.36 (0.78-2.36) p=0.283 | 1 |
| Peripheral Vascular Disease | 34 (4.1%) | 18 (3.8%) | 9 (2.1%) | 0.206 | 3.44 (1.56-7.59) p=0.002 | 1.67 (0.74-3.78) p=0.218 | 1 |

Incidence of acute STEMI in South Yorkshire

Ex-smokers and never smokers had similar incidence rates of acute STEMI, whereas this was much higher in the current smokers (Figure 2). This peaked in the 60-69 year old age group with an incidence rate of over 350 cases per 100,000 patient years at risk. By comparison, the peak age for incidence of STEMI in ex- and never smokers was 10 years later, in the 70-79 year age group, with over 100 cases per 100,000 patient years at risk.

Incidence rate ratio analysis

Rate ratio analysis to compare incidence rates between current smokers, and their age-matched ex- and never smoking counter-parts was performed (Figure 3). Although not statistically significant for risk factors other than a previous history of IHD, ex-smokers tended towards higher odds for each risk factor than never smokers. Combining these two groups therefore provides a more conservative estimate of the comparison with current smokers than comparing to never smokers alone. This analysis showed that for all ages, current smokers were 3.26 (95% CI 2.98-3.57) more likely to suffer acute STEMI than ex- and never smokers grouped together. Stratification by age group showed the highest rate ratio in the youngest age group analysed. Current smokers, under 50 years were 8.47 (95% CI 6.80-10.54) times more likely to suffer an acute STEMI compared to their age-matched ex- and never smokers. The incidence rate ratio subsequently decreased in the older age groups. Those aged 50-65 years had a RR of 5.20 (95% CI 4.76-5.69) and those aged over 65 years the RR=3.10 (95% CI=2.67-3.60).

DISCUSSION

The main finding of this study is that for all age groups, current smokers were over three times more likely to have an acute STEMI than the comparison group, comprising of ex- and

never smokers. Although previous studies have demonstrated a significant increase in risk of AMI in smokers, our analysis is the first to quantify this risk using incidence rate ratio analysis (8-12) The detrimental effect of smoking was most marked in the younger age group; smokers under 50 years of age had more than 8 times the risk of an acute STEMI, compared to their age-matched ex- and never smokers.

In this incidence analysis of STEMI patients the population was predominantly male and smoking prevalence was higher in the younger age groups. There was a mean age difference of 10-11 years between current and non-smokers. These results mirrored other large AMI studies (10, 13-14). However, one other AMI reported an even larger 14 year age difference (5).

Ex- smokers and never smokers share similar incidence rates of STEMI

Incidence rate analysis clearly shows that smokers who quit or those who have never smoked have a significantly lower incidence rate of acute STEMI. Of note is the similarity of incidence of acute STEMI between ex- smokers and never smokers. Both ex- smokers and never smokers presented at similar ages with acute STEMI, and the mean age difference was not statistically significant (ex-smoker mean age 68.54; 95% CI= 67.48-69.61, never smoker mean age 66.67; 95% CI=65.50-67.84). This data indicates that giving up smoking reduces the incidence of acute STEMI to that of someone who has never smoked, in all age groups. One paper has suggested that ex-smokers can approach the same risk of a first or second MI as never-smokers, but this benefit may be seen after 15 years of smoking cessation (9). However, another paper found an elevated risk of a major IHD event remained even at 20 years of smoking cessation (10). Undoubtedly however, smoking cessation is associated with marked reduction of coronary heart disease mortality (11).

Analysis of the risk factor profile of ex-smokers and never smokers may partly explain this similar incidence rate in the two groups. Other than a previous history of IHD, which was higher in ex-smokers, the risk factor profile between the two groups was largely similar. This may explain why similar levels of acute STEMI occurred. However, ex-smokers, who were much more likely to have a diagnosis of previous IHD, may have received secondary preventative therapy. It may also be a reflection of the benefits of smoking cessation regardless of duration of the cessation period, although this was not measured in this study.

Those who are youngest experienced the greatest risk from smoking

Using the incidence rates of acute STEMI in different groups, incidence rate ratio analysis allowed comparison of risk associated with smoking across various age groups. A recent study explored the odds ratio (OR) of being a smoker in those who presented with STEMI across different age groups (12). Those in the youngest age group were the most likely to be smokers (11.4; 95% CI 10.0-12.8), compared to those aged over 65 whose OR peaked at only 3.4 (95% CI 3.3-3.4). Our study examined this trend from a different angle, using current, ex- and never smokers as the starting points, and using incidence analysis to calculate their risk of STEMI across different age groups conferred by their smoking.

From this analysis, we found that those who were under the age of 50 years had the highest likelihood of acute STEMI attributable to their smoking, compared to their age matched ex- and never smokers. Indeed, this group was over eight times more likely to suffer an acute STEMI. The older age groups did not appear to confer such a high risk from their smoking when compared to age-matched ex- and never smokers. Those aged 50-65 years were over five times more likely to suffer an acute STEMI and those aged over 65 years were over three times as likely. The MONICA trials found similar results: those who were young and smoked were more at risk and that the relative risk associated with smoking decreased with the ageing

groups, a trend mirrored in our data (6). The INTERHEART study also looked at the risk profiles across age groups and reported that younger smokers compared with age matched never smokers experienced a larger effect from current smoking (OR=3.53, 95% CI 3.23–3.86) with respect to increased risk to AMI than in older individuals. However, these studies predated the newer AMI classification and did not identify acute STEMI patients in particular.

From our data alone, it is difficult to explain the much higher risk of acute STEMI imparted by smoking on the youngest patients and raises important questions as to why this should occur. It is recognised that the youngest populations tend to demonstrate fewer risk factors such as hypertension, hyperlipidaemia or diabetes and this has been demonstrated in young STEMI patients who smoke (15). Therefore, smoking appears to be much more potent risk of STEMI in the young, as it is one of very few risk factors present in this group. The GRACE registry reported that smokers presented with ACS with a much more favourable risk profile, and as smokers were on average around 10 years younger than non-smokers, this may support the above theory (8). Whilst other studies concur that smoking prevalence is higher in younger age groups with myocardial infarction, other risk factors have also been identified as more prevalent in younger age groups, such as family history of CAD and hyperlipidaemia (5, 16-18).

The high rate ratio seen in the youngest smokers may indicate that smoking is perhaps the most powerful of all risk factors, exerting its effect much sooner than any other. This is supported by other studies which identified smoking as not only the most prevalent, but also one of the most important risk factor in the young (16).

Recent evidence suggests that the histological composition of plaque differs between smokers and non-smokers (19). Cigarette smokers appear to be more vulnerable to arterial plaque rupture due to the higher burden of a necrotic core (20.7% vs 17.2% in non-smokers; $p=0.04$).

This suggests that smoking may induce plaque instability. In addition, a recent study has demonstrated an unexpected finding that post-STEMI smokers have not demonstrated a significant reduction in the risk of all-cause mortality (15), despite receiving evidence based therapies. This strengthens the argument for a focus on prevention of smoking in the youngest age groups.

Older age groups experience less risk from smoking

Whilst an increased risk of acute STEMI persisted in older current smokers (RR=3.10), it was much lower than what is seen in the younger age groups (RR=8.47). The epidemiological landscape of risk factors in the older patients is more complex, and cardiac risk factors are more prevalent. Therefore, it may be expected that the incidence of STEMI across the whole population would increase similarly for the ex-, never and current smokers, thus diluting the detrimental effect smoking seen in the youngest age group. This can be demonstrated by the steadily increasing incidence rate of acute STEMI of ex- and never smokers with age (figure 2) and the subsequent lower rate ratio in the oldest age groups.

Interestingly, incidence of STEMI in current smokers decreases markedly between the ages of 70-79, which contributed to the smaller rate ratio seen in the older current smokers. There may be a few reasons for this decrease. Firstly, there may be some element of survival bias. Those who were current smokers may have died, decreasing the incidence of acute STEMI in this group, resulting in a distorted representation of this outcome. Secondly, it may be that plaque composition changes, which occur over time, may have a direct bearing on incidence of acute STEMI, as the plaques become more calcified and less vulnerable in older patients.

Study strengths

The study accurately determined the incidence of STEMI in South Yorkshire using data on smoking prevalence within this region. By comparing the smoking habits of patients with an acute STEMI to that of the general population of the area we have not only reported an increased smoking prevalence in the young, but also quantified the risk this habit imparts upon them. This can guide health policy on targeting the most important groups to promote preventative measures. This study may also help to tackle the misconception by young smokers that acute STEMI is a disease of the elderly, by showing that this group is very vulnerable and has the highest risk from their smoking.

Study limitations

This study is based on retrospective analysis of prospectively collected data. Whilst the inclusion criteria for this study are broad, only those suffering an acute STEMI who underwent PCI at the South Yorkshire Cardiothoracic Centre were studied. Patients who died before admission or who were deemed unsuitable for PCI, were not included in the analysis. Although we do not have exact data, we would highlight that the well-established and monitored primary PCI service in South Yorkshire successfully identifies and refers nearly all patients with acute STEMI to the South Yorkshire Cardiothoracic Centre. It is rare for a patient to be excluded from such proven treatment and the alternative (and less effective) thrombolytic therapy has now been largely forgotten. It is also rare for a patient, who may be experiencing severe chest pain and feeling very unwell, to refuse to give their consent to undergo primary PCI. We estimate that fewer than 1% of patients would be excluded for these reasons.

CONCLUSIONS

This is the first study to use population data combined with case data to conclusively show that rate ratios are much higher in younger smokers compared with older smokers in acute STEMI. The difference between the ages is striking: young smokers are over 8 times more likely to suffer acute STEMI compared with age matched counterparts, whereas those aged 50-65 are just 5 times as likely and those aged 65 and over only 3 times more likely.

ACKNOWLEDGEMENTS

The team would like to acknowledge The Office for National Statistics for providing Integrated Household Survey and census data for the incidence analysis.

LIST OF ABBREVIATIONS

| | |
|---------|--|
| AMI | Acute myocardial infarction |
| IHD | Ischaemic heart disease |
| MI | Myocardial infarction |
| ONS-IHS | Office for national statistics integrated household survey |
| PCI | Percutaneous coronary intervention |
| STEMI | ST-segment elevation myocardial infarction |

FIGURE LEGENDS

Figure 1 Smoking prevalence (%) within the STEMI cohort and in South Yorkshire derived from ONS Integrated Household Survey (IHS) responses. Weighted patient years for the IHS are presented, with unweighted responses reported in brackets.

Figure 2 Incidence of acute STEMI by smoking status in South Yorkshire, calculated using patient time from the Office of National Statistics Integrated Household Survey and a cohort of patients presenting with STEMI. Current smokers had a peak incidence of acute STEMI at age 60-69, whereas for ex- and never smokers, the peak incidence was 10 years later at 70-79 years.

Figure 3 Rate ratios of smokers compared to ex/never smokers for the incidence of acute STEMI by age group, calculated using patient time from the Office of National Statistics Integrated Household Survey and a cohort of patients presenting with STEMI. Those in the youngest age group <50 years had the highest likelihood of an acute STEMI conferred by smoking (RR=8.47). The risk conferred by smoking on acute STEMI was lowest in the oldest age groups.

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