

Admission for and mortality from primary venous thromboembolism in women of fertile age in Denmark, 1977-95

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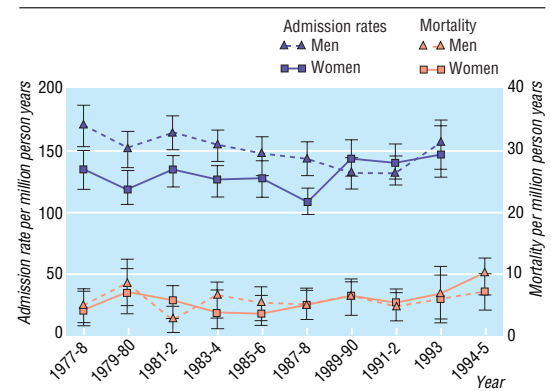
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Epidemiological studies indicate that use of third generation oral contraceptives increases the risk of venous thromboembolism more than does use of second generation oral contraceptives.¹⁻³ Critics have suggested that this finding may be confounded by indication, since third generation pills were considered to be safer and were therefore perhaps prescribed more often to women at high risk. If confounding by indication is the only explanation for the observed association, the incidence of venous thromboembolism in the population should not have changed when prescribing patterns changed from second generation to third generation pills with no increase in overall use of oral contraceptives. Vandembroucke et al and Thomas reported increasing mortality from venous thromboembolism among young women in the Netherlands and in England and Wales from the mid-1980s to the 1990s, when the use of third generation pills was increasing.^{4,5} Since mortality from venous thromboembolism depends on both aetiological and prognostic factors, however, it may be more appropriate to look at incidence.

In Denmark, roughly a quarter of women aged 15-44 used oral contraceptives during the 1980s and the beginning of the 1990s. The first third generation oral contraceptive, containing desogestrel, was released in 1984, and the third generation preparations containing gestodene and norgestimate were introduced in 1988 and 1990, respectively. Use of third generation pills represented 0.2% of the total use of oral contraceptives in 1984, 17% in 1988, 40% in 1990, and 66% in 1993.

Subjects, methods, and results

We used admission rates for venous thromboembolism in Denmark as a proxy measure of the incidence of this condition. For people aged 15-49 all admissions during 1977-93 with a registration of pulmonary embolism (ICD-8 (international classification of diseases, 8th revision) code 450.9), deep venous thrombosis (ICD-8 code 451), and other embolic or thrombotic disorders (ICD-8 code 453) were obtained from the Danish National Registry of Patients. Patients were excluded if they had cancer before the venous thromboembolism, surgery within the six months before the venous thromboembolism, or a pregnancy or obstetric diagnosis in the nine months before or three months after the venous thromboembolism or if venous thromboembolism was recorded as a supplemental diagnosis. Multiple admissions for venous embolism for a given person were counted in the numerator of the admission rates provided that the admissions were separated by at least three months. Death rates were calculated from the death certificate file, with no exclusions; during 1994-5 these rates were based on ICD-10 (codes I26, I80, I82). All rates were standardised to the world standard population.



Admission rates and mortality from venous thromboembolism per million person years for men and women aged 15-49, by calendar year. Rates standardised to world standard population; bars show 95% confidence intervals

Admission rates for primary venous thromboembolism among women fluctuated around 120 per million person years during 1977-88 but increased to about 140 per million person years during 1989-93 (figure). For men the admission rates remained stable throughout the period, at a rate similar to that for women in recent years. The mortality curves for men and women followed largely the same course throughout the period. For women the admission rates were based on a total of 2883 discharges with venous thromboembolism during 1977-93, while the death rates were based on only 120 deaths from venous thromboembolism in the same years.

Comment

The increase in admission rates for venous thromboembolism among women seems to correlate with the increase in use of third generation oral contraceptives. The increase is not likely to be explained by changes in diagnostic procedures or in the threshold for admission since no increase was seen for men.

These data support the hypothesis that third generation oral contraceptives increase the risk of venous thromboembolism to a greater extent than other oral contraceptives, and the result cannot be explained by confounding by indication. Our result must, however, be interpreted with caution: the numbers are small, and it is based on data that are subject to misclassification.

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design and data analysis, and edited the paper. JO discussed core ideas and participated in the writing of the paper. JHO discussed core ideas, participated in the protocol design, edited the paper, and is guarantor for the study.

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Association between alcohol consumption and mortality, myocardial infarction, and stroke in 25 year follow up of 49 618 young Swedish men

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Several epidemiological studies have shown that moderate alcohol consumption is associated with reduced mortality from cardiovascular diseases in middle aged and elderly subjects,¹ but its effect in younger people is unknown. High alcohol consumption is associated with increased total mortality, but the findings for stroke have varied.^{1,2} We analysed the association between alcohol consumption and the incidence of myocardial infarction, stroke, and mortality in a 25 year follow up of military conscripts.

Subjects, methods, and results

This study is based on 49 618 Swedish men conscripted between 1 July 1969 and 30 June 1970 and born between 1949 and 1952.² At conscription, all men were given two questionnaires with questions covering social background, behaviour, and use of alcohol and tobacco, and all met with a psychologist for assessment. The percentage of non-responders was between 1% and 2%.

From questions about quantity and frequency of consumption of different alcoholic beverages, we calculated usual consumption in terms of grams of 100% ethanol a day and categorised subjects into different consumption groups.¹ Social, psychosocial, and behavioural variables were included as confounders, based on earlier studies and on bivariate analyses of the data in this study (see table).² Using the Swedish personal identification number, we linked the questionnaire data to the Swedish register of causes of deaths and to the new national inpatient care register for 1970-95. We estimated unadjusted and adjusted relative risks in logistic regression analyses and calculated attributable proportions.³ Outcomes were total mortality (n = 1473) and incidences of myocardial infarction (n = 279, 38 fatal) and stroke (n = 233, 30 fatal) as underlying causes of death or as main diagnoses at hospitalisation.

Compared with abstainers, alcohol consumers had higher unadjusted relative risks for all three outcomes,

and the risks increased with increasing alcohol consumption, being significantly higher for consumers of ≥ 15 g ethanol/day. Adjusted analyses showed an increasing risk of death (significant) and stroke (non-significant) with increasing alcohol consumption but a decreasing risk of myocardial infarction (non-significant) (table). To a considerable extent, the increased mortality with high alcohol consumption was due to the strong association between drinking and smoking and the high risk associated with smoking; compared with not smoking, the relative risk of death was 3.02 for smoking 1-10 cigarettes a day and 5.20 for smoking ≥ 11 cigarettes a day. Consuming ≥ 15 g ethanol/day was associated with a relative risk of death of 1.37 (95% confidence interval 1.01 to 1.85). The attributable proportion in multivariate analysis for alcohol consumption, relative to abstinence, was 14% for mortality (alcohol use caused 205 deaths) and 37% for stroke (causing 86 cases), while alcohol prevented 44 (16%) myocardial infarctions.

Comment

The validity of self reported alcohol consumption at conscription and as a measure of consumption during the follow up period can be questioned.³ Both non-differential underreporting at conscription and

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website
extra

A more detailed
Methods section
appears on the
BMJ's website

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Relative risks (95% confidence intervals)* of death, myocardial infarction, and stroke in relation to alcohol consumption in a 25 year follow up of 49 618 military conscripts

Alcohol consumption (g 100% ethanol/day)	Death (n=1473)	Myocardial infarction (n=279)	Stroke (n=223)
0	1	1	1
0.1-14.9	1.13 (0.85 to 1.50)	0.90 (0.45 to 1.80)	1.59 (0.64 to 3.92)
15-30	1.32 (0.98 to 1.79)	0.77 (0.37 to 1.63)	1.52 (0.57 to 4.00)
≥ 30	1.53 (1.08 to 2.16)	0.61 (0.26 to 1.44)	2.30 (0.81 to 6.43)
≥ 15	1.37 (1.01 to 1.85)	0.73 (0.35 to 1.52)	1.70 (0.66 to 4.40)

*Calculated from logistic regression analysis with adjustments for blood pressure at conscription (continuous), body mass index (weight (kg)/(height (m))²), father's social class, running away from home, poor school wellbeing, parental divorce, poor emotional control, few (0-1) friends, unemployment for >3 months during life, poor health, and smoking as reported at conscription.