RESEARCH

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Declining mortality from coronary heart disease in Europe

You wait ages for a paper bringing good news, and then three come along at once. Kate Smolina and colleagues report that, in England, total mortality from myocardial infarction was halved for both men and women between 2002 and 2010 (p 16). Their analysis of linked routine data attributed just over half of the decline in mortality to the falling incidence of acute myocardial infarction and just under half to a decline in case fatality.

SIMON FRASER/CCU FREEMAN HOSPITAL/SPL

Piotr Bandosz and colleagues found that over half of the fall in mortality from coronary heart disease in Poland between 1991 and 2005 was explained by reductions in major risk factors and about a third to evidence based medical treatments (p 18). Such analyses from Poland and other central European countries are particularly interesting, because runaway rates of premature coronary mortality in the 1980s sharply reversed in the early 1990s after the Iron Curtain fell.

Morten Schmidt and colleagues went further back and dug a bit deeper (p 17). They looked at a quarter of a century's data on Danes' myocardial infarctions, between 1984 and 2008. The pattern was the same as in Smolina and colleagues' English study: mortality nearly halved and was explained by more or less equal falls in incidence and short term mortality. By 2008 Danish men and women had the same age standardised risk of dying in the year after their myocardial infarction, with differences in mortality risk attributed mainly to comorbidity.

In a linked editorial entitled "The decline in coronary heart disease; did it fall or was it pushed?" Hugh Tunstall-Pedoe notes the role of governments in preventing coronary heart disease (p 9): "One indicator is the ability of the health department to counteract vested interests, such as those of the tobacco industry and manufacturers of processed foods, thereby knocking out the props that hold disease rates up." Will less developed countries repeat our mistakes, he asks.

EDDIE LAWRENCE/SPL

Maternal use of SSRIs and risk of persistent pulmonary hypertension of the newborn

Depression during pregnancy is common, and use of selective serotonin reuptake inhibitors (SSRIs) to treat it is increasing. However, use in late pregnancy may be a risk factor for persistent pulmonary hypertension of the newborn (PPHN), a life threatening condition, but studies so far have had inconsistent results. Helle Kieler and colleagues used data from the national health registers of five Nordic countries to assess whether maternal use of SSRIs does increase the risk of PPHN, and whether such an effect might differ between specific SSRIs (p 20). In a cohort of more than 1.6 million infants, exposure to SSRIs in late pregnancy was associated with more than doubling of the low risk of PPHN (absolute risk 3 per 1000 compared with the background incidence of 1.2 per 1000). The increased risks were similar for each of the specific SSRIs, so it seems to be a class effect.

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Effects of physical activity in cancer survivors After successfully completing cancer treatment patients are often left with increased fatigue, decreased physical activity, and a reduction in quality of life. Daniel Fong and colleagues conducted a meta-analysis of 34 randomised controlled trials that assessed the potential benefit of physical activity (mainly aerobic exercise). It had positive effects on physiology, body composition, physical functions, psychological outcomes, and quality of life in patients (doi:10.1136/bmj.e70).

Long term use of proton pump inhibitors and risk of hip fracture Proton pump inhibitors (PPIs) are common treatments for indigestion and heartburn, but does their long term use increase the risk of bone fracture? In a cohort of almost 80 000 postmenopausal women, Hamed Khalili and colleagues found that the risk of hip fracture among women who regularly used PPIs for at least two years was 35% higher and that this increased risk was concentrated among women with a history of smoking (doi:10.1136/bmj.e372).

Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study

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EDITORIAL by Tunstall-Pedoe

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STUDY QUESTION How much of the recent decline in mortality from acute myocardial infarction in England is attributable to changes in the event rate of acute myocardial infarction and how much to changes in case fatality?

SUMMARY ANSWER From 2002 to 2010, the age standardised total mortality rate for acute myocardial infarction decreased by half, while the age standardised event and case fatality rates each declined by one third. Just over half of the decline in mortality can be attributed to a decline in rates of acute myocardial infarction and just under half to a decline in case fatality.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Population based mortality rates from coronary heart disease and acute myocardial infarction have been declining in England since the 1970s, but the determinants of the decline are not known. This large national study reports the relative contribution of changes in the event rate and case fatality to the changes in mortality from acute myocardial infarction over the past decade.

Trends in event rate, 30 day case fatality, and mortality from acute myocardial infarction by sex, 2002-10, England

	Men		Women	
Outcome	<75 years	All ages	<75 years	All ages
Event rate:				
Overall change	−34	−33	−34	−31
Annual trend	−4.7	−4.8	−5.0	−4.5
Case fatality:				
Overall change	−23	−24	−32	−29
Annual trend	−3.5	−3.6	−5.0	−4.2
Mortality:				
Overall change	−51	−50	−58	−53
Annual trend	−8.6	−8.6	−10.3	−9.1
Contribution to decline in mortality:				
Event rate	57	57	50	52
Case fatality	43	43	50	48

Participants and setting

840 175 residents of England of all ages who were admitted to hospital for acute myocardial infarction or who died suddenly from acute myocardial infarction.

Design

Population based study using person linked national hospital and mortality data between 2002 and 2010. We calculated the relative contribution of event rate and case fatality to the decline in mortality from acute myocardial infarction using the same statistical method as in the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease study.

Main results

Between 1 January 2002 and 31 December 2010, 861 134 acute myocardial infarctions occurred in 840 175 residents of England. In that period, the event rate, case fatality, and total mortality rates in men decreased by 33%, 24%, and 50%, respectively. In women, the corresponding rates decreased by 31%, 29%, and 53%. Declines were observed in all three rates for all age groups, both sexes, and all geographical regions. Overall for England, the relative contributions of the reductions in event rates and case fatality to the decline in mortality from acute myocardial infarction were, respectively, 57% and 43% for men and 52% and 48% for women. The relative contributions differed by age, sex, and region. Changes in case fatality played a greater part for women and older people, but there was no consistent geographical pattern in the determinants of the decline in mortality from acute myocardial infarction.

Bias, confounding, and other reasons for caution

The main limitation of this study was reliance on the accuracy and validity of routine data. The introduction of the new diagnostic criteria for acute myocardial infarction in 2000, which relied on the use of more sensitive biochemical markers (troponins) for detection of acute myocardial infarction, could have influenced our estimates of event rate in the early 2000s. Our data did not include clinical information on risk factors, comorbidities, disease history, or current and past drug prescriptions for the population studied, and thus we could not address the relative importance of specific elements of prevention and treatment.

Generalisability to other populations

The findings of this study are representative of the English population. Generalising the results to other populations should be done with caution.

Study funding/potential competing interests

KS is funded by the Rhodes Trust. FLW is funded by the Medical Research Council. MR is funded by the British Heart Foundation. MJG is partly funded by the National Institute for Health Research; the institute funded the work to build the English national linked dataset of hospital episode statistics and Office for National Statistics records.

25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study

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STUDY QUESTION

How much did incidence of and mortality from acute myocardial infarction change from 1984 through 2008 in Denmark, and how did sex and comorbidity affect prognosis?

SUMMARY ANSWER

The rate of first time hospitalisation for myocardial infarction and subsequent short term mortality both declined by nearly half between 1984 and 2008 for all patients, independent of sex and comorbidity, but comorbidity burden was a strong prognostic factor for short and long term mortality, whereas sex was not.

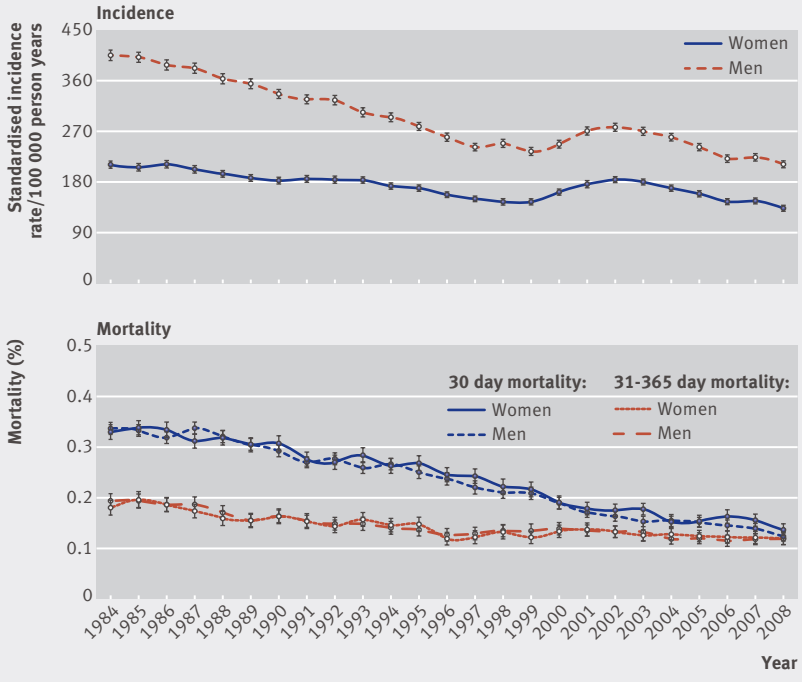
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

No studies have reported on 25 year trends in a nationwide unselected population. In Denmark almost 50% reduction has occurred both in myocardial infarction incidence and in subsequent short term mortality, with the latter strongly influenced by comorbidity.

Participants and setting

Patients with a first time hospitalisation for myocardial infarction in Denmark from 1984 through 2008.

Incidence of first time hospitalisation for myocardial infarction and subsequent mortality



Transient increase in incidence starting around 2000 probably due to new diagnostic criteria for myocardial infarction

Design, size, and duration

Using the Danish National Registry of Patients, we conducted a nationwide, population based, cohort study of 234 331 patients with a first time hospitalisation for myocardial infarction. We calculated the standardised incidence rate of myocardial infarction and 30 day and 31–365 day mortality by sex. We defined normal, moderate, severe, and very severe comorbidity categories according to the Charlson comorbidity index. We used Cox regression to compute mortality rate ratios comparing comorbidity categories.

Main results and the role of chance

The standardised incidence rate per 100 000 people decreased in the 25 year period by 37% for women (from 209 to 131) and by 48% for men (from 410 to 213). The 30 day, 31–365 day, and one year mortality declined from 31%, 16%, and 42% in 1984–8 to 15%, 11%, and 24% in 2004–8, respectively. After adjustment for age at time of myocardial infarction, men and women had the same one year risk of dying. The mortality reduction was independent of comorbidity category. Comparing patients with very severe versus normal comorbidity during 2004–8, we found the mortality rate ratio, adjusted for age and sex, was 1.96 (95% confidence interval 1.83 to 2.11) within 30 days and 3.89 (3.58 to 4.24) between 31 and 365 days.

Bias, confounding, and other reasons for caution

The population based design within the setting of a tax supported, universal healthcare system and the high data quality on diagnoses of myocardial infarction and comorbidities largely removed selection and information biases. The ratio of mortality rates associated with comorbidity categories should be unbiased because the comparisons over time were made between patients all with myocardial infarction.

Generalisability to other populations

The observed trends for incidence of and mortality from myocardial infarction are likely generalisable to most industrial Western societies where changes in lifestyle, risk factor modification, and increasing use of aggressive treatments have followed international recommendations.

Study funding/potential competing interests

The study was supported by the Danish Medical Research Council, the Clinical Epidemiological Research Foundation, Denmark, and Aarhus University. None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

Decline in mortality from coronary heart disease in Poland after socioeconomic transformation: modelling study

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STUDY QUESTION

What are the reasons for the rapid decline in mortality from cardiovascular disease in Poland after the political, social, and economic transformation in the early 1990s?

SUMMARY ANSWER

Over half of the fall in mortality from coronary heart disease in Poland between 1991 and 2005 can be attributable to reductions in major risk factors and about a third to evidence based medical treatments.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

In Poland and several other central European countries, soaring trends in premature coronary mortality in the 1980s sharply reversed in the early 1990s after the transition into a market economy. This modelling study suggests that large and rapid effects on coronary mortality can follow population-wide decreases in exposure to cardiovascular risk factors (mainly reflecting economic changes).

IMPACT model explaining fall in mortality from coronary heart disease in Poland, 1991-2005

	Percentage*
Risk factors worse (–7%):	
Obesity (increase)	–4
Diabetes (increase)	–2
Risk factors better (60%)	
Cholesterol (diet)	39
Smoking	11
Physical activity	10
Population fall in blood pressure	0
Treatments (37%):	
Acute coronary syndrome	9
Secondary prevention	7
Heart failure	12
Angina: CABG surgery	2
Angina: aspirin	1
Treatments for hypertension	2
Statins (primary prevention)	3
Unexplained	9

*Percentages might not sum to 100 because of rounding.

Design

A modelling study with data from controlled trials and meta-analyses, national surveys, and official statistics.

Selection criteria for studies

To explain the changes in cardiovascular mortality in Poland between 1991 and 2005 we used the IMPACT model of mortality from coronary heart disease. This has been previously validated in the United Kingdom, Italy, Sweden, Canada, the United States, and elsewhere. We systematically identified and critically reviewed all available Polish data sources as potential model inputs. The analysis was confined to adults aged 25-74.

Primary outcome

Number of deaths prevented or postponed in 2005 attributable to specific treatments for coronary heart disease and changes in risk factors. The observed fall in deaths from coronary heart disease from 1991 to 2005 was then partitioned among specific treatments and changes in risk factors.

Main results

From 1991 to 2005, the death rate from coronary heart disease halved in people aged 25-74 in Poland, resulting in 26 200 fewer coronary deaths in 2005. About 54% of this fall was attributed to changes in major cardiovascular risk factors (minimum estimate 41%, maximum estimate 65%), mainly reductions in total cholesterol concentration (39%) and an increase in leisure time physical activity (10%). These were partially offset, however, by increases in body mass index (–4%) and the prevalence of diabetes (–2%). Blood pressure fell in women, explaining about 29% of their decrease in mortality, but rose in men generating a negative influence (–8%). About 15% of the observed decrease in mortality was attributable to reduced smoking in men but was negligible in women.

About 37% (minimum estimate 13%, maximum estimate 77%) of the decrease in mortality was attributable to treatments, including treatments for heart failure (12%), initial treatments for acute coronary syndrome (9%), secondary prevention treatments after myocardial infarction or revascularisation (7%), chronic angina treatments (3%), and others (6%).

Bias, confounding, and other reasons for caution

In Poland, data for the initial year of analysis (1991) were less representative than in subsequent years. We also assumed a minimal lag time between changes in risk factors and changes in mortality. This, however, seems reasonable. Our model failed to explain 9% of the overall reduction in deaths from coronary heart disease: residual confounding in many of the estimates of the effect of risk factors is likely. Furthermore, the model does not quantify all potential risk factors (such as psychosocial variables).

Study funding

This study was funded by the Polish Ministry of Health, the European Commission PHEA and the UK Medical Research Council (grant No 91367).

The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalaemia and acute kidney injury: systematic review and meta-analysis

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STUDY QUESTION

Is combination therapy with aliskiren and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers associated with an increased risk of hyperkalaemia?

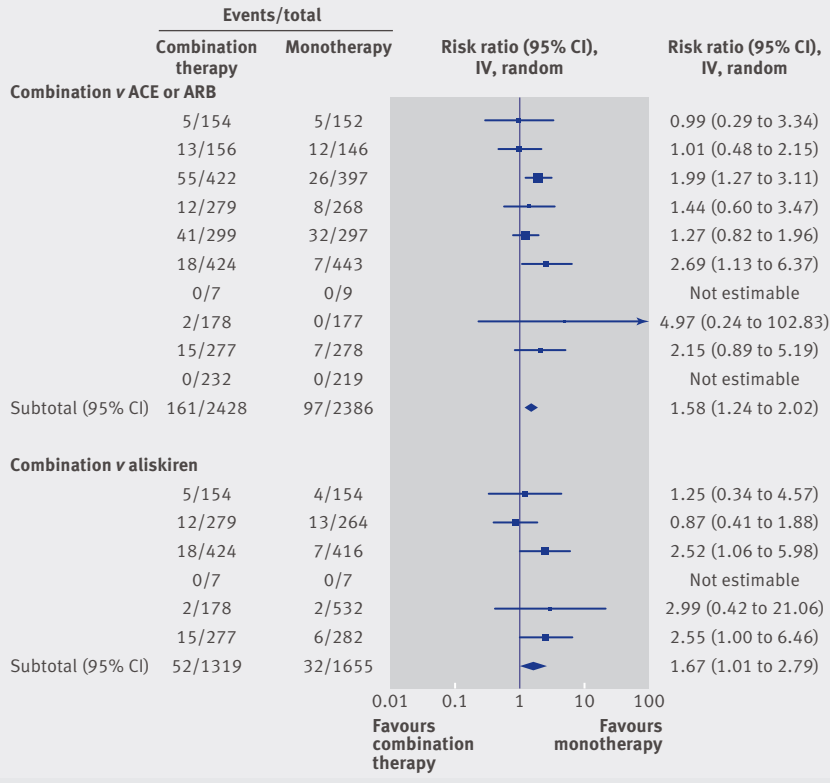
SUMMARY ANSWER

The combined use of aliskiren with ACE inhibitors or angiotensin receptor blockers is associated with a significantly increased risk of hyperkalaemia compared with monotherapy with either drug class.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Hyperkalaemia is an important consequence of blockade of the renin-angiotensin system using combination therapy; however, most trials comparing combination therapy with aliskiren and ACE inhibitors or angiotensin receptor blockers have been underpowered to provide robust estimates. Further research to clarify the role and safety of such combination therapy on important clinical outcomes is needed before widespread use can be advocated.

Risk of hyperkalaemia among participants given combination therapy with aliskiren and an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) versus monotherapy



Selection criteria for studies

We searched Ovid Medline, Embase, and the Cochrane central register of controlled trials, along with the clinical trials registry (www.clinicaltrials.gov), the Novartis clinical trial results database, and abstracts of the past five years from conferences of the American Society of Nephrology and the European Renal Association. We included all randomised controlled clinical trials of at least four weeks' duration involving aliskiren in combination with either ACE inhibitors or angiotensin receptor blockers that provided data on the incidence of hyperkalaemia compared with monotherapy with either aliskiren, ACE inhibitors, or angiotensin receptor blockers. All dosing regimens were considered, and all ACE inhibitors and angiotensin receptor blockers used in clinical practice were eligible for inclusion. We excluded drug combinations with agents other than ACE inhibitors and angiotensin receptor blockers (for example, telmisartan and hydrochlorothiazide combination), studies that enrolled patients receiving long term dialysis, and studies published only as abstracts.

Primary outcomes

The primary outcome was hyperkalaemia, defined as a serum potassium concentration greater than 5.5 mmol/L (meq/L).

Main results and role of chance

Ten randomised controlled studies (4814 participants) were included. Combination therapy with aliskiren and an ACE inhibitor or angiotensin receptor blocker significantly increased the risk of hyperkalaemia compared with monotherapy using an ACE inhibitor or angiotensin receptor blocker (relative risk 1.58, 95% confidence interval 1.24 to 2.02; P=0.0002) or aliskiren alone (1.67, 1.01 to 2.79; P=0.05).

Bias, confounding, and other reasons for caution

We pooled the results of a group of studies that were funded by Novartis Pharmaceuticals, the manufacturer of aliskiren (Rasilez), and not originally intended to explore safety outcomes. Many of these studies were small, resulting in few adverse safety events. As a result, the confidence intervals for the risk ratios for hyperkalaemia for individual studies were wide. Also, we did not have access to original data for any of these studies and included participants who were clinically heterogeneous. Thus, we were unable to account for all important differences in the risk for hyperkalaemia between different groups. Notably, most participants had preserved baseline kidney function, which may have limited the likelihood of hyperkalaemia, even among those using combination therapy.

Study funding/potential competing interests

This study was unfunded. We have no competing interests.

Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries

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STUDY QUESTION

Does maternal use of selective serotonin reuptake inhibitors (SSRIs) increase the risk of persistent pulmonary hypertension of the newborn (PPHN), and does such an effect differ between specific SSRIs?

SUMMARY ANSWER

Use of SSRIs in late pregnancy increased the risks of PPHN from 1.2 per 1000 liveborn infants to 3 per 1000. The increased risks seemed to be a class effect.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

PPHN is a rare but life threatening condition and has been associated with maternal characteristics and use of specific drugs during pregnancy. Use of SSRIs is increasing among pregnant women and the risk of PPHN is associated with use of SSRIs after gestational week 20.

Participants and setting

From the national birth registers in Denmark, Finland, Iceland, Norway, and Sweden we included all singleton infants born after gestational week 33, from 1996 to 2007. By linkage with the drug registers on filled prescriptions we identified women who used SSRIs. Information on outcome and previous maternal psychiatric disorders was obtained from the birth, patient, and cause of death registers.

Design, size, and duration

In this population based cohort study we identified 30 115 infants of mothers who had used SSRIs during pregnancy and 1 588 140 infants of mothers who had not. Risks of PPHN in association with SSRI use in late pregnancy (after gestational week 20) or early pregnancy (before gestational week 8) were calculated, adjusting for maternal age, purchased non-steroidal anti-inflammatory drugs, antidiabetes drugs, diseases recorded during pregnancy, level of delivery hospital, and infants' country of birth, birth year, and birth order.

Main results and the role of chance

Of the infants, 0.7% (n=11 014) had been exposed to an SSRI during late pregnancy and 1.1% (n=17 053) during early pregnancy only. Mothers who used SSRIs were generally older and more often smokers than non-users. Exposed infants had a shorter gestational age at birth and were more often small for gestational age. For exposure in late pregnancy the absolute risk of PPHN was 3 per 1000 liveborn infants, more than double that of the background incidence of 1.2 per 1000. The adjusted odds ratio for exposure to any SSRI was 2.1 (95% confidence interval 1.5 to 3.0). For fluoxetine, citalopram, sertraline, and paroxetine the risk estimates ranged from two to three. For exposure to SSRIs in early pregnancy the adjusted odds ratio was 1.4 (1.0 to 2.0). The adjusted odds ratio for infants of mothers with a previous admission to hospital for a psychiatric disorder and not exposed to SSRIs was 1.3 (1.0 to 1.6), whereas for infants of mothers with a previous admission to hospital for a psychiatric disorder and exposed in late pregnancy it was 3.1 (1.9 to 4.9).

Bias, confounding, and other reasons for caution

We assessed exposure to SSRI as dispensed drugs. Some women could have filled a prescription without taking the drug and some might have used SSRIs in late pregnancy with no filled prescriptions during that period because of stockpiling drugs. Misclassification of exposure would if anything bias the risk estimates towards the null. Confounding by indication cannot be precluded, although the risk was increased for infants to mothers with a previous admission to hospital for a psychiatric disorder if they had been exposed to an SSRI.

Generalisability to other populations

The study was carried out in five countries, which increases its generalisability compared with a national study.

Study funding/potential competing interests

This study was supported by the Swedish Pharmacy Company and the authors' affiliations. We have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years.

Exposure to selective serotonin reuptake inhibitors (SSRIs) in gestational week 20 or later and risk of persistent pulmonary hypertension of the newborn (PPHN)

	No of infants with PPHN (per 1000)		Odds ratio (95% CI)	
Drugs	Not exposed	Exposed	Unadjusted	Adjusted*
Any SSRIs	1899 (1.2)	33 (3.0)	2.5 (1.8 to 3.6)	2.1 (1.5 to 3.0)
Fluoxetine	1952 (1.2)	9 (2.7)	2.3 (1.2 to 4.3)	2.0 (1.0 to 3.8)
Citalopram	1936 (1.2)	11 (3.3)	2.8 (1.5 to 5.0)	2.3 (1.2 to 4.1)
Paroxetine	1959 (1.2)	5 (3.9)	3.2 (1.3 to 7.8)	2.8 (1.2 to 6.7)
Sertraline	1949 (1.2)	10 (3.5)	2.9 (1.6 to 5.4)	2.3 (1.3 to 4.4)
Escitalopram	1966 (1.2)	1 (1.8)	1.5 (0.2 to 10.5)	1.3 (0.2 to 9.5)

*Adjusted for maternal age, dispensed non-steroidal anti-inflammatory and antidiabetes drugs, pre-eclampsia, chronic diseases during pregnancy, country of birth, birth year, level of delivery hospital, and birth order.