Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up

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ABSTRACT

Objective To investigate the impact of coexistent psychiatric morbidity on risk of suicide after a suicide attempt.

Design Cohort study with follow-up for 21-31 years.

Setting Swedish national register based study.

Participants 39 685 people (53% women) admitted to hospital for attempted suicide during 1973-82.

Main outcome measure Completed suicide during 1973-2003.

Results A high proportion of suicides in all diagnostic categories took place within the first year of follow-up (14-64% in men, 14-54% in women); the highest short term risk was associated with bipolar and unipolar disorder (64% in men, 42% in women) and schizophrenia (56% in men, 54% in women). The strongest psychiatric predictors of completed suicide throughout the entire follow-up were schizophrenia (adjusted hazard ratio 4.1, 95% confidence interval 3.5 to 4.8 in men, 3.5, 2.8 to 4.4 in women) and bipolar and unipolar disorder (3.5, 3.0 to 4.2 in men, 2.5, 2.1 to 3.0 in women). Increased risks were also found for other depressive disorder, anxiety disorder, alcohol misuse (women), drug misuse, and personality disorder. The highest population attributable fractions for suicide among people who had previously attempted suicide were found for other depression in women (population attributable fraction 9.3), followed by schizophrenia in men (4.6), and bipolar and unipolar disorder in women and men (4.1 and 4.0, respectively).

Conclusion Type of psychiatric disorder coexistent with a suicide attempt substantially influences overall risk and temporality for completed suicide. To reduce this risk, high risk patients need aftercare, especially during the first two years after attempted suicide among patients with schizophrenia or bipolar and unipolar disorder.

INTRODUCTION

A suicide attempt is a risk factor for completed suicide; the absolute risk in people followed-up for 5-37 years was 7-13%,[1-6] corresponding to a 30-40 times increased risk of death from suicide in those who had attempted suicide compared with the general population.[7] The impact of coexistent psychiatric morbidity on risk of suicide after suicide attempts is largely unknown.

The interval between first communication of suicidal ideation or suicidal behaviour and completed suicide varies with coexisting mental disorder; it is reportedly shorter in depressive disorders than in personality and psychotic disorders.[8] We investigated the impact of coexistent psychiatric morbidity on risk of suicide after a suicide attempt in a cohort of 39 685 people in Sweden.

METHODS

We linked data on all 9.4 million people living in Sweden during 1973-82 to the hospital discharge register, cause of death register, 1970 population and housing census, and education and migration registers. We identified people aged 10 or older who had been admitted to inpatient care because of suicidal behaviour, defined as a definite suicide attempt or an uncertain suicide attempt (n=49 509). In case of more than one admission for a suicide attempt we used the first admission as the index attempt. We excluded people who had immigrated within two years before baseline (n=860). Cases were those with one of the studied psychiatric diagnoses at discharge from the index admission or at discharge from the first inpatient episode beginning within one week after this index episode (n=12 681). Those without a diagnosis of mental disorder within one year after the suicide attempt were used as reference subjects (n=27 004). We did not include people with different psychiatric diagnosis to those studied, or a diagnosis after one week but within one year after the suicide attempt (n=8964). The study cohort thus consisted of 39 685 people; 18 642 males and 21 043 females, mean age 38.4 (SD=16.5) years and 37.0 (SD 17.0) years. The reference group comprised 68% of the study cohort and consisted of people who had attempted suicide but had none, subclinical, or milder forms of psychiatric morbidity at the index episode and within one year thereafter.

We studied eight psychiatric disorders: schizophrenia, bipolar and unipolar disorder, other depressive disorder, anxiety disorder, adjustment disorder or post-traumatic stress disorder, alcohol abuse or dependence, drug abuse or dependence, and personality

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disorder. We introduced the potential confounders of age, educational level, and immigrant status as covariates in the regression analyses. We measured education on a seven point ordinal scale.

Analyses

Patients were followed from discharge after attempted suicide to a definite or uncertain suicide, death other than suicide, first emigration, or end of follow-up (31 December 2003). Thus we followed-up patients for 21-31 years.

We used Kaplan-Meier survival curves to plot temporal patterns of suicide after a suicide attempt; we excluded adjustment disorder or post-traumatic stress disorder owing to absence of risk effect and substance misuse owing to low prevalence. For each diagnostic category and sex we determined separately absolute and relative mortality from suicide after a suicide attempt and taking time at risk into account used Cox regression models to compute hazard ratios (95% confidence intervals). We adjusted the hazard ratios for age, highest level of education, and immigrant status. For each psychiatric disorder we calculated the population attributable fractions, expressing the impact of coexistent psychiatric disorder on suicide in people who had previously attempted suicide (see bmj.com). We used SPSS for Windows (version 15) for the statistical analyses.

RESULTS

Death from suicide occurred primarily within the first five years after the index suicide attempt for all diagnostic groups, including those without a psychiatric diagnosis, but the risk prevailed over the follow-up period (see bmj.com). A high proportion of all suicides in each diagnostic group occurred within the first year (table). People who had attempted suicide and had a diagnosis of schizophrenia or bipolar and unipolar disorder had a highly increased risk, especially in the short term. For bipolar and unipolar disorder, 64% of suicides in men and 42% in women occurred within the first year; the corresponding proportions for schizophrenia were 56% and 54%. The total mortality from suicide in the reference group was comparatively low,

Absolute rates, hazard ratios, and population attributable fractions for death from suicide by psychiatric disorder in 39 685 people who attempted suicide and were admitted to hospital during 1973-82 in Sweden and followed to 2003

		Completed suicide within one year after suicide attempt		Completed suicide during entire follow-up		
Diagnosis	Mean (SD) age at suicide attempt (years)	Suicide rate (%) (No)	Proportion of all suicides during follow-up (%)	Suicide rate (%) (No)	Adjusted hazard ratio* (95% CI)	Population attributable fraction
Bipolar and unipolar disorder:						
Male (n=395)	49.1 (16.4)	22.8 (90)	63.8	35.7 (141)	3.5 (3.0 to 4.2)	4.0
Female (n=648)	48.2 (15.4)	8.5 (55)	42.3	20.1 (130)	2.5 (2.1 to 3.0)	4.1
Other depressive disorder:						
Male (n=1718)	40.4 (15.3)	6.0 (103)	37.7	15.9 (273)	1.4 (1.2 to 1.6)	3.1
Female (n=3364)	40.1 (15.7)	4.0 (135)	31.4	12.8 (430)	1.7 (1.5 to 1.9)	9.3
Schizophrenia:						
Male (n=397)	34.1 (11.8)	21.7 (86)	56.2	38.5 (153)	4.1 (3.5 to 4.8)	4.6
Female (n=316)	38.7 (13.1)	13.0 (41)	53.9	24.1 (76)	3.5 (2.8 to 4.4)	2.8
Anxiety disorder:						
Male (n=429)	35.0 (13.2)	8.2 (35)	41.2	19.8 (85)	1.9 (1.5 to 2.3)	1.6
Female (n=899)	34.9 (14.1)	3.3 (30)	30.3	11.0 (99)	1.5 (1.3 to 1.9)	1.7
Adjustment disorder or post-traumatic stress disorder:						
Male (n=244)	36.1 (14.6)	1.6 (4)	17.4	9.4 (23)	0.9 (0.6 to 1.3)	−0.1
Female (n=520)	34.0 (14.4)	1.3 (7)	20.0	6.7 (35)	1.0 (0.7 to 1.4)	0.0
Alcohol abuse or dependence:						
Male (n=2200)	41.2 (12.2)	2.7 (60)	20.4	13.4 (294)	1.1 (1.0 to 1.3)	1.1
Female (n=502)	39.2 (12.1)	1.8 (9)	14.3	12.5 (63)	1.7 (1.3 to 2.1)	1.4
Drug abuse or dependence:						
Male (n=206)	32.2 (14.1)	2.4 (5)	13.5	18.0 (37)	1.6 (1.1 to 2.2)	0.6
Female (n=179)	34.8 (15.8)	2.8 (5)	16.7	16.8 (30)	2.3 (1.6 to 3.3)	0.9
Personality disorder:						
Male (n=329)	31.8 (11.1)	5.2 (17)	26.2	19.8 (65)	1.8 (1.4 to 2.3)	1.2
Female (n=335)	30.8 (12.3)	2.1 (7)	19.4	10.7 (36)	1.5 (1.1 to 2.1)	0.6
Reference group:						
Male (n=12 724)	37.9 (17.4)	5.1 (643)	45.1	11.2 (1426)	Reference	Reference
Female (n=14 280)	36.0 (17.6)	2.8 (402)	39.6	7.1 (1015)	Reference	Reference

Diagnoses were principal diagnoses assigned during an inpatient episode starting within one week after index suicide attempt.
*Hazard ratio for each coexistent psychiatric disorder compared with reference group (without any coexistent psychiatric disorder) category obtained with Cox regression modelling over total follow-up period. Hazard ratios were adjusted for age, educational level, and immigrant status.

although 45% of suicides in men and 40% in women took place within the first year. Schizophrenia and bipolar and unipolar disorder conferred the highest risks for suicide during the entire follow-up; hazard ratios adjusted for age, education, and immigrant status ranged from 2.5 for bipolar and unipolar disorder in women to 4.1 for schizophrenia in men (table). Patients with most other disorders had lower, but still significantly increased, risks for suicide. Those with adjustment disorder or post-traumatic stress disorder and alcohol misuse (men only) did not have significantly increased risks.

The highest population attributable fractions for suicide among people who had previously attempted suicide were for other depression in women (9.3), schizophrenia in men (4.6), and bipolar and unipolar disorder in women (4.1) and men (4.0).

DISCUSSION

Type of coexistent psychiatric morbidity in people who have previously attempted suicide is related to risk of death from suicide. We investigated the risk for completed suicide in patients who had attempted suicide as a function of eight psychiatric disorders and found substantial differences in risk across the diagnoses. The rate of suicide after a previous suicide attempt was particularly increased among both sexes with schizophrenia or bipolar and unipolar disorder. Population attributable fractions suggested a modest but significant impact for other depression in women, schizophrenia in men, and bipolar and unipolar disorder in both sexes. The larger population attributable fractions for these reflect their respective prevalence and the associated relative risk of suicide in the study cohort. Thus other depressive disorder had a comparatively high impact owing to its high prevalence, despite the risk of completed suicide not being as high as for schizophrenia or bipolar and unipolar disorder. As we only studied patients with previous suicidal behaviour and controlled for age, education, and immigrant status or ethnic minority group, hazard ratios and population attributable fractions were related to risks contributed by the mental disorder itself, or some unmeasured confounders.

Death from suicide was heavily skewed towards the first years after the suicide attempt particularly in people with schizophrenia or bipolar and unipolar disorder, probably because of symptom rich phases.

We expected a relatively high impact of substance misuse or dependence on risk of suicide[1] but the hazard ratio exceeded 2.0 only in females with drug misuse or dependence who had attempted suicide. Yet we cannot rule out the possibility that deaths in people with physical stigma of substance misuse are less likely to be classified as suicide. Moreover, alcohol misuse could be comorbid with several disorders judged as principal. Anxiety disorder conferred a comparably increased risk for suicide in both sexes. A complicating depression may be instrumental in risk of suicide in people with anxiety disorder.[9]

WHAT IS ALREADY KNOWN ON THIS TOPIC

A previous suicide attempt is a well established risk factor for completed suicide

The impact of coexistent psychiatric morbidity on risk of suicide after suicide attempts is largely unknown

WHAT THIS STUDY ADDS

Schizophrenia and bipolar disorder substantially influence overall risk and temporality for completed suicide after a suicide attempt in both sexes

Schizophrenia, bipolar and unipolar disorder, and other depression have the strongest population impact on risk of completed suicide in people who have previously attempted suicide

By using an epidemiological framework and a total population sample we tried to minimise selection bias and power problems. The national cohort we followed for at least 21 years is the largest with data on people who have attempted suicide and on psychiatric morbidity. Because the cause of death register has excellent coverage, loss to follow-up should be minimal. Limitations of our study were that we included only people with suicide attempts that led to an episode of inpatient care and we did not study the contribution of physical illness[4 10] and multiple psychiatric comorbidity or analyse subcategories of the diagnostic groups. Adjustment disorder or post-traumatic stress disorder was infrequently diagnosed during 1973-82 and the size of this group might be underestimated. Also, a narrow definition for bipolar disorder was used in Sweden during the years of inclusion; primarily for patients with more obvious manic symptoms and similar to the type I diagnosis for bipolar disorder from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. Furthermore, among the disorders labelled as manic depressive in the international classification of disease, eighth revision, the depressed type (296.2), which could be labelled recurrent severe depression, contributed strongly to the high risk of suicide in the bipolar and unipolar group. We also defined coexistent psychiatric morbidity as any disorder diagnosed within one week of the suicide attempt. People who attempted suicide may have been diagnosed as having one or more psychiatric disorders before or after this period, thereby resulting in misclassification of patients with coexistent psychiatric morbidity as reference subjects. It is likely that many subjects in the reference group had subclinical psychiatric morbidity.

Specific treatment of patients who have attempted suicide is often discussed on the basis of previous suicide attempts[11] and an estimate of suicidal intent. Our results imply that interventions should take into account coexistent mental disorder and the time that has elapsed since the previous suicide attempt.

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Hospital admissions for self harm after discharge from psychiatric inpatient care: cohort study

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ABSTRACT

Objective To determine the risk of non-fatal self harm in the 12 months after discharge from psychiatric inpatient care.
Design Cohort study based on national hospital episode statistics.
Setting England.
Population Patients aged 16-64 years discharged from psychiatric inpatient care between 1 April 2004 and 31 March 2005 and followed up for one year.
Results 75 401 people were discharged from psychiatric inpatient care over the study period, 4935 (6.5%) of whom were admitted at least once for self harm in the following 12 months. Risk of self harm was greatest in the four weeks after discharge; one third (32%, n=1578) of admissions for self harm occurred in this period. The strongest risk factor for self harm after discharge was admission for self harm in the previous 12 months (hazard ratio 4.9, 95% confidence interval 4.6 to 5.2). The risk of self harm was also higher in females, younger people, those with diagnoses of depression, personality disorders, and substance misuse, and those with short lengths of stay.
Conclusion More than 6% of patients discharged from psychiatric inpatient care are readmitted for an episode of self harm within 12 months, with one third of these episodes occurring in the month after discharge. Self harm after discharge from hospital shares many of the features of suicide after discharge. Interventions should be developed to reduce risk in this period.

INTRODUCTION

The risk of suicide in the month after psychiatric inpatient care is around 100 times greater than that for the general population.[1-3] Although the high risk of suicide shortly after discharge is well documented, less is known about the rates of non-fatal self harm. Using routine hospital discharge data for England we investigated the incidence and timing of self harm in the year after discharge from psychiatric inpatient care.

METHODS

From the hospital episode statistics database for England we selected all patients (n=75 401) aged 16-64 years who had been discharged from hospital after general adult psychiatric care on at least one occasion for the index year 2004-5.

We created a unique patient identifier from the patient's NHS number, postcode, date of birth, and sex. This was used to search the database for 2004-5 and 2005-6 to identify readmissions within one year of discharge, and for 2003-4 to identify previous admissions for self harm or admissions to a psychiatric hospital.

We derived the main diagnosis for admission from the international classification of diseases (10th revision): organic disorders, substance misuse, schizophrenia and related psychoses, mania, depression and anxiety, eating disorders, and other. The last category comprised behavioural syndromes, disorders of adult personality and behaviour, and unspecified diagnoses. (See bmj.com for codes.) We classed readmissions for self harm as intentional self harm, event of undetermined intent, and accidental poisoning by exposure to noxious substances (see bmj.com).

Analysis

We used Cox proportional hazards regression models to investigate the associations of age (16-24, 25-34, 35-44, and 45-64), sex, diagnosis, and psychiatric admission or

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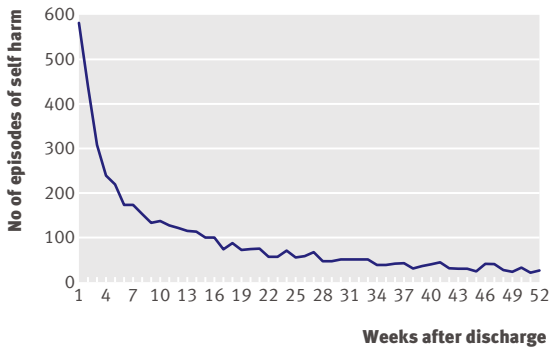

Timing of admissions for self harm in year after discharge from inpatient psychiatric care

admissions for self harm in the year preceding the index admission to a psychiatric hospital with the risk of being readmitted with self harm in the year after discharge. If patients were readmitted to a psychiatric hospital during the follow-up period we censored their data at the date of readmission. Thus, if readmission for a psychiatric disorder preceded readmission for self harm during follow-up, we excluded this episode of self harm from the analysis as it was likely to be related to the subsequent admission. All records were censored after 52 weeks follow-up. We fitted appropriate interaction terms to investigate whether risk of self harm in relation to diagnosis differed between men and women. We also investigated whether the length of stay differed between those who did or did not self harm.

As length of stay was highly positively skewed we compared median length of stay for each diagnostic group and used Wilcoxon's rank sum test to compare the lengths of stay of patients admitted or not admitted to hospital for self harm in the year after discharge. To assess whether any such associations were confounded by differences in age and sex between those who did and did not self harm we used log transformed length of stay as the outcome variable in a linear regression analysis to assess the effect of controlling for both these factors in models.

RESULTS

Between 1 April 2004 and 31 March 2005, 75 401 patients were discharged from psychiatric inpatient care in England (see bmj.com), of whom 11.7% (n=8837) had been admitted to hospital for self harm in the year before their index psychiatric admission. Overall, 18 650 (24.7%) of those discharged were readmitted to psychiatric bed within a year and 4935 (6.5%) were readmitted to a general hospital or psychiatric bed for self harm. The risk of readmission for self harm was higher in females than in males (8.0% *v* 5.3%; χ^2 216 (df=1); P<0.001). More than one third of those who self harmed (38.5%) after discharge had been admitted to hospital for self harm in the year before their index admission.

Risk of self harm diminished rapidly in the weeks after discharge. One third (32.0%; 1578/4935) of admissions for self harm occurred in the month after

Associations of sex, age, and psychiatric diagnosis with risk of self harm after discharge from inpatient psychiatric care

Risk factor	No in sample	Hazard ratio (95% CI)	P value	Adjusted hazard ratio* (95% CI)	P value
Sex:					
Male	40 751	1.00		1.00	
Female	34 650	1.57 (1.49 to 1.66)	P<0.001	1.40 (1.33 to 1.49)	P<0.001
Age group (years):					
16-24	10 149	1.00		1.00	
25-34	19 185	0.91 (0.84 to 1.00)		0.96 (0.88 to 1.04)	
35-44	22 263	0.85 (0.78 to 0.92)		0.86 (0.79 to 0.93)	
45-64	23 804	0.63 (0.58 to 0.69)	P<0.001	0.68 (0.62 to 0.75)	P<0.001
Diagnosis:					
Organic disorders (F00-F09)	561	1.26 (0.78 to 2.04)		1.47 (0.90 to 2.38)	
Substance misuse (F10-F19)	12 948	3.00 (2.69 to 3.34)		2.64 (2.37 to 2.95)	
Schizophrenia and related psychoses (F20-29)	18 513	1.00		1.00	
Mania (F30, F31)	7655	1.23 (1.06 to 1.44)		1.17 (1.00 to 1.37)	
Depression and anxiety (F32-F49)	17 905	3.74 (3.38 to 4.14)		2.69 (2.42 to 2.98)	
Eating disorders (F50)	469	2.54 (1.74 to 3.69)		1.74 (1.19 to 2.53)	
Other (F51-F69, F99)	6088	5.75 (5.14 to 6.44)		3.71 (3.31 to 4.17)	
None of above codes	11 262	2.53 (2.26 to 2.84)	P<0.001	2.16 (1.92 to 2.43)	P<0.001
Psychiatric admission in year before index admission:					
No	63 574	1.00		1.00	
Yes	11 827	0.71 (0.65 to 0.78)	P<0.001	1.25 (1.14 to 1.37)	P<0.001
Admission for self harm in year before index admission:					
No	66 564	1.00		1.00	
Yes	8837	5.94 (5.61 to 6.29)	P<0.001	4.85 (4.57 to 5.16)	P<0.001

*Controlling for all variables in table.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The risk of suicide in the month after discharge from psychiatric care is about 100 times greater than that for the general population

The incidence of non fatal self harm and risk factors for self harm shortly after discharge are unknown

WHAT THIS STUDY ADDS

More than 6% of patients discharged from psychiatric inpatient care were readmitted for self harm in the following year, with a third occurring within one month

The strongest risk factor for self harm was admission for self harm in the year before psychiatric admission

The risk of self harm was higher in females than in males and declined with increasing age and length of hospital stay and is greatest in people with diagnoses of personality disorder, depression, and substance misuse

discharge, with 585 (11.9%) occurring within a week of discharge; 2826 (57.3%) occurred within 12 weeks (figure).

Although 1671 (33.9%) patients admitted for self harm had a primary diagnosis of depression or anxiety such patients comprised only 23.7% of those discharged from hospital. In contrast, only 483 (9.8%) patients admitted for self harm had a diagnosis of schizophrenia and related psychoses at discharge, whereas this was the commonest diagnosis at discharge from psychiatric care (n=18 513, 24.6% of discharges). In total, 688 (85.9%) of the 801 patients coded as "other" who self harmed had personality disorder as their primary diagnosis.

In fully adjusted models, risks were 40% higher in females than in males and declined with increasing age —the risk of self harm after discharge was 32% (95% confidence interval 25% to 38%) lower in those aged 45-64 than in those aged 16-24. The strongest risk factor for self harm after discharge was an admission for self harm in the previous year (hazard ratio 4.85, 95% confidence interval 4.57 to 5.16; table). The greatest risks with specific diagnostic groups was for "other" diagnoses, mainly personality disorder (hazard ratio 3.71), depression and anxiety (2.69), and substance misuse (2.64). The apparent protective effect in univariable models of previous psychiatric admission (hazard ratio 0.71, 0.65 to 0.78) was because a disproportionate number of those with a psychiatric history had diagnoses of schizophrenia or psychosis (38%) and this group are at reduced risk of self harm. This effect was reversed (1.25, 1.14 to 1.37) in the multivariable models controlling for a history of self harm.

Across all diagnostic groups patients who self harmed tended to have shorter hospital stays than those who did not self harm (see bmj.com). In linear regression models with log length of stay as the outcome and controlling for age and sex, differences in length of stay were little changed between those who did and did not self harm.

DISCUSSION

At least 6% of people discharged from psychiatric inpatient care in England self harm within a year. The actual figure is likely to be higher as less than half the episodes of self harm result in admission to hospital.[4] One third of these episodes occurred within a month. A higher proportion of females than males were readmitted with self harm (8.0% *v* 5.3%), and the risk was greatest among people with depression, anxiety, personality disorder, or substance use disorder and lowest among those with schizophrenia and related psychoses. An admission for self harm in the year before the index psychiatric admission was the strongest risk factor for self harm after discharge (hazard ratio 4.85); one third of people admitted for self harm after hospital discharge had been admitted with self harm in the preceding year.

Strengths and limitations

This is a large study based on NHS hospital discharge data for England. The hospital episodes statistics database includes information on a patient's NHS number and date of birth, which enable readmissions to be identified. Discharge diagnoses coded according to the international classification of diseases (10th revision) allowed us to estimate the risks of self harm for the main psychiatric diagnoses.

Our study has four main limitations. Firstly, as we were only able to identify episodes of self harm leading to hospital admission we will have underestimated the magnitude of the problem. If the likelihood of admission after presentation to hospital with self harm differs by age, sex, and diagnosis then this will bias our risk estimates. However, our results are likely to reflect the more serious episodes of self harm. Secondly, data in the database are collected for administrative reasons and some patients may have been miscoded; research indicates that the reliability of these data for studies such as ours is reasonable.[5] Thirdly, the range of personal data on the database is relatively sparse—for example, information on occupation is lacking. Lastly, we did not examine comorbidity, which is likely to be strongly associated with risk of deliberate self harm and repetition after discharge, nor were we able to investigate the effect of aftercare on risk of self harm.

Findings in relation to other studies

In keeping with our findings, a US based study found that patients with personality disorder had the greatest risk of self harm after discharge from psychiatric inpatient care.[6] In contrast with our findings, however, no great increase in risk was found in the first 10 weeks after discharge compared with later weeks. This may be because the authors relied on information from face to face interviews and because response rates at the first follow-up interview were only 74%.

Two studies investigated the risk of self harm among adolescents discharged from psychiatric hospital.[7 8] Both found that the risk was highest in the first few

months after discharge, with risks of self reported self harm of 12-20% in the year after discharge. It is likely that these higher risks are due to both the increased incidence of self harm among young people and the use of self report data.

Our findings of the high incidence of self harm in the month after hospital discharge are in keeping with those for suicide from other UK studies.[1 2 9] In the most recent analysis of data from the national confidential inquiry 32% of suicides in the three months after discharge occurred in the first two weeks[9]; in our study the equivalent figure for self harm was 35% (1028/2941). In studies of suicide after discharge from a psychiatric hospital and our study of self harm after discharge, rates among people with psychoses were low compared with those for depression in analyses based studies carried out in England[1] and Scotland.[2]

Clinical implications

About 5% of deaths from suicide in England and Wales occur within three months of discharge from a psychiatric hospital. Our analysis suggests that over 10% of patients may self harm after discharge and that the risk is greatest in the first month. Interventions need to be developed to reduce this risk. Our findings suggest that those patients who have self harmed previously are at the greatest risk of self harm after discharge. Other groups at increased risk include females, young people, and those with diagnoses of depression, personality disorder, and substance misuse, as well as people with short lengths of stay.

Hospital episode statistics data were provided through agreements with the South West Public Health Observatory. The views and opinions expressed in this paper do not necessarily reflect those of the Department of Health or National Institute of Health Research. The funders played no role in the analysis or drafting of this paper.

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Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study

CARE Study Group

EDITORIAL by Olsen and Bech

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ABSTRACT

Objective To examine the association of maternal caffeine intake with fetal growth restriction.

Design Prospective longitudinal observational study.

Setting Two large UK hospital maternity units.

Participants 2635 low risk pregnant women recruited between 8-12 weeks of pregnancy.

Investigations Quantification of total caffeine intake from 4 weeks before conception and throughout pregnancy was undertaken with a validated caffeine assessment tool. Caffeine half life (proxy for clearance) was determined by measuring caffeine in saliva after a caffeine challenge. Smoking and alcohol were assessed by self reported status and by measuring salivary cotinine concentrations.

Main outcome measures Fetal growth restriction, as defined by customised birth weight centile, adjusted for alcohol intake and salivary cotinine concentrations.

Results Caffeine consumption throughout pregnancy was associated with an increased risk of fetal growth restriction (odds ratios 1.2 (95% CI 0.9 to 1.6) for 100-199 mg/day, 1.5 (1.1 to 2.1) for 200-299 mg/day, and 1.4 (1.0 to 2.0) for >300 mg/day compared with <100 mg/day; test for trend P<0.001). Mean caffeine consumption decreased in the first trimester and increased in the third. The association between caffeine and fetal growth restriction was stronger in women with a faster compared to a slower caffeine clearance (test for interaction, P=0.06).

Conclusions Caffeine consumption during pregnancy was associated with an increased risk of fetal growth restriction and this association continued throughout pregnancy. Sensible advice would be to reduce caffeine intake before conception and throughout pregnancy.

INTRODUCTION

Maternal caffeine intake has been reported to be associated with a reduction in birth weight,[1-5] but the level of intake above which the risk is increased remains unknown. Caffeine intake of ≥300 mg/day has been associated with fetal growth restriction,[6-8] but one study found a significant reduction in infant weight with just 141 mg/day.[9] More controversially, maternal caffeine concentration has been to shown to have an inverse association with birth weight when confounders such as smoking are taken into account.[2 10 11]

Caffeine is rapidly absorbed and crosses the placenta freely. After ingestion of 200 mg caffeine, intervillous blood flow in the placenta has been found to be reduced by 25%.[12] Cytochrome P450 1A2, the principal enzyme involved in caffeine metabolism, is absent in the placenta and the fetus. The amount of caffeine and metabolites available to the fetoplacental unit therefore depends on the maternal caffeine metabolism, which shows marked variation between individuals. Variations in caffeine metabolic activity have been found to be more closely associated with fetal growth restriction than have blood caffeine concentrations.[13]

We used a validated robust caffeine assessment tool to quantify total caffeine intake from all possible sources throughout pregnancy.[14] Using these data, and taking into account individual variation in caffeine metabolism, we aimed to establish the safe upper limit of caffeine consumption with respect to adverse pregnancy outcome (specifically fetal growth restriction).

METHODS

Participants

We prospectively recruited low risk pregnant women at 8-12 weeks' gestation from two large UK teaching hospital maternity units (Leeds and Leicester) from September 2003 to June 2006. Inclusion criteria included age 18-45 years and singleton pregnancies, dated by ultrasound. Demographic details were recorded at baseline by means of a questionnaire.

Quantification of caffeine intake

Caffeine intake was estimated with a validated caffeine assessment questionnaire which recorded habitual caffeine intake before and during pregnancy, including estimates of caffeine content from all potential dietary sources and over the counter drugs, and details of potential confounders such as smoking, alcohol intake, and nausea (see bmj.com).[14] Caffeine intake was assessed throughout pregnancy by a caffeine assessment tool administered three times: the first from four weeks before pregnancy until recruitment into the study; the second covered the period 13-28 weeks of pregnancy; and the third included the period 29-40 weeks of pregnancy.

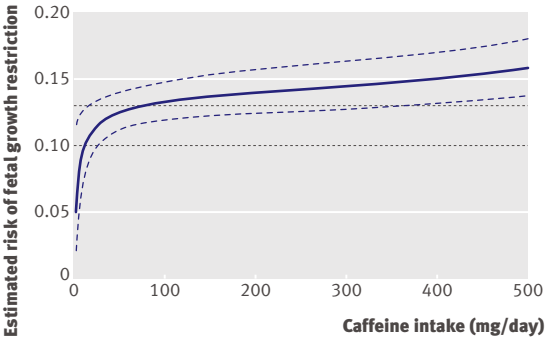
Saliva samples

Saliva samples for determining nicotine exposure were collected from women at recruitment. We assessed caffeine half life from a caffeine challenge test performed within two weeks of recruitment (see bmj.com for details).

Risk of fetal growth restriction among offspring of 2635 pregnant women according to caffeine intake during pregnancy

	Unadjusted risk*		Adjusted risk†	
Caffeine intake (mg/day)	Odds ratio (95% CI)	Test for trend	Odds ratio (95% CI)	Test for trend
Average over pregnancy:				
<100	1	P<0.001	1	P=0.02
100-199	1.2 (0.9 to 1.6)		1.2 (0.9 to 1.6)	
200-299	1.6 (1.2 to 2.3)		1.5 (1.1 to 2.1)	
≥300	1.8 (1.3 to 2.5)		1.4 (1.0 to 2.0)	
In weeks 5-12:				
<100	1	P<0.001	1	P=0.05
100-199	1.2 (0.9 to 1.6)		1.1 (0.8 to 1.5)	
200-299	1.4 (1.0 to 2.0)		1.3 (0.9 to 1.9)	
≥300	1.8 (1.3 to 2.5)		1.4 (1.0 to 1.9)	
In weeks 13-28:				
<100	1	P=0.001	1	P=0.02
100-199	1.5 (1.1 to 2.0)		1.4 (1.0 to 2.0)	
200-299	1.8 (1.3 to 2.6)		1.7 (1.2 to 2.4)	
≥300	1.6 (1.1 to 2.4)		1.3 (0.9 to 2.0)	
In weeks 29-40:				
<100	1	P<0.001	1	P=0.004
100-199	1.4 (1.0 to 1.9)		1.4 (1.0 to 2.0)	
200-299	1.9 (1.3 to 2.8)		1.8 (1.2 to 2.7)	
≥300	1.9 (1.3 to 2.8)		1.6 (1.0 to 2.4)	

*Unadjusted odds ratios take account of maternal age, weight, height, ethnicity, and parity and neonatal gestational age at delivery and sex.
†Adjusted odds ratios are also adjusted for smoking status (salivary cotinine concentration) and alcohol intake.



Relation between risk of fetal growth restriction and caffeine intake (mg/day) during pregnancy. The relation is modelled by the best fitting, second order, fractional polynomial, with 95% confidence intervals. The graph is restricted to <500 mg/day for clarity. Horizontal dotted lines mark national average risk of fetal growth restriction (10%) and average risk in study cohort (13%)

Pregnancy outcomes

We obtained information on antenatal pregnancy complications and delivery details from the electronic maternity databases. The primary outcome measure was fetal growth restriction defined as birth weight <10th centile on a customised centile chart which takes into account maternal height, weight, ethnicity, and parity and neonatal birth weight and sex (www.gestation.net). We assessed the association of maternal caffeine intake with birth weight. Other pregnancy outcomes studied were late miscarriage, preterm delivery, gestational hypertension, proteinuric hypertension, and stillbirth.

Statistical methods

From our sample size calculation, 3000 births were required to give 80% power to detect a difference of 30 mg/day in caffeine intakes between mothers with appropriate and growth restricted babies. Individual caffeine consumption was expressed in mg/day averaged over the whole pregnancy and for the individual trimesters. We conducted logistic regression modelling for fetal growth restriction and general linear modelling for birth weight, with stratification for the two maternity units. Maternal height, weight, ethnicity, and parity at booking and neonatal gestation at delivery and sex were taken into account in the definition of fetal growth restriction and were adjusted for in the model for birth weight. We made statistical adjustments for salivary cotinine levels and self reported alcohol consumption and conducted sensitivity analyses to assess the robustness of the results. From our caffeine challenge test we categorised women as having a shorter half life (faster caffeine clearance from the circulation) or longer half life (slower clearance). We stratified the odds ratio for fetal growth restriction by caffeine half life and intake after taking account of potential confounders. (See bmj.com.)

RESULTS

Over a period of three years, 13 071 eligible women were invited to participate and 2635 (20%) consented. See bmj.com for details of demographic and clinical characteristics. The prevalence of fetal growth restriction in the cohort was 343/2635 (13%). The mean alcohol intake during pregnancy was 0.4 (95% confidence interval 0 to 9) units/day, with the highest consumption occurring before conception and during the first four weeks of pregnancy.

Caffeine intake during pregnancy

The mean maternal caffeine intake during pregnancy was 159 mg/day. It decreased from 238 mg/day before pregnancy to 139 mg/day between weeks 5 and 12 of pregnancy and remained at about this level until the third trimester, when it gradually increased to 153 mg/day. About 62% of the caffeine ingested by the women during pregnancy was from tea. Other important sources were coffee (14%), cola drinks (12%), chocolate (8%), and soft drinks (2%). Hot chocolate, energy drinks, and alcoholic drinks contributed 2%, 1%, and <1% respectively. Over the counter drugs made a negligible contribution to the total caffeine intake.

Relation between caffeine intake in pregnancy and fetal growth

The relation between total caffeine intake in pregnancy and fetal growth restriction showed a significant trend with increasing caffeine intake (table). Caffeine consumption of >200 mg/day during pregnancy was associated with a reduction in birth weight of about 60-70 g, with a significant trend for greater reduction in birth weight with higher caffeine intake (P=0.004). This relation was consistent across all three trimesters.

We analysed the relation between the estimated risk of delivering a growth restricted fetus and maternal caffeine intake during pregnancy measured as a continuous variable (figure). There was a rapid increase in associated risk from increasing caffeine intake up to about 30 mg/day. Thereafter, estimated risk continued to rise roughly linearly in a dose-response relation. At no point did the estimated risk cease to increase with increasing caffeine intake. There was no observed plateau effect.

Relation between caffeine clearance and fetal growth

Using maternal caffeine half life as a proxy for clearance rate, we found some evidence that the association between caffeine intake and fetal growth restriction was stronger in women with a faster caffeine clearance than in those with slower clearance (test for interaction, P=0.06).

Relation between smoking in pregnancy and fetal growth

Women classified as active smokers had nearly twice the risk of fetal growth restriction compared with women classified as non-smokers (adjusted odds ratio 1.9 (95% confidence interval 1.4 to 2.6), P<0.001). The birth weights of babies born to active smokers were

178 g lighter (95% confidence interval 127 to 230 g) than those born to non-smokers (P<0.001).

DISCUSSION

Maternal caffeine intake was associated with an increased risk of fetal growth restriction even after adjustment for smoking and alcohol intake. We could find no level of intake at which there was no association with increased risk of fetal growth restriction. The size of the association for caffeine was of a similar size to that for alcohol intake in pregnant women in this study (data not shown).

The strong association between caffeine intake and birth weight was maintained across all of the trimesters. However, from these results we cannot define a critical time window for any maximal effect.

Strengths and weaknesses of the study

Although only 20% of the women we invited took part in the study, this low response rate does not lessen the validity of our data, as the association of caffeine with birth weight should not be different from that in the general population, especially as various confounders were taken into consideration. In addition, examination of our maternity databases indicated that the population we studied was similar to that of the maternity units as a whole.

A strength is that we have objectively quantified caffeine from all known sources. Since 26% of caffeine intake in our cohort was from neither coffee nor tea, studies that concentrated on coffee and tea alone will underestimate caffeine intake.

Study results in comparison with other studies

Caffeine consumption almost halved in early pregnancy. The mean caffeine intake throughout pregnancy was much lower than the recommended limit of 300 mg/day.[15 16]

WHAT IS ALREADY KNOWN ON THIS TOPIC

Caffeine is the most common xenobiotic consumed in pregnancy, and there are conflicting results regarding the association of increased caffeine intake in pregnancy with fetal growth restriction and low birth weight

These differences could be explained by inconsistencies in accurate quantification of caffeine and in the definition of fetal growth restriction

WHAT THIS STUDY ADDS

Maternal caffeine intake is associated with an increased risk of fetal growth restriction after adjustment for smoking and alcohol intake

The size of the association for caffeine intake with fetal growth restriction is similar to that for alcohol intake

The association of caffeine with fetal growth restriction seems to be stronger in women with faster caffeine clearance

Sensible advice to pregnant women would be to reduce caffeine intake before conception and during pregnancy

Several studies have concluded that caffeine intake of >300 mg/day is associated with low birth weight or fetal growth restriction.[6-8] We could find no level of intake at which there was no association with increased risk of fetal growth restriction, and this risk was maintained throughout pregnancy. However, the steep decline in risk associated with caffeine intakes of <30 mg/day may be attributable to unmeasured confounding. Although, the overall size of the reduction in birth weight may be seen as small, an extra 60-70 g in weight could reduce perinatal morbidity and mortality in an already compromised fetus.

We found that average caffeine consumption of >100 mg/day was associated with a reduction in birth weight of 34-59 g in the first trimester, 24-74 g in the second, and 66-89 g in the third (after adjustment for smoking status and alcohol intake). Similar results were seen in a prospective US study, where mean birth weight was reduced by 28 g for every 100 mg/day of caffeine consumed, but the risk for fetal growth restriction was unchanged.[17]

In a cohort of Danish women drinking at least three cups of coffee a day before 20 weeks of pregnancy and randomised to receive either caffeinated or decaffeinated instant coffee there was no significant difference in birth weight between the two groups.[18] However, these women were recruited only in the second half of pregnancy, and there was no biochemical confirmation of participants' compliance. No association was found between maternal caffeine consumption and low birth weight after adjusting for confounding variables in a case-control study in Brazil.[19]

Caffeine metabolism

We complemented our assessment of caffeine intake with a measure of caffeine metabolism and observed that the association of caffeine intake with fetal growth restriction was greater among women with faster caffeine clearance. Caffeine is primarily metabolised in the human liver to paraxanthine, but there are few data about metabolism in pregnant women. (See bmj.com for further discussion.)

Conclusion

This study has demonstrated that maternal caffeine intake is associated with an increased risk of fetal growth restriction. Our data confirm that the association of fetal growth restriction with caffeine is reduced for those consuming <100 mg/day. We suggest that sensible advice for women contemplating pregnancy is to reduce their caffeine intake from all sources before conception. Once pregnancy is confirmed, they should make every effort to stop or markedly reduce caffeine consumption.

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Drug use in children: cohort study in three European countries

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ABSTRACT

Objective To provide an overview of drug use in children in three European countries.

Design Retrospective cohort study, 2000-5.

Setting Primary care research databases in the Netherlands (IPCI), United Kingdom (IMS-DA), and Italy (Pedianet).

Participants 675 868 children aged up to 14 (Italy) or 18 (UK and Netherlands).

Main outcome measure Prevalence of use per year calculated by drug class (anatomical and therapeutic). Prevalence of "recurrent/chronic" use (three or more prescriptions a year) and "non-recurrent" or "acute" use (less than three prescriptions a year) within each therapeutic class. Descriptions of the top five most commonly used drugs evaluated for off label status within each anatomical class.

Results Three levels of drug use could be distinguished in the study population: high (>10/100 children per year, moderate (1-10/100 children per year), and low (<1/100 children per year). For all age categories, anti-infective, dermatological, and respiratory drugs were in the high use group, whereas cardiovascular and antineoplastic drugs were always in the low use group. Emollients, topical steroids, and asthma drugs had the highest prevalence of recurrent use, but relative use of low prevalence drugs was more often recurrent than acute. In the top five highest prevalence drugs topical inhaled and systemic steroids, oral contraceptives, and topical or systemic antifungal drugs were most commonly used off label.

Conclusion This overview of outpatient paediatric prescription patterns in a large European population could provide information to prioritise paediatric therapeutic research needs.

INTRODUCTION

Recent years have seen growing concerns about the incompleteness of the evidence relating to the efficacy and safety of drugs used in children. Almost all of the drugs prescribed to children are the same as those originally developed for adults. They are often prescribed on an unlicensed or "off label" basis (percentages ranging from 11-80%[1]) simply by extrapolating data for adults. Both the Food and Drug Administration (FDA) and the European Medicines Agency for the Evaluation of Medicinal Products (EMEA) now offer extensions of drug licences to companies who provide evidence concerning the efficacy and safety in children of new drugs or off label

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drugs.[2-5] We investigated the current use of paediatric drugs in children in three European countries, using population based data on primary care prescriptions.

METHODS

Data collection

We used the same protocol to study prescription patterns in three countries: the UK, Netherlands and Italy. We used the Pedianet database (paediatric electronic medical records from 150 paediatricians since 2000) in Italy, the integrated primary care information (IPCI) database (comprising adult and paediatric electronic medical records from more than 400 doctors since 1996) in the Netherlands, and the IMS disease analyser database (IMS-DA: electronic medical records on adults and children from 670 doctors) in the UK. All databases include the complete automated medical records of primary care physicians and have been used and proved valid for pharmacoepidemiological research.[6] The age and sex distribution in the various databases is representative for the country of origin.

Study population and drug prescriptions

The study population in each country consisted of all children aged 0-18 years (0-14 years in Italy) who had a database history of at least six months or who were born during the study period (1 January 2000 to 31 December 2005). We calculated the person time of follow-up for each child, stratified by calendar year and age group. Age was assessed on 1 January of each year and grouped as <2, 2-11, and 12-18. Each child was followed from the start of the study period or the date of registration with the primary practice (whichever was the latest) until the cancellation of registration with the practice or the end of the study. We used the person time accumulated in each calendar year as the denominator to calculate prevalence rates. Over the study period children could contribute to more than one age category. The drug prescriptions were grouped on the basis of the WHO Anatomical Therapeutic Chemical (ATC) classification system, which made comparison between countries possible.

Statistical analysis

We estimated user prevalence rates (per 1000 person years) by counting the number of children using a specific drug in a specific calendar year. The prevalence rates were calculated by age and country.

For each anatomical class of drug we assessed the age and country specific user prevalence rates for all individual drugs in 2005. We evaluated the five drugs with the highest prevalence per anatomical class in each country for off label status considering age only. A drug was considered to be off label for age if the child's age at the time of use was below the lowest approved age mentioned in the summary of product characteristics of that drug in each country.[7] We also identified the treatments more commonly used for chronic than acute paediatric diseases. See bmj.com.

RESULTS

Study population

Our population of 675 868 children generated 2 334 673 person years of follow-up; the mean individual follow-up was 3.5 years. Most of the children (66%) came from the IMS database in the UK, 19% from Italy, and 15% from the Netherlands. The databases recorded more than five million paediatric prescriptions. In all three countries the prescription rate was highest for the children aged under 2 and, in each age group, was significantly higher in the UK and Italy than in the Netherlands (P<0.001). See bmj.com.

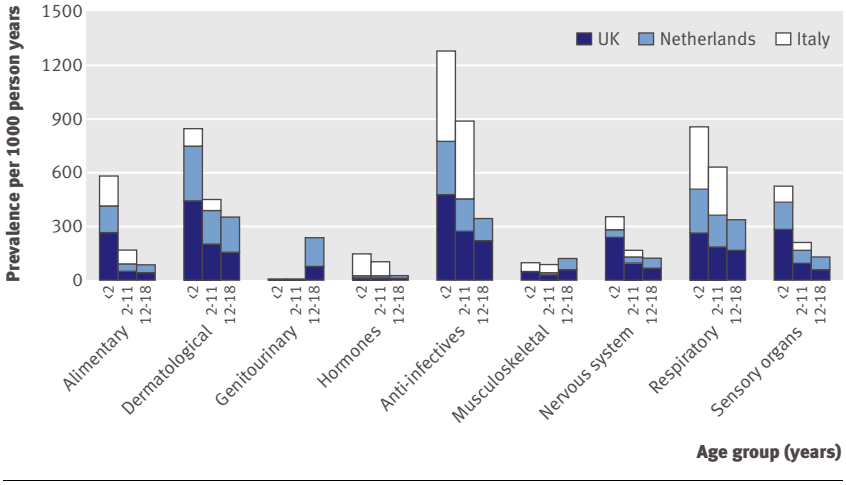
Drug use by anatomical class

The highest prevalence rates among the children aged under 2 were for anti-infective drugs, respiratory drugs, and dermatological drugs, which were used by 48%, 30%, and 30% of the children, respectively. Among the children aged 2-11, the prevalence of use of anti-infective, respiratory, and dermatological drugs decreased to 30%, 21%, and 17%, respectively.

In adolescents (12-18 years), anti-infective, respiratory, and dermatological drugs were used by more than 10% per year. Most of the other drug classes were used by 1-10%, but the prevalence of use of cardiovascular and antineoplastic drugs was less than 1%.

In the youngest age groups, most of the drugs were equally prescribed to both sexes or more commonly prescribed to boys than girls (rate ratio <1). This pattern reversed in adolescence, when user prevalence for almost all drug classes (except non-sex hormones) was higher among girls than boys. This sex pattern, which was consistent across countries, was most pronounced for genitourinary drugs, with a user prevalence more than 60 times higher in girls because they include oral contraceptives, which accounted for 95% of the use of genitourinary drugs in girls.

The age trend of prevalence of use was consistent across countries, although there were some variations



Year prevalence of drug use (per 1000 person years) by age (<2, 2-11, 12-18), country, and anatomical class for most prevalently used drug classes (data for Italy excluded age category 12-18)

in the age specific rates (figure). See bmj.com for details.

Prevalence of drug use in therapeutic class

Within the most commonly used anatomical drug classes, antibacterial drugs accounted for most of the anti-infective drug use; and the therapeutic classes, antiasthmatic drugs, other respiratory products, and nasal preparations were the most commonly used drugs in the respiratory group. The therapeutic classes with the highest prevalence of use among the dermatological drugs were topical corticosteroids and emollients and barrier creams.

When we ranked the therapeutic classes within each anatomical class on the basis of the ratio between recurrent (chronic) and non-recurrent (acute), we observed a different pattern. In absolute terms, emollients, topical corticosteroids, sex hormones, anti-infectives, and drugs for obstructive airways disease showed the highest prevalence of recurrent use.

Most commonly used off label drugs in each anatomical class

Among the dermatological drugs the topical triazoles/imidazoles were off label in most countries for at least one or more age categories. In the anti-infectives group cefalexin (UK, <2 years) was the only off label drug. Among the respiratory drugs, beclometasone, xylometazoline, and cetirizine were off label in the youngest children (<2 years) in the UK and the Netherlands.

Among the most commonly prescribed alimentary tract drugs ranitidine and laurilsulfate were off label in children <2 years. For the genitourinary drugs, the percentage of off label use of oral contraceptives and antifungals was high in the Netherlands and the UK. Among drugs for the nervous system, diazepam for children under 12 in the Netherlands was off label. In the group of sensory organ drugs the most commonly prescribed drugs in the Netherlands (fusidic acid, levocabastine) and the UK (chloramphenicol) were off label. See bmj.com for details of the low prevalence drugs that are off label.

DISCUSSION

We have provided a unique overview of primary care prescription patterns in a large multinational European paediatric population. The data could be used to improve the prioritisation of research into long term safety of paediatric drugs, as well as efficacy and effectiveness studies in paediatric medicine. Off label use in some of the most commonly and recurrently used drugs is high (such as oral contraceptives) and these should be considered for prioritisation.

Our data support the conclusions of the recently published EMEA consensus/expert derived list of research priorities concerning off patent medicinal products,[8] which emphasised the need for paediatric studies of the safety of topical, systemic, and inhaled steroids. EMEA also lists topical and systemic antifungals, acid reducing drugs, and antineoplastic drugs as research priorities. These drugs are often or recurrently used and are mostly off label. Sex hormones are not listed on the priority list, whereas they are commonly and recurrently prescribed, mostly off label. Further studies on the efficacy and long term safety effects of these drugs in young women are warranted.

Although patterns of drug use and labelling status can inform decisions on prioritisation of research, these data also inform us about suboptimal use and might even uncover undesirable prescribing practices. For example, fusidic acid and chloramphenicol are often used and often off label for the treatment of conjunctivitis. Here the emphasis should be on educating clinicians not to prescribe rather than a call for more research.

Patterns of drug use

The percentage of off label use varied highly between countries, and similar drugs differed in off label status between countries. This confirms that the differences in the paediatric status of the drugs, instead of the different prescription habits or medical cultures as postulated by many authors, represent the real reason for the variability reported by years and from many European studies and surveys on the off label use in children.[9]

Previous studies

Previous European studies have been country or region specific and have concentrated on specific conditions, except for studies from Sweden, the Netherlands, and Denmark in the late 1990s and a recent Italian study covering data from 2000-6.[10-13] These studies took all types of drugs into account but the methods to calculate prevalence and ranking and age ranges varied largely, which complicates direct comparisons. The overall results—highest drug use in lowest age category, ranking of the most commonly used drugs, and sex pattern are consistent with our findings.[10 14 15]

WHAT IS ALREADY KNOWN ON THIS TOPIC

Most previous research on drug use in children has focused on specific high use areas such as antibiotics and respiratory and neuropsychiatric drugs, therefore most of these drugs have a paediatric licensing status

Paediatric expert groups have been established by the European Medicines Evaluation Board (EMEA) to identify those drugs that are important for the paediatric community and that require additional efficacy and safety data

WHAT THIS STUDY ADDS

Data on frequency of prescriptions and off label status of drugs could provide objective evidence for the prioritisation of research in paediatric drugs

Information on the safety and efficacy of some of the most commonly used drugs in children (such as oral contraceptives, steroids, and triazoles/imidazoles) is lacking, and not all such drugs are on the list of research needs

Limitations

We captured only outpatient, primary care drug prescriptions and not use of over the counter drugs. Drugs given in hospital and the monitoring of chemotherapeutic and biological drugs are unlikely to be fully captured by our databases. As the UK accounted for 60% of the study population the pooled results are dominated by UK prescription patterns so we conducted stratified analyses as much as possible. Finally, we studied drug prescriptions rather than drug intake, and so the prevalence of actual drug exposure might be lower than estimated here.

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Test, episode, and programme sensitivities of screening for colorectal cancer as a public health policy in Finland: experimental design

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ABSTRACT

Objectives To report the sensitivities of the faecal occult blood test, screening episode, and screening programme for colorectal cancer and the benefits of applying a randomised design at the implementation phase of a new public health policy.

Design Experimental design incorporated in public health evaluation using randomisation at individual level in the target population.

Setting 161 of the 431 Finnish municipalities in 2004-6.

Participants 106 000 adults randomised to screening or control arms. In total, 52 998 adults aged 60-64 in the screening arm received faecal occult blood test kits.

Main outcome measures Test, episode, and programme sensitivities estimated by the incidence method and corrected for selective attendance and overdiagnosis.

Results The response for screening was high overall (70.8%), and significantly better in women (78.1%) than in men (63.3%). The incidence of cancer in the controls was somewhat higher in men than in women (103 *v* 93 per 100 000 person years), which was not true for interval cancers (42 *v* 49 per 100 000 person years). The sensitivity of the faecal occult blood test was 54.6%. Only a few interval cancers were detected among those with positive test results, hence the episode sensitivity of 51.3% was close to the test sensitivity. At the population level the sensitivity of the programme was 37.5%.

Conclusions Although relatively low, the sensitivity of screening for colorectal cancer with the faecal occult blood test in Finland was adequate. An experimental design is a prerequisite for evaluation of such a screening programme because the effectiveness of preventing deaths is likely to be small and results may otherwise remain inconclusive. Thus, screening for colorectal cancer using any primary test modality should be launched in a public health programme with randomisation of the target population at the implementation phase.

Sensitivities in Finnish screening programme for colorectal cancer, 2004-6

Indicator (%)	Men	Women	Total
Test sensitivity	61.8	47.8	54.6
Episode sensitivity	57.1	45.8	51.3
Programme sensitivity	39.0	36.0	37.5

INTRODUCTION

Screening for colorectal cancer using the faecal occult blood test has been shown to reduce mortality in four randomised screening trials,[1-4] but effectiveness at reducing mortality has not been shown routinely within a public health policy. Finland started an organised screening programme for colorectal cancer in 2004, with individuals randomised at implementation of the programme. Although the effect on mortality will not be known for several years we monitored the programme using intermediate indicators. We estimated the sensitivity of screening in identifying unrecognised disease at the level of the faecal occult blood test, screening episode, and programme. We also determined the benefits of the experimental design using randomisation at the implementation phase.

METHODS

The screening programme was started in September 2004 in 22 volunteer municipalities. Randomisation at individual level into screening and control groups was done at the first screening round, in adults aged 60, 62, and 64. By 2006, the programme covered 161 of the 431 municipalities in Finland.

The population was sampled through the Population Register Centre, which keeps records and personal identifiers on every Finnish citizen. After sampling from the population register, people were stratified into groups according to municipality, year of birth, and sex. Within each group participants were alternately randomly allocated to screening or control groups. Those in the screening arm were invited to respond by post; those in the control arm were identified but not contacted.

A national screening centre was established in Tampere at the local cancer society to deal with the invitations, responses, and recommendations for referrals and to analyse the faecal samples. Faecal occult blood test kits (Hemoccult; Beckman Coulter, USA) were posted to those offered screening along with an invitation to the programme and advice on taking the sample. The centre analysed the kits and posted the findings to the respondents independently of the result. If blood was detected in the sample, the respondent was given the contact details of their health centre. Simultaneously, a letter was sent to the health centre for colonoscopy to be arranged.

The aim of screening for cancer is to detect the disease in the preclinical (unrecognised) phase. We estimated sensitivity at the level of the test, screening episode, and programme.[5] Test sensitivity measures how well the test identifies the disease in the preclinical phase, episode sensitivity also takes into account the diagnostic confirmation after a positive test result, and programme sensitivity indicates the proportion of patients with cancers in the target population detected by screening. We corrected each of these estimates for bias caused by overdiagnosis and selective attendance.[5] (See bmj.com for formulas used to determine sensitivities.)

We estimated sensitivity using the incidence method.[6] No direct observation of the disease in the detectable preclinical phase is available, and therefore estimates were based on the failure of screening. To estimate the proportion of false negative test results we measured failure by the incidence of interval cancer (incidence of colorectal cancer between two screening rounds) and compared this with the incidence of colorectal cancer in the control arm and in non-responders.

We estimated the incidence rates for people invited to take part in the first round of screening and for controls from 2004-6. Follow-up was through routine measures by the cancer registry. The latest linkage was in June 2008, when cancers diagnosed in 2007 had almost been reported to the registry. Follow-up started from the date of random sampling, including linkage of postal addresses. Follow-up ended at the date of the next (second round) linkage of addresses, the date of diagnosis of colorectal cancer, or 31 December 2007 (latest date with follow-up for cancer), whichever came first. Screening is offered every second year, but owing to differences between municipalities, the first screening interval varied between 1.5 and 2.7 years. In case linkage for the second round had not been done by the end of 2007 (those in the first round in 2006), the follow-up ended on 31 December 2007. In addition, 2461 people missed the second round and therefore, for these individuals follow-up ended after two years. We recorded the number of colorectal cancers diagnosed during follow-up. Patients with colorectal cancer already diagnosed before random sampling or at the first screen and those with a date of diagnosis as the month of random sampling did not contribute to follow-up time in the analysis. We excluded from the estimation of incidence of interval cancer, patients with cancer but no follow-up time and screen detected cancers.

RESULTS

Overall, 106 000 adults were randomised in 2004-6: 52 998 to screening and 53 002 to the control arm (see

bmj.com). Attendance was 70.8%, better in women than in men (78.1% *v* 63.3%). Of 806 people with a positive test result 65 had a diagnosis of cancer (see bmj.com). During a mean follow-up of 1.9 years, 35 interval cancers and 26 cancers in non-responders were diagnosed (see bmj.com). Of the interval cancers, 32 were in people who tested negative and three in those who tested positive but with a negative colonoscopy result. The number of colorectal cancers diagnosed in the control population was 98 during a mean follow-up of 1.9 years.

Incidence of colorectal cancer in the control population was 98 per 100 000 person years and the incidence of interval cancer in those with a negative result at first screening episode was 49 per 100 000 person years (see bmj.com). About every second case of colorectal cancer in the preclinical phase was identified by the test (test sensitivity 54.6%; table). The incidence of cancer in the controls was somewhat higher in men than in women (103 *v* 93 per 100 000 person years), which was not true for interval cancers (42 *v* 49 per 100 000 person years). Only three interval cancers were diagnosed among those with a positive test result but no cancer at colonoscopy. Therefore episode sensitivity at 51.3% was close to test sensitivity. Despite a high attendance rate programme sensitivity remained low (37.5%).

DISCUSSION

We found high attendance in the screening programme for colorectal cancer that was run as a public health policy in Finland. The faecal occult blood test was able to detect a major proportion (55%) of cancers in the detectable preclinical phase and more than one third (38%) in the total target population.

With screening every two years using the faecal occult blood test the reduction in mortality from colorectal cancer varies between 25% at 18 years[7] and 12% at eight years.[4] In one trial with a follow-up of 18 years, a 20% reduction in incidence of colorectal cancer was also seen.[8] Several organisations therefore recommend screening for colorectal cancer as a public health policy.[9] Finland was, to the best of our knowledge, the first country to start a national screening programme.

Public health policies that include screening are generally evaluated by non-experimental means. Such approaches are likely to result in inconclusive evidence, especially if the effect is expected to be small.[10] Therefore a sensitive and unbiased design including randomisation at the implementation phase of the programme was chosen in Finland.[11]

We investigated the sensitivity of the colorectal cancer screening programme at the level of the faecal occult blood test, screening episode, and programme. Traditionally, sensitivity has been regarded as an indicator of the test.

Test sensitivity and episode sensitivity could be expected to be identical, because colonoscopy is considered the ideal investigation in the diagnosis of colorectal cancer. This was not true, however, even if the sensitivities were close (54.6% and 51.3%). Experts in many countries expressed concern about sufficient capacity for colonoscopy from routine screening with the faecal occult blood test.[12] This was not a problem as the 2% test positivity rate did not radically increase the need for resources. Instead, proper targeting may reduce the number of unnecessary colonoscopies in the future.

The response rate in Finland was relatively high (70.8%), especially in women (78.1%). The sensitivity of the programme remained low, however, at 37.5%, similar in both sexes. It has been proposed that screening in women should be started at an older age than in men to give a similar yield.[13]

Limitations

Follow-up in this study was for a mean 1.9 years, slightly less than one full screening interval. As reliable data on cancer incidence were available only until the end of 2007, some people randomised in 2006 were followed-up for only part of the full interval at the end of follow-up in December 2007. However, the mean follow-up time for those starting in 2006 was 1.7 years. If anything, the completed follow-up data up to two years is likely to show a decrease rather than an improvement in the sensitivity estimates, since the incidence of interval cancer in the first interval is at its highest close to the second round.

Not all cancers diagnosed in Finland in 2007 had been reported to the cancer registry by the time of linkage in June 2008. We estimated the number of possible missing cases from the first screening round by comparing data on screen detected cases from the screening centre with the files of the cancer registry. No cases of colorectal cancer were unknown to the registry from the first screening round in 2004-6, with diagnostic confirmation done by the end of 2007.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised controlled trials using faecal occult blood tests to screen for colorectal cancer have shown a reduction in mortality in those invited compared with controls

Several countries have started screening, many as spontaneous activity or non-organised screening

Many organisations recommend screening through public programmes although no conclusive evidence on their effectiveness is available

WHAT THIS STUDY ADDS

Four of 10 cases of colorectal cancer were detected by a public screening programme in Finland

This programme provides a model on how to implement a new screening programme using the principles of experimental design with randomisation to obtain conclusive evidence on effectiveness

Implications

The sensitivity of the Finnish screening programme at the first round was adequate even if relatively low. Two trials reported episode sensitivities only,[1 3] at 49.5% and 44.2%. Although the analyses of those trials are not comparable with ours, it seems that our episode (and test) sensitivities are slightly higher than those from the trials in the United Kingdom and Denmark.

A rigorous design is a prerequisite for evaluating the process and the effectiveness of the programme on the number of deaths prevented from colorectal cancer. Thus routine primary screening for colorectal cancer should only be launched as an organised programme, including randomisation at the implementation phase.

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Diogenes syndrome

Diogenes syndrome, otherwise known as senile self neglect syndrome, is used to describe an older adult living in squalor but with no sign of mental or cognitive impairment sufficient to explain the self neglect. Some commentators have written that the squalor and hoarding are just signs of obsessive-compulsive disorder, dementia, or other mental disorder, but most workers in older adult psychiatry will have seen plenty of cases with no explanatory psychiatric disorder.

Alternatively, Diogenes syndrome may simply be a description of a social situation. This would fit with my impression that referrals for Diogenes syndrome have tailed off since reality television programmes started showing celebrity cleaning ladies helping "normal" people living in squalor. Age seems to be a factor: perhaps it is a sign of our paternalistic culture that a person younger than 65 living in squalor is seen by millions on television, whereas those past the age of 65 are seen by a psychiatrist.

The title Diogenes syndrome, proposed in Clark and others' original study from 1975,[1] is at least as controversial as the condition itself. There were at least four philosophers of note with that name, but the syndrome is named after Diogenes of Sinope, who famously lived in a barrel. Clark et al gave a potted biography of Diogenes but did not spell out exactly why they chose to name the condition after him. The *Oxford Textbook of Older Age Psychiatry* has described the name as "inept," and the latest edition gives alternatives better suited to describing the squalor.[2]

If we think of Diogenes syndrome purely in terms of housekeeping, then the label does seem presumptuous. Diogenes supplied his day to day needs by begging and had an unconventional home, but for all we know he may have kept the barrel spick and span, dusting obsessively while pondering the mysteries of the universe.

There is, however, another aspect to the Diogenes story. Diogenes helped found the Cynic movement, which preached a defiance of social conventions. Clark et al's biography does mention en passant that Diogenes was renowned for his "lack of shame" and "contempt for social organisation." It is said that Alexander the Great went to meet Diogenes and asked him if there was anything he could do for him. Diogenes squinted at the most powerful man in the ancient world and replied yes, could he move over a bit as he was blocking the philosopher's sunlight.

This side of the Diogenes story will strike a chord with many psychiatrists who find themselves caught between angry relatives, bewildered social workers, and an independent older adult contemptuous of a society obsessed with risk. Perhaps a syndrome deserves to be named after Diogenes after all, not to emphasise the dirt or neglect, but rather in celebration of frail elderly people who choose to cock a snook at doctors, social workers, and a society that tries to tell them what to do with their lives just because of their age. Diogenes, by the way, lived to a ripe old age.

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