Papers

Population based study of risk factors for underdiagnosis of asthma in adolescence: Odense schoolchild study

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Abstract

Objective: To describe factors related to underdiagnosis of asthma in adolescence.

Design: Subgroup analysis in a population based cohort study.

Setting: Odense municipality, Denmark.

Subjects: 495 schoolchildren aged 12 to 15 years were selected from a cohort of 1369 children investigated 3 years earlier. Selection was done by randomisation (n = 292) and by a history indicating allergy or asthma-like symptoms in subject or family (n = 203).

Main outcome measures: Undiagnosed asthma defined as coexistence of asthma-like symptoms and one or more obstructive airway abnormalities (low ratio of forced expiratory volume in 1 second to forced vital capacity, hyperresponsiveness to methacholine or exercise, or peak flow hypervariability) in the absence of physician diagnosed asthma. Risk factors (odds ratios) for underdiagnosis.

Results: Undiagnosed asthma comprised about one third of all asthma identified. Underdiagnosis was independently associated with low physical activity, high body mass, serious family problems, passive smoking, and the absence of rhinitis. Girls were overrepresented among undiagnosed patients with asthma (69%) and underrepresented among diagnosed patients (33%). Among the risk factors identified, low physical activity and problems in the family were independently associated with female sex. The major symptom among those undiagnosed was cough (58%), whereas wheezing (35%) or breathing trouble (50%) was reported less frequently than among those diagnosed. Less than one third of those undiagnosed had reported their symptoms to a doctor.

Conclusions: Asthma, as defined by combined symptoms and test criteria, was seriously underdiagnosed among adolescents. Underdiagnosis was most prevalent among girls and was associated with a low tendency to report symptoms and with several independent risk factors that may help identification of previously undiagnosed asthmatic patients.

Introduction

Epidemiological surveys have shown asthma-like symptoms to be far more prevalent than physician diagnosed asthma,[1] and underdiagnosis of asthma has repeatedly been suspected during the past two decades, especially in children and young adults.[2 3] Screening studies that used a combination of symptoms and objective indicators of asthma have confirmed this view.[4–6] In the present cohort children who reported asthma-like symptoms but not asthma at age 10 had impaired lung function.[7]

Some risk factors for the underdiagnosis of asthma have recently been proposed, including female sex,[6 8] low socioeconomic status,[9] or belonging to an ethnic minority,[10] whereas the diagnostic process seems to be facilitated if previous episodes of acute bronchitis or a family history of asthma are reported.[6]

This population based study examined a broad selection of potential risk factors for underdiagnosis of asthma among adolescents with coexisting asthma-like symptoms and obstructive airway abnormalities.

Subjects and methods

The Odense schoolchild study is a prospective multidisciplinary epidemiological study in a community based cohort of 1369 schoolchildren first investigated during their third school year in 1985-6.[11] The present analysis is based on data from 495 children aged 12 to 15 years and of Danish origin recruited from the original cohort for an extensive asthma and allergy screening programme. Subjects were selected either at random (n = 292) or on the basis of a history indicating asthma, allergy, or related symptoms or a family history of asthma or allergic rhinitis (n = 203).[12] Subjects completed a comprehensive questionnaire and monitored their peak expiratory flow twice daily for 2 weeks. Laboratory examinations included anthropometric measurements, puberty staging, spirometry, treadmill exercise testing, and provocation with inhaled methacholine. Subjects were asked to stop taking bronchodilators (but not inhaled steroids) before testing. Informed consent was obtained from all children and parents or guardians before participation. The study was approved by the local research ethics committee, the local school board, and the Danish Data Surveillance Authority.

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For the present analysis, currently symptomatic subjects were grouped according to the presence or absence of physician diagnosed asthma and positive test results. The variables analysed are listed in the box. Current asthma-like symptoms (ongoing or within the previous year) were identified by questionnaire as previously reported.[12] Symptoms accepted included non-infectious cough, wheezing, and trouble breathing. Physician diagnosed asthma was identified by an affirmative answer to the question, "Is it your doctor's opinion, that you have asthma?" or the use of prescribed asthma medication, or both. Subjects with no previous diagnosis of asthma but asthma-like symptoms and at least one positive test result (hypervariability in peak expiratory flow, hyper-responsiveness to exercise or inhaled methacholine, or low ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC)) were labelled as having undiagnosed asthma.

Details of test procedures have been reported previously.[12] The body mass index (weight (kg)/(height (m)^2)) was also calculated. Puberty staging was done according to Tanner and Whitehouse[13] and corrected for age by sex. Forced expiratory volumes were measured according to European recommendations.[14] For the 6 minute treadmill provocation test results were expressed as the lowest FEV_1 obtained during the first 10 minutes after exercise in percentage of the best value before exercise. Bronchoprovocation with methacholine was performed according to Yan et al[15] and expressed as the methacholine dose response slope.[16] It was ensured that all subjects regained their baseline FEV_1 (within 10%) either spontaneously or aided by inhaled terbutaline (Bricanyl Turbohaler). Peak expiratory flow was recorded twice daily for 14 consecutive days with a Mini-Wright adult type peak flow meter. Variability in peak expiratory flow was expressed as the average of the two lowest values as a percentage of the period mean, after the first three recording days were discarded (the two lowest % mean index).[17] Test results were considered abnormal if they were beyond the value delimiting the 5% "most asthmatic" part of the test distribution in 150 asymptomatic, non-smoking, and non-asthmatic reference subjects from the randomly selected part of the present cohort. The association of a range of medical, environmental, social, school, and activity related factors (see box) with undiagnosed versus diagnosed asthma and with asthma versus asthma-like symptoms only was assessed by logistic regression with SPSS.[18]

Variables that seemed to be differently distributed (P<0.15) between the groups compared were included in the logistic regression analysis by using backward selection (final removal criterion P>0.05). Questionnaire information and test results directly related to grouping criteria were not included in the regression models but were analysed separately. The Medstat program (Astra Denmark, Copenhagen) was used to calculate 95% confidence intervals on proportions. Proportions were compared with χ^2 statistics with Yates's correction.

Results

Among 495 subjects investigated, 128 had current asthma-like symptoms. Of these, 15 (12%) were excluded from analysis because of missing data for

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Variables analysed

Anthropometric and related measurements
Sex
Puberty stage
Standing height
Sitting height/standing height
Body mass index
Diastolic blood pressure
Systolic blood pressure

Questionnaire information at age 10
Birth weight
Dyspnoea (nights or mornings)
Wheezing or cough on exertion
Bronchitis (explained)
Eczema at elbows or knees (explained)

Questionnaire information at age 13
Family and home environment:
　Number of subjects sharing home
　Number of children <15 years
　Serious family problems
　Living with father/male guardian
　Passive smoking (hours/day)
　Active smoking
　Type of home (house or apartment)
　Size of home
　Age of building
　Pet in bedroom
　Carpets in bedroom
　Signs of high humidity in home
School environment:
　Inner city school
　Distance to school
　Absence with illness (days)
　Happy with school
　Bad indoor environment
Activities:
　Physical activity (hours per week)
　Sitting down more than half of spare time
　Given up job due to health problem
　Given up sport due to health problem
　Biking to school
Allergy: history and test:
　Predisposition for asthma, hay fever, or eczema
　Colic in first year of life
　Frequent diarrhoea in first year of life
　Passive smoking in first year of life
　Pets at home in first year of life
　Breast feeding time (months)
　Eye itching
　Serial sneezing (≥ 3)
　Watery nasal secretion
　Eczema ever (explained)
　Urticaria (explained)
　Diet restrictions (allergy/intolerance)
Frequency of extrarespiratory symptoms:
　Headache
　General indisposition
　Unprovoked articular pain
　Stomach ache
　Diarrhoea

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group allocation. Forty five had physician diagnosed asthma, and 26 were considered as having undiagnosed asthma. The 42 remaining subjects had "symptoms only" (negative test results and not diagnosed with asthma). Despite the "normalising" effect of treatment with inhaled steroids on test results,[12] the sensitivity of the test battery for symptomatic physician diagnosed asthma was high (87%). The proportion of undiagnosed asthmatic sub-

Table 1 Unadjusted associations of selected risk factors with undiagnosed asthma as opposed to asthma diagnosed by doctor

Risk factor and categories	Mean* or proportion in subjects with asthma	Odds ratio	P value
Sex (female v male)	33/71	4.50	0.005
Body mass index† (per kg/m²)	19.9*	1.24	0.03
Systolic blood pressure (per mm Hg)	116*	1.04	0.07
Symptoms on exercise at 10 years (any v none)	22/61	0.12	0.008
Problems in family† (severe v trivial)	6/70	3.82	0.14
Living with father (yes v no)	56/70	0.36	0.09
Passive smoking† (per hours/day)	2.3*	1.46	0.005
Type of home (apartment v house)	11/70	3.68	0.06
Pet in bedroom (yes v no)	30/71	2.11	0.14
Carpets in bedroom (yes v no)	46/71	7.33	0.004
Physical activity† (per hours/week)	9.0*	0.86	0.004
Spare time spent sitting (more v less than half)	18/71	5.57	0.004
Given up sport (yes v no)	21/64	0.39	0.12
Biking to school (yes v no)	53/69	12.4	0.02
Diarrhoea before age 1 (frequent v none)	12/69	0.12	0.05
Itching eyes (yes v no)	39/70	0.25	0.008
Serial sneezing† (yes v no)	33/70	0.14	0.0007
Watery nasal secretion (yes v no)	26/70	0.12	0.002
Diet restrictions (yes v no)	26/70	0.36	0.07
Headache (monthly) (yes v no)	24/71	2.36	0.10
Stomach ache (monthly) (yes v no)	21/71	2.57	0.08

*N=62 for passive smoking, ≥69 for other continuous variables.
†Included in final model (see table 2).

jects among all asthmatic subjects (36.6%) did not differ significantly between subjects selected randomly or by history. The prevalence of any positive test result among 256 non-asthmatic subjects in the random group was 16.0% (not significantly different from the expected value $1-(0.95)^4=18.5\%$ for four independent tests), and the symptom prevalence was 12.1%. Thus, about eight subjects (16% of 12% (1.9%) of 435 subjects with no previous diagnosis of asthma) may have been misclassified as having asthma by chance. After correction for this the proportion of asthmatic patients not previously diagnosed was 29% $(18/(18+45))$.

Undiagnosed versus diagnosed asthma

Individual regression data for the 21 variables selected for logistic regression are shown in table 1. Adjusted odds ratios for independently contributing risk factors are given in table 2. Undiagnosed asthma was independently associated with self reported problems in the family ("we have very stressful problems in our family" (highest of three levels)), daily exposure to environmental tobacco smoke ("for how many hours a day are you usually exposed to indoor tobacco smoking"), low physical activity ("state average number of hours a week spent with physical activities"), high body mass index, and the absence of serial sneezing ("attacks of more than three consecutive sneezes")). No significant interactions between these factors were found.

Among those with diagnosed asthma only 33% (95% confidence interval 20% to 49%) were girls compared with 69% (48% to 86%) among those undiagnosed (P=0.007). The sex distribution was about neutral in the "symptoms only" group (52%

(36% to 68%) girls) and in the reference group (45% (37% to 54%) girls). A negative association was found between female sex and physical activity (odds ratio 0.91 (0.84 to 1.00) per hours/week, $\chi^2=4.12$, df=1, P=0.04, n=59), whereas female sex and problems in the family were positively associated (14.8 (1.0 to 220), $\chi^2=3.97$, df=1, P=0.05, n=59).

Cough was equally prevalent among diagnosed (58%) and undiagnosed subjects (58%), but the latter group reported less breathing trouble (50% v 100%, P<0.001) and wheezing (35% v 96%, P<0.001). Among undiagnosed subjects only 31% had reported any asthma-like symptom to a doctor. Subjects with diagnosed asthma had a significantly higher response to inhaled methacholine than did undiagnosed subjects with asthma (median methacholine dose response slope 12.0 v 4.8 µmol/l, P=0.02), whereas the results of baseline spirometry, exercise provocation, and peak flow monitoring did not differ between groups. No significant differences in test results were found between those subjects without asthma who had symptoms but negative test results and the reference group.

Undiagnosed asthma versus symptoms only

Among symptomatic subjects not previously diagnosed with asthma, independent risk factors (see box) for having undiagnosed asthma as opposed to asthma-like "symptoms only" were bronchitis at age 10 (odds ratio 7.35 (1.52 to 35.4), $\chi^2=6.2$, df=1, P=0.01), signs of humidity in home (0.28 (0.08 to 1.00), $\chi^2=3.81$, df=1, P=0.05), and physical activity (0.89 (0.79 to 1.00), $\chi^2=3.80$, df=1, P=0.05). The odds ratios stated were adjusted for all contributing variables (n=66, two missing). No significant interactions were found between the variables contributing to model.

Discussion

Few studies have investigated the characteristics of previously undiagnosed asthmatic patients, probably in part because of the lack of an accepted definition of this condition and the need for objective measurements to confirm the diagnosis to avoid overestimation.[19] For epidemiology a pragmatic definition of asthma as the coexistence of recent wheeze and methacholine hyperresponsiveness has been proposed.[20] Cough, however, may be the sole expression of asthma,[21] and various tests of airway responsiveness may identify different types of abnormalities of the airways.[12] Therefore, we extended our definition of asthma to comprise non-infectious cough or any breathing trouble, or both, in combination with any test result confirming abnormal variations in airway calibre

Table 2 Associations of independent risk factors with undiagnosed asthma as opposed to asthma diagnosed by doctor

Risk factor and categories	No of subjects	Odds ratio (95% CI)*	χ^2 (df=1)	P value
Body mass index (per kg/m²)	59	3.01 (1.16 to 7.83)	5.12	0.02
Problems in family (serious v trivial)	59	846 (2.22 to ∞)	4.94	0.03
Passive smoking (per hours/day)	59	2.39 (1.16 to 4.92)	5.59	0.02
Physical activity (per hours/week)	59	0.60 (0.41 to 0.87)	7.24	0.01
Serial sneezing (any v none)	59	0.005 (0.00 to 0.34)	5.99	0.01

*Adjusted for all factors included in model.

Key messages

- One third of young people with asthma are not diagnosed; most are girls
- Undiagnosed asthma is associated with low physical activity, high body mass index, serious family problems, passive smoking, and the absence of symptoms of rhinitis
- Cough is the most common symptom among those with undiagnosed asthma
- Two thirds of those with undiagnosed asthma do not report their symptoms to a doctor, suggesting a need for targeted asthma campaigns

including monitoring of peak expiratory flow, airway responsiveness to methacholine or exercise, and resting spirometry. By this definition subjects with previously undiagnosed asthma made up about one third of all asthmatic patients identified. True asthmatic patients were unlikely to hide in the "symptoms only" group because test results did not differ between those with symptoms but negative test results and reference subjects without symptoms.

Undiagnosed versus diagnosed asthma

Independent risk factors for undiagnosed as opposed to previously diagnosed asthma were serious family problems, low physical activity, high body mass index, high exposure to environmental tobacco smoke, and no history of serial sneezing, a characteristic symptom of allergic rhinitis. The first two of these risk factors were significantly associated with female sex, which, in accordance with previous reports,[6][8] comprised two thirds of the undiagnosed but only one third of the diagnosed patients with asthma.

The logistic regression analysis was based on a relatively large number of potential risk factors (n = 51) compared with the number of asthmatic subjects identified (n = 71). Thus, mass significance could not be excluded. The relevance of the five independent risk factors, however, was supported by the presence of several associated factors competing for entry in the final model (see table 1).

Why is asthma overlooked?

The presence of one or more of the five independent risk factors could in several ways lead to misinterpretation or neglect of asthma-like symptoms by patients, parents, or medical professionals. A low level of physical activity is relatively unlikely to provoke symptoms of asthma induced by exercise and may serve as a means of self "treatment" in childhood asthma. Furthermore, low activity promotes weight gain (high body mass index) which in turn may lead to misinterpretation of asthma symptoms as due to lack of physical fitness. Social status, previously associated with underdiagnosis of asthma,[9] was not directly measured but may be related to parents' smoking habits as well as problems in the family. Family problems may reduce focus on a child's symptoms, and parents who smoke may be disinclined to get a doctor's advice regarding symptoms related to smoking in the family. Environmental tobacco smoke has previously been shown to be a risk factor for childhood wheeze[22] and is

likely to be strongly advised against and thus probably reduced when a child is diagnosed with asthma.

In accordance with previous reports,[6] symptoms were rarely reported to a physician by undiagnosed subjects with asthma, who thereby effectively avoided getting diagnosed and properly treated. Cough seemed to be particularly overlooked as an expression of asthma. Even though the more severely affected patients with asthma (in terms of airway responsiveness and symptoms) were also the most likely to get diagnosed, several moderately to severely affected subjects were first identified as a result of the present study.

The role of atopy as a risk factor for asthma has been established by population based studies with physician independent markers of asthma such as lung function impairment, bronchial responsiveness to methacholine, or typical asthma symptoms.[23–25] We speculate, however, that the traditional emphasis on two associated risk factors[26] for asthma—namely, atopy and male sex—may have led to the underrecognition of non-atopic girls with asthma suggested by our data. It seems likely that allergy affecting nose or eyes facilitates a diagnosis of asthma, both by promoting contact with a doctor and by increasing the doctor's awareness towards this diagnosis.

Undiagnosed asthma versus symptoms only

Undiagnosed patients with asthma also differed from those with symptoms but with no evidence of asthma. In this context, previously undiagnosed asthma at age 13 was positively associated with symptoms of bronchitis—that is, periodic cough for many days or weeks—at age 10, confirming earlier reports on misclassification of asthma as bronchitis[4] and suggesting that the asthma had been unrecognised for several years. The negative association between undiagnosed asthma and the level of physical activity suggests that exercise induced symptoms limit the activity level in undiagnosed subjects more than in subjects with respiratory symptoms unrelated to asthma. The independent association of indicators of high humidity in the home with non-asthmatic respiratory symptoms was unexpected but may be related to indoor microbial factors.[27]

Summary

Substantial underdiagnosis of asthma in the adolescent population was confirmed by combined subjective and objective criteria. Underdiagnosis was independently associated with low physical activity, high body mass, serious family problems, passive smoking, and the absence of rhinitis symptoms. Girls were overrepresented among subjects with undiagnosed asthma and equally underrepresented among those with diagnosed asthma, indicating sex bias in the diagnostic process. Most patients with undiagnosed asthma had not reported their symptoms to a physician, suggesting a need for targeted asthma campaigns in the community.

above, had the original idea for the present analysis, and wrote the manuscript. HCS also carried out the statistical analysis after thorough discussion with JB and GM. All coauthors made valuable comments to the manuscript and approved the final version. HCS is the guarantor for the study.

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Commentary: Risk factors for underdiagnosis of asthma in adolescence

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The Odense schoolchild study of asthma symptoms has provided previous data on this same group of children.[1] The results in adolescents with diagnosed asthma showed that different objective tests (spirometry, responsiveness to methacholine or exercise, variability in peak flow at home) may pick up different subsets of airway pathophysiology. In the current study they have shown that around a third of children who have asthma-like symptoms and one positive test result have not been given a diagnosis of asthma. They suggest that this may be a reason to go out and search for these cases in the community.

Firstly, we need to know whether this underdiagnosis of asthma matters. Possible reasons for such a search might be that these children have current problems such as persistent symptoms which could be relieved by appropriate treatment, have restricted activity because of respiratory symptoms on exercise, or are at risk of severe asthma attacks because of the absence of diagnosis and treatment. Alternatively, there might be longer term risks of more troublesome asthma symptoms in the future or the development of irreversible airway damage which could have been prevented by treatment.

Only 31% of the undiagnosed group had presented an asthma-like symptom to a doctor. In a few cases this might have been reticence related to an anxiety about the doctor's response to parental smoking. The association found between undiagnosed asthma and limited activity or a higher body mass index suggests that a healthier life style might have brought symptoms to light or that symptoms might have been related inappropriately to weight or lack of fitness.

Overall, the symptoms in the undiagnosed group were milder; breathlessness was less common than in the diagnosed group and methacholine responsiveness was lower. In some cases, however, the findings were less reassuring as "several moderately to severely affected subjects were first identified as a result of the present study." Some of these subjects in the undiagnosed group may have been poor perceivers of their asthma,[2] a group of patients who need particular care and who may be particularly susceptible to future acute problems.[3]

These might be legitimate reasons to search for such cases or, at least, to be ready to suspect the diagnosis with few symptoms and the associations shown here. Any argument that the longer term clinical course of asthma might be favourably changed by early diagnosis and treatment of these cases with

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mild symptoms is more difficult to sustain on the present evidence. There is a suggestion that persistent inflammation may cause remodelling of the airways, leaving them less able to reverse back to their full calibre.[4] Early intervention with corticosteroids is known to control symptoms, reduce inflammation,[5] and improve bronchial responsiveness. There are suggestions that such treatment might even prevent irreversible change,[6] but the evidence is not strong enough to recommend this approach in all of the undiagnosed group with minimal symptoms.

So where does this leave us? It does not provide the evidence for screening in the community until we know that this is beneficial on quality of life or long term outlook. It does show that there are still people with asthma with significant problems who remain undiagnosed and untreated because they or their doctors fail to appreciate the importance of their symptoms. This paper shows some associated features such as physical inactivity, high body mass index, and lower socioeconomic class, which should raise suspicions that the diagnosis is being missed where

symptoms are mild. An exercise test, peak flow at home, methacholine challenge, or a combination should be used to confirm the diagnosis. The advantage of the first two tests is that they can be performed easily by primary care physicians who see most of these children. A positive diagnosis or a high degree of suspicion with significant symptoms should prompt a trial of treatment.

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Commentary: Identifying the correct risks in diagnosis

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This is a study of young people selected in two ways: firstly, a simple random sample of 292 (21%) children from 1369 in an epidemiological study, and, secondly, a 100% sample (203) of those with personal or family history of asthmatic-like symptoms. (The consequences for analysis of this method of sample selection have been ignored but probably hardly affect the conclusions.) These children were classified into three groups: firstly, those who described themselves as having physician diagnosed asthma; secondly, those with asthma-like symptoms and a positive test result but without a doctor's diagnosis—undiagnosed asthma; and, thirdly, those non-smokers with no symptoms or diagnosis of asthma—the reference group (smokers with no symptoms were excluded).

Logistic regression is a statistical technique that may be used to combine factors that discriminate between two groups. It requires a "gold standard" diagnostic test (which may be invasive or expensive or one for which the result can be obtained only retrospectively) and putative features to be used for discrimination to be measured on all those classified by the gold standard. Generally the groups studied are those with and without disease. Logistic regression can be used to estimate a probability, from the measured features, that a particular individual has the disease.

This study uses the technique to examine features that might be used in those children with asthma to discriminate between those who are diagnosed and those who are not diagnosed. Is this discrimination of value? It may be of marginal interest in theory but does not seem to help practitioners. When a doctor is faced with a patient, the problem is to discriminate between those who have and those who do not have asthma, so that he or she can give appropriate treatment. If they

have already made a diagnosis then distinctions between those with and those without such a diagnosis are no longer of interest.

The fact that being a girl is a "risk factor" for being undiagnosed does not necessarily help unless it also distinguishes between having symptoms only and being undiagnosed. It does suggest that boys are more likely to be diagnosed, but there may be more girls in the non-asthmatic group as a whole. The tables and most of the text of the paper do not contribute to the useful distinction. The results for the discrimination between "symptoms only" and "undiagnosed asthma" are neither very significant (only bronchitis at age 10 is conventionally significant) nor are they the same set of variables for distinguishing between diagnosed and undiagnosed asthma. Physical activity shows a similar trend but is not very helpful in making the clinical decisions with which a doctor is faced in the clinic or general practice.

The message of this paper is that statistical techniques can serve to produce analyses which, while arithmetically correct, are irrelevant. It is an error of the third kind: "Finding the right answer to the wrong question."

Correction

Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol

An editorial error occurred in this paper by Li Wan Po and Zhang (13 December, pp 1565-71). In figure 2 the mean rate ratios (95% confidence intervals) for moderate to excellent pain relief between treatments should have been given as numbers [not as percentages, as published].

Commentary: Improving the diagnostic rate in asthma: a community issue

Hans C Siersted

Our definition of asthma—the coexistence of asthma-like symptoms and obstructive airway abnormality—is widely accepted. The test battery and the diagnostic algorithm are routinely used in specialist clinics, and similar principles are applied by general practitioners. Thus we believe that asthma diagnosed in our community based study would also be diagnosed as such if the children visited an observant general practitioner. Our study shows, however, that in many patients asthma is not properly diagnosed.

Most importantly, most of these patients with undiagnosed asthma did not even report their symptoms to a doctor. Therefore we asked ourselves the question: can characteristics of these children with undiagnosed asthma be identified to help to increase awareness about the possibility of asthma in children with respiratory symptoms that are not obviously abnormal to parents, guardians, and school teachers? We believe that knowledge of the risk factors identified for not having asthma diagnosed could certainly promote the diagnostic decision process, especially at the community level (figure), leading new candidates for asthma evaluation to the doctor's waiting room. If then the doctor, considering also risk factors for underdiagnosis, agrees that a patient's symptoms could possibly be asthma, it is not the right time to wonder if more risk factors could help differentiate between asthma and "symptoms only." Instead, it is the time for tests such as peak flow monitoring
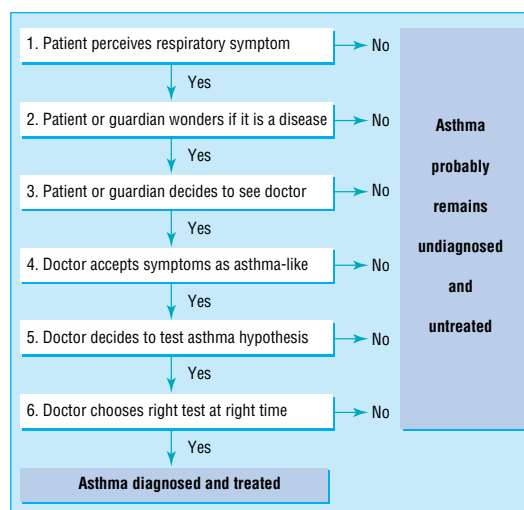
Stepwise path for diagnosing asthma in patients with respiratory symptoms

and (if these are negative) challenge with methacholine or exercise.

Thus, knowledge of pitfalls (risk factors for underdiagnosis)—for example, explaining cough alone as a natural response to passive smoking and exercise dyspnoea as simply the result of obesity—may be helpful at all stages of the diagnostic path towards the right answer to the asthma question.

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Numbers of deaths related to intrapartum asphyxia and timing of birth in all Wales perinatal survey, 1993-5

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Abstract

Objectives: To investigate the relation between the timing of birth and the occurrence of death related to an intrapartum event.

Design: Analysis of 107 206 births to Welsh residents in 1993-5, including 608 cases of stillbirth and 407 of neonatal death identified in the all Wales perinatal survey, the cause of death classified with the clinicopathological system.

Subjects: 79 normally formed babies stillborn or who died in the neonatal period, birth weight > 1499 g, for whom cause of death was related to an intrapartum event.

Main outcome measures: Relative risk of death due to an intrapartum event according to the hour, day, and month of birth.

Results: Mortality was higher in babies born between 9 00 pm and 8 59 am than in those born between 9 00 am and 8 59 pm; relative risk (95% confidence interval) 2.18 (1.37 to 3.47). July and August births also had a higher death rate than births in other months; relative risk 1.99 (1.23 to 3.23). Weekend births had a higher death rate but it was not significant.

Conclusions: The excess of deaths at night and during months when annual leave is popular may indicate an overreliance on inexperienced staff at these times. Errors of judgment may also be related to physical and mental fatigue, demanding a more disciplined systematic approach at night. Mistakes may be ameliorated by increasing shiftwork, but shifts should be carefully designed to avoid undue disruption of circadian rhythms. In addition, greater supervision by senior staff may be required at night and during summer months.

Editorial by Spencer

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Introduction

The sharp fall in perinatal mortality in the United Kingdom in recent decades has been ascribed both to an improvement in general health and to specific advances in perinatal care.[1] Death due to intrapartum asphyxia of a mature and normally formed baby is now uncommon, but because labour is a time of maximum clinical supervision these deaths are widely considered to be the most preventable component of perinatal mortality.[2] Indeed, in a low risk pregnancy the incidence of stillbirths or neonatal deaths due to intrapartum asphyxia is regarded as a sensitive measure of the quality of care around the time of labour and delivery.[3-5]

In 1992 the confidential inquiry into stillbirths and deaths in infancy was established in England, Wales, and Northern Ireland.[6] This inquiry initially focused on deaths related to intrapartum events to delineate the components of perinatal care most frequently associated with a poor outcome. The fourth annual report of the inquiry concentrated on the results of 873 "intrapartum related deaths" that took place in 1994 and 1995 and showed that more than half the cases were linked to suboptimal care; the most common deficiencies were related to clinical management, with staff failing to recognise problems or failing to act appropriately once a problem was identified.[7] These issues were linked with deficiencies in training and a lack of senior supervision around the time of delivery.

Maintaining a consistent level of readily available and experienced staff for the management of labour is sometimes difficult because the occurrence of a perinatal emergency is largely unpredictable. Problems may occur when training grade staff begin working in a specialty in which initially they have little experience. Also, staffing levels may fluctuate during holiday periods, when annual leave is most popular, and during unsociable hours (nights and weekends).[8] In this study we investigated the relation between the hour, day, and month of delivery and the incidence of deaths related to an intrapartum event.

Subjects and methods

We identified 608 stillbirths and 407 neonatal deaths in 1993-5, using the all Wales perinatal survey, a population based surveillance of mortality between 20 completed weeks of gestation and 1 year of age.[9] The births were to women usually resident in Wales, irrespective of the place of delivery. Information about each death was collected on the survey questionnaire that was normally completed by the team in whose unit the baby died.[9] This included details about the mother (medical and obstetric history, current pregnancy, labour, and delivery) and baby (sex, birth weight, gestation, clinical management, and postmortem findings). This information was used by local staff to classify the cause of death by using the clinicopathological system[10 11] and verified for accuracy by the regional coordinating team. Completeness of ascertainment of stillbirths and neonatal deaths was validated by cross checking with data from the Office for National Statistics and the Child Health System Database.[12]

Data on surviving infants were obtained from the Child Health System Database, which collects information on Welsh residents from the birth notification record.[12] There were 107 206 registrable births during the period of investigation, maternity care being delivered in 16 consultant obstetric units and 11 general practitioner units within Wales and several hospitals in neighbouring English health authorities; home deliveries accounted for 1.8% of all births. The rate of caesarean section in Welsh maternity units in 1993-5 was 16.8%, and the elective caesarean section rate was 6.7%.[9]

The study relates to deaths in 1993-5 classified as being due to an intrapartum related event[9 11] for babies with a birth weight > 1499 g who died during labour or within 28 completed days of life. The hour, day, and month of birth of these infants was compared with that of surviving infants. The effect of being born at night was analysed by comparing the death rate for births between 9 00 am and 8 59 pm (day) with that between 9 00 pm and 8 59 am (night). July and August were considered the peak months of annual leave so the death rate for births in these months was compared with that for the rest of the year. Senior house officers in Wales rotate to new posts in February and August; the effect of this was assessed by comparing the death rate for births in these months with that during the rest of the year.

Relative risks and 95% confidence intervals were calculated to assess the effect of each factor on death rates. Multiple logistic regression was used to determine whether the different factors contributed independently to the rate of death.

Results

A total of 79 deaths (0.74/1000 total births) related to an intrapartum event were identified. Birth weight ranged between 1500 g and 4805 g (median 3050 g) and gestational age between 29 and 43 weeks (median 39 weeks). Seventy cases were from singleton pregnancies and nine from twin pregnancies; in one set of twins both fetuses were stillborn. Twelve deaths (eight at night) were after an induction of labour, 38 (25 at night) at emergency caesarean section, and none at elective caesarean section. There were 33 deaths during labour, 42 early neonatal deaths, and four late neonatal deaths.

The intrapartum related death rate was higher in babies born at night. There were 27 deaths from 56 892 births between 9 00 am and 8 59 pm (0.47/1000) compared with 52 deaths from 50 314 births between 9 00 pm and 8 59 am (1.04/1000), a relative risk of death of 2.18 (95% confidence interval 1.37 to 3.47). If babies born during the daytime by elective caesarean section (rate 6.7%) and therefore not exposed to labour are excluded from the analysis, the difference remains significant with a relative risk of death of 1.95 (1.22 to 3.10).

Births in July and August (annual leave effect) had a significantly higher rate of intrapartum related death (1.25/1000 births) compared with births in other months (0.63/1000/births), with a relative risk of death of 1.99 (1.23 to 3.23) (table). The death rate for births in February and August (rotation effect) was also significantly higher (1.25/1000 births), with a relative risk of death of 1.97 (1.21 to 3.22). As August births feature in both the annual leave and rotation months, further analysis with multiple logistic regression was performed to establish whether the two effects were independent. When these factors were analysed

Numbers of intrapartum related deaths and month of birth in all Wales perinatal survey, 1993-5

Month of birth	No of deaths	No of births
January	4	8 858
February	10	8 305
March	4	9 139
April	5	8 894
May	6	9 398
June	6	9 118
July	11	9 092
August	12	9 237
September	2	9 200
October	5	8 788
November	5	8 484
December	9	8 693
Total	79	107 206

together the rotation effect was no longer significant (P = 0.1088).

Using the same methodology we tested whether night, annual leave, and rotation effects all influenced the death rate when analysed together. We found that the annual leave and night effects were significant (P = 0.0056 and P = 0.0011, respectively) but that the rotation effect was not (P = 0.1082).

There was a tendency for babies born towards the end of the week to have a higher rate of intrapartum related deaths. Monday and Tuesday births had the lowest relative risk of death of 0.78 (0.39 to 1.57) and 0.71 (0.36 to 1.43), respectively, in contrast with 1.20 (0.68 to 2.21) and 1.48 (0.82 to 2.68) on Saturday and Sunday. These differences, however, were not significant.

Discussion

This population based study has highlighted a variation in the risk of death due to an intrapartum event according to the time of birth, with the most striking feature being the higher risk of death for babies born at night. In view of the recognised association of care around the time of delivery with outcome, this must raise concerns about variability in the quality of perinatal care.

The increased risk of being born at night could be explained if induced labours, which have a higher risk of intrapartum complications, are selectively more likely to result in a delivery at night. These data were not available for all births, but in one health district with 15% of deliveries and comparable induction rates, night time birth was less common after an induction of labour (48%) than after a spontaneous labour (52%) (J Bethel, personal communication). Induction of labour is therefore unlikely to be the explanation.

Specific information on staffing levels and the availability of experienced staff at the moment of birth was not available. Nevertheless, one of the more plausible explanations for intrapartum related deaths being associated with birth during the night is a reduced availability of skilled and experienced staff at this time. This view is supported by an audit by Meer et al, who reported that in the West Midlands most suboptimal obstetric practice occurs out of office hours.[13] It is also consistent with a finding of the confidential inquiry into perioperative deaths that the risk of surgery conducted out of hours is higher because it tends to be performed by junior surgeons without supervision.[14]

Hours of work

Errors of judgment are more likely if staff are physically and mentally tired.[15] Obstetrics differs from other medical specialties in the excess night time hours (9 pm to 9 am) worked by junior medical staff compared with staff in other disciplines.[8] Night time tiredness should have been lessened by the recent widespread introduction of shiftwork among junior medical staff, but this pattern of work is unpopular,[16] and continuity of patient care may be affected. Shiftwork can also be profoundly affected by circadian rhythms, resulting in fatigue during the last few hours of the night, especially if the person is on a new night shift.[17] In comparison to staff who work only nights, those who rotate shifts report twice as many errors related to tiredness.[17] The adverse effects of shifts on health and performance are most pronounced when rotations last fewer than 3 weeks, and circadian rhythms are further disrupted if the shift rotation is counterclockwise.[15]

Effect of month of birth

We have also found an increased risk of an intrapartum related death among babies born in July and August, when annual leave is popular. At these times junior medical staff may be less well supervised and perinatal services may rely more heavily on locum staff employed to cover annual leave. This effect is exacerbated if the staffing establishment has no built in allowances to cover staff absence. Indeed, research commissioned by the Department of Health into patterns of staffing in obstetrics found that during holiday periods one of the units surveyed was on occasion nearly crippled by staff shortages.[8] Babies born in February and August, when senior house officers rotate to new posts, were not at a significantly increased risk. This may indicate that critical decisions are usually made by other members of staff, but nevertheless it is unfortunate that inexperienced medical staff rotate to new posts in August, when senior staff may be on annual leave.

Conclusion

Deaths related to an intrapartum event are more common among babies born at night and during months when annual leave is popular. Errors of judgment are probably related to mental fatigue, and staff need to be aware how their performance may vary at different times, demanding a more disciplined systematic approach at night. Mistakes may also be ameliorated by

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Key messages

- In low risk pregnancies the incidence of death due to intrapartum asphyxia is regarded as a sensitive measure of the quality of perinatal care

- Babies born at night and during summer months are at increased risk of death due to intrapartum asphyxia, raising concerns about variability in care around the time of delivery

- Errors of judgment may be related to mental fatigue. Staff need to be aware of how their performance may vary, and a more disciplined systematic approach at night may be needed

- Greater supervision by senior staff may be required at night and during summer months

the increased use of shiftwork, but shifts need to be carefully designed to avoid an excessive disruption of circadian rhythms and consequent fatigue. In addition, greater supervision by senior staff may be required at night and during summer months.

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Effectiveness of screening older people for impaired vision in community setting: systematic review of evidence from randomised controlled trials

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Abstract

Objective: To assess whether population screening for impaired vision among older people in the community leads to improvements in vision.

Design: Systematic review of randomised controlled trials of population screening in the community that included any assessment of vision or visual function with at least 6 months' follow up.

Subjects: Adults aged 65 or over.

Main outcome measure: Proportions with visual impairment in intervention and control groups with any method of assessing visual impairment.

Results: There were no trials that primarily assessed visual screening. Outcome data on vision were available for 3494 people in five trials of multiphasic assessment. All the trials used self reported measures for vision impairment, both as screening tools and as outcome measures. The inclusion of a visual screening component in the assessments did not result in improvements in self reported visual problems (pooled odds ratio 1.04: 95% confidence interval 0.89 to 1.22). A small reduction (11%) in the number of older people with self reported visual problems cannot be excluded.

Conclusions: Screening of asymptomatic older people in the community is not justified on present evidence. Visual impairment in this age group can usually be reduced with treatment. It is unclear why no benefit was seen. Further work is needed to clarify what interventions are appropriate for older people with unreported impairment of vision.

Introduction

The introduction of the sight test fee in 1990 increased concern about undetected visual problems in older people,[1] and visual screening for older people in general practice was advocated.[2] Renewed concern has been expressed recently by the Royal National Institute for the Blind[3] and the Department of Health.[4]

Since 1990 general practitioners have been required to offer an annual screening assessment to all patients aged 75 and over,[5] specifically including an assessment of vision. While multiphasic screening of older people has been shown to be beneficial overall,[6] exactly which procedures are effective is uncertain. The 75 and over programme is currently under review.[7]

Rationale for screening older people for visual problems

Visual impairment is common among older people. In community based surveys of unselected older people undertaken in the United Kingdom, visual acuity of less than 6/12 has been found in around 2% of those aged 65 to 74 and around 20% of those aged 75 and over.[8 9] This level of visual acuity is below the requirements for driving in the United Kingdom.[10] Larger surveys have been performed in the United States,[11–13] and, though the prevalence of reduced visual acuity is lower in one of these,[11] similar overall trends are seen. Various adverse factors have been reported in association with visual impairment. These include reduced functional status and quality of life,[14–16] depression,[16–18] and falls.[19–21]

Visual problems in older people may go unreported for several reasons, including decreased expectations in old age and a belief that nothing can be done to help,[14] failure by the patient to recognise visual loss,[22] or the presence of another handicap that dominates the perception of difficulties.[23] Other possible inhibiting factors include fears about surgical treatment and costs[24] and the stigma of blindness.[25]

How and why vision should be assessed was not specified in the 1990 general practitioner contract.[5] The Royal College of General Practitioners advocates a simple question about visual function to identify unreported problems.[26] Specific screening procedures for glaucoma or diabetic retinopathy have not been included in the over 75 programme nor in trials of multiphasic screening.

Methods

The research question was defined as, what is the effectiveness of population screening for visual impairment in improving vision among unselected older people (aged 65 or over) in a community setting, either alone or as part of a multiphasic assessment programme?

Search methods

A systematic Medline search for randomised controlled trials evaluating screening in older people was performed for the period 1966 to December 1996 by using a published optimally sensitive search strategy.[27] The exploded (that is, including all sub-branches) MeSH terms "mass screening," "preventive health services," "eye diseases," and "diagnosis, eye," and the non-exploded MeSH terms "health promotion" and "geriatric assessment" were used. Titles and abstracts were searched for the words "geriatric" or "elderly" combined with any of "screening," "assessment," "health," "function," or "surveillance." Other textword searches used the words "macular degeneration," "cataract," and "presbyopia." Wild card characters were used to ensure all forms of words were included. At all stages articles about animals and children were excluded. The October 1997 Cochrane Library (which includes the Cochrane Controlled Trials Register and the Database of Abstracts of Reviews of Effectiveness) was also searched for both trials and relevant reviews.[28] Other review articles and books were consulted. Bibliographies of all relevant articles were scanned. Experts in screening for older people and in ophthalmology were consulted.

Inclusion criteria

The inclusion criteria were in two stages. In the first stage, articles were included only if they were randomised controlled trials of either visual or multiphasic screening of unselected subjects in a community setting that included patients aged 65 and over. Trials of screening undertaken on selected groups of patients were excluded on the grounds that the results would not answer the question under review. Studies including adults aged under 65 only were also excluded. Because visual screening may have been only one small part of a multiphasic screening programme and data about visual outcomes may not have been included in published reports of trials, therefore, the named author for correspondence for all trials identified in the first stage was contacted (at their current addresses verified by telephone) to ask for any further unpublished data about visual screening tests used and visual outcomes. Non-responders were sent two reminders and were telephoned.

The second stage inclusion criteria were then applied to all the trials included from the first stage: the availability of any visual outcome data, whether formally tested or self reported; and a follow up of at least six months to allow intervention for detected visual problems.

Study selection and data extraction

The full texts of articles selected for retrieval and review from the abstracts and citations were obtained. A checklist of the first stage inclusion criteria was then applied by both authors independently. All criteria had to be met. After contact with the trial authors a structured data extraction form was used, again by both authors independently. Data was extracted as follows: setting; subjects; overall intervention; visual screening test(s) used; duration of follow up; and visual outcome measures and visual outcome data. Data about randomisation process, the degree of allocation concealment, and blinding of outcome assessors was also extracted. Authors were contacted for clarification if required. Disagreements between reviewers were discussed and a consensus reached on all articles.

Critical appraisal

There is empirical evidence that inadequate randomisation to intervention and control groups can affect the outcome of a trial.[29] In particular, it is important that the treatment assignment is known only after the decision has been taken for the patient to enter the trial. This is known as concealed allocation. Studies were therefore classified for allocation concealment by using previously developed categories: A = trials in which allocation appeared to be adequately concealed (for example, a central randomisation procedure); B = trials in which allocation concealment was unclear, either because the approach was not reported or in which the randomisation process did not match categories A or C; and C = trials in which allocation concealment was inadequate (such as alphabetical use of surname).[30] In addition, data were extracted about the degree of blinding of outcome assessors in the trials.

Outcome measures

The aims of multiphasic screening of older people are broad—for example, to improve quality of life and reduce admission to hospital. Any benefit arising from the inclusion of a visual assessment, however, will necessarily be dependent on improved vision, which was therefore used as the outcome measure for this review. Any method of visual assessment (such as acuity chart, questions about vision, or measures of visual function) was accepted as an outcome measure. We felt that stricter inclusion would excessively limit the data included in the review.

Analysis

We used RevMan software.[31] Heterogeneity between trials was tested for with χ^2 test. Odds ratios were combined with the fixed effects Mantel-Haenszel method. The relative risk is presented as well as the odds ratio because it is more easily understood by some.[32]

Table 1 Randomised controlled trials of screening older people that included data on visual outcome: subjects, settings, and interventions. In all trials concealment of allocation was adequate (see text for details)

Reference	Subjects and setting	Overall trial intervention	Follow up period	Blinding of outcome assessors
Vetter 1984[w3] (UK)	People aged over 70 living at home registered with one of two general practices	Annual assessment at home by health visitor (n=577) v usual care (n=571)	2 years	Yes
McEwan 1990[w9] (UK)	People aged 75 and over registered with one general practice	Multiphasic nurse assessment at home (n=151) v usual care (n=145)	20 months	No
Vetter 1992[w13] (UK)	People aged over 70 living at home registered with one general practice	Annual assessment at home by health visitor, specifically aimed at reducing falls and fractures (n=350) v usual care (n=324)	4 years	Yes
Van Rossum 1993[w14] (Netherlands)	Respondents to postal invitation to all people aged 75-84 living at home in defined geographical area	Four visits a year for three years by trained nurses (n=292) v usual care (n=288)	3 years	Yes
Wagner 1994[w16] (US)	Health maintenance organisation customers aged 65 and over	Multiphasic assessment by nurse, which included a visual assessment (n=635) v general health promotion visit with no visual assessment (n=317) v usual care (n=607)	2 years	Postal questionnaires used

Table 2 Visual screening methods and outcome measures

Reference	Visual screening method	Visual outcome measure
Vetter 1984[w3] (UK)	Two questions about glasses and difficulty seeing	Proportion with positive response to question "Do you have any difficulty seeing (even when wearing your glasses)"
McEwan 1990[w9] (UK)	Series of questions about vision and glasses	Proportion who "always" or "quite often" had difficulty reading ordinary newsprint (with glasses if worn)
Vetter 1992[w13] (UK)	As Vetter 1984, with additional question about recent eye test	As Vetter 1984[w3]
Van Rossum 1993[w14] (Netherlands)	One question "How do you assess your vision at present?" Possible answers: excellent, good, fair, not so good, or bad	Proportion answering "fair," "not so good," or "bad" to screening question at end of study
Wagner 1994[w16] (US)	Simple questions about visual function and use of glasses in postal questionnaire	Proportion reporting visual problems on repeated mailed questionnaire at 2 years

Results

In total 2246 citations and abstracts were screened, and 147 full text articles were reviewed in detail. Seventeen trials met the first stage inclusion criteria, all of which were trials of multiphasic screening. The reference details are given on the web.[w1-17] There were no trials that primarily assessed visual screening. Requests for further information led to replies from authors of 16 of the 17 trials. Five trials met the final inclusion criteria—that is, visual outcome data with follow up of at least 6 months.[w3 w9 w13 w14 w16] These trials are summarised in table 1.

All five trials adequately concealed randomisation. Regarding blinding of outcome assessors, the trial participants were aware of whether they had received a screening assessment. Thus, despite attempts to blind the outcome assessors, which arm of the trial subjects were in could clearly emerge during the face to face assessments of outcome. This phenomenon was noted by Vetter in two trials[w3 w13] and led McEwan to consider such blinding impossible.[w9]

Individuals in the trial by Wagner and colleagues were recruited from a health maintenance organisation and may have differed in their overall baseline health from the general population.[w16] This trial had three arms. For the purposes of our review subjects in the two arms who did not receive any form of visual screening assessment were analysed together as control patients.
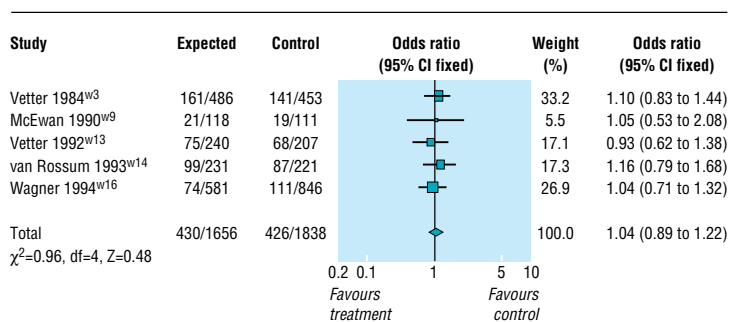
Table 2 shows the visual assessment methods and outcome measures. All the trials used self reported measures to assess impaired vision, both as the screening assessment and as the outcome measure.

Effects of screening on visual impairment

Statistical testing showed no evidence of heterogeneity of effect in the five trials ($\chi^2 = 0.96$, df = 4, P = 0.92). When odds ratios were pooled there was no reduction in the proportion of individuals with visual impairment as a result of screening (pooled odds ratio 1.04; 95% confidence interval 0.89 to 1.22). The figure shows the outcome data, and individual and pooled odds ratios. The pooled relative risk for visual impairment was 1.03 (0.92 to 1.15).

Discussion

The evidence from randomised controlled trials does not support the inclusion of an assessment of vision in regular multiphasic assessment programmes for unselected older people in a community setting or visual screening in primary care.[2] Although a reduction of 11% in the number of older people with visual impairment cannot be excluded, even this figure is disappointingly low.

Study	Expected	Control	Odds ratio (95% CI fixed)	Weight (%)	Odds ratio (95% CI fixed)
Vetter 1984[w3]	161/486	141/453		33.2	1.10 (0.83 to 1.44)
McEwan 1990[w9]	21/118	19/111		5.5	1.05 (0.53 to 2.08)
Vetter 1992[w13]	75/240	68/207		17.1	0.93 (0.62 to 1.38)
van Rossum 1993[w14]	99/231	87/221		17.3	1.16 (0.79 to 1.68)
Wagner 1994[w16]	74/581	111/846		26.9	1.04 (0.71 to 1.32)
Total $\chi^2=0.96$, df=4, Z=0.48	430/1656	426/1838		100.0	1.04 (0.89 to 1.22)

0.2 0.1   1   5   10
Favours treatment   Favours control

Outcome data: individual and pooled odds ratios for visual screening as part of multiphasic screening package versus standard care. Outcome was not seeing well, as defined by each trial

Results from community surveys in the over 75 age group suggest that over half the visual impairment in this age group could potentially be reduced with treatment, notably by cataract surgery or refractive correction.[8 13] In light of this the lack of improvement seen in these trials is somewhat surprising and cannot be explained from the data presented. Several factors, however, may have contributed. Firstly, the visual assessment was only one component of the screening package in all five trials, and visual screening performed in isolation may have produced a greater effect. This hypothesis was previously suggested as an explanation of the lack of effectiveness of screening for visual impairment seen in a trial of a multiphasic screening assessment among middle aged men.[33 34] In clinical practice, however, screening for visual impairment is highly likely to be one part of a broader screening package, and therefore an assessment of effectiveness within a broader package is the most pragmatically useful measure. Secondly, the people who reported visual problems when prompted to do so in a screening programme may not have perceived their previously unreported visual impairment as a "need" for intervention. Lastly, there is evidence that considerable obstacles exist to improving visual impairment among older people. In the United Kingdom fear of costs has been repeatedly cited by a proportion of older people as a barrier to attending an optometrist and obtaining glasses.[3 14 24 35] In addition, ophthalmic services are unable to meet current demands for treatment, with long waiting lists for cataract surgery in many areas.[36]

The aim of population screening of older people for visual impairment is presumably to discover visual impairment in those who are not presenting to the health services and to offer them interventions to improve their vision. Further work is required, however, to determine the needs of older people with unreported visual problems. Before population screening can be effective, existing obstacles to the reduction of visual impairment among older people must be overcome.

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Association of glutamine 27 polymorphism of β_2 adrenoceptor with reported childhood asthma: population based study

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The prevalence of asthma in children has doubled over the past 25 years.[1] Two common polymorphisms exist in the β adrenoceptor at amino acids 16 (glycine for arginine) and 27 (glutamic acid for glutamine). Both are functionally relevant in cultured cells, with the glycine 16 form of the receptor showing enhanced downregulation and the glutamic acid 27 form showing attenuated downregulation after exposure to β agonists.[2] The glutamine 27 polymorphism is associated with raised IgE concentrations in families with a history of asthma, and with increased reactivity of the airways in people with asthma.[3 4] We measured the prevalence of these polymorphisms in a random population of children to identify their importance in the expression of reported asthma.

Subjects, methods, and results

We approached children between the ages of 5 and 15 years (mean 10.5 years) and an accompanying parent who were attending the accident and emergency department of the Royal Aberdeen Children's Hospital. Approval from an ethics committee and written consent were obtained from the parents and participating children, and 425 (97%) of 438 agreed to participate. After completing a brief questionnaire each child provided a mouth wash sample (10 ml of boiled distilled water).[1] From the resulting suspension of buccal epithelial cells DNA was extracted, and the β_2 adrenoceptor polymorphisms were identified using the polymerase chain reaction and an allele specific oligonucleotide assay.[3] Frequency tables and Pearson's χ^2 test were used for bivariate comparisons and logistic regression employed in the multivariate analysis.

Complete information including phenotype information on both parents and genotype information in children was available for 410 children with genotyping data in 419. The childhood prevalence of reported asthma (104 out of 425, 24%) was similar to that observed in a recent postal questionnaire study from the same population.[5]

Thirty nine were arginine 16 homozygotes, 179 were glycine 16 homozygotes, and 201 were heterozygotes. Ninety three were glutamic acid 27 homozygotes, 107 were glutamine 27 homozygotes, and 219 were heterozygotes for the two. The two polymorphisms were in partial linkage disequilibrium. The allelic prevalences of the β_2 polymorphisms in this child population were virtually identical with those found in a random sample of adults in Nottingham (unpublished data). Both polymorphisms were in Hardy-Weinburg equilibrium.

Genotype at position 16 was not associated with reported asthma. Both homozygosity and heterozygosity for the glutamine 27 polymorphism were associated with reported asthma (table), with a significant association between the presence of this allele and reported asthma ($\chi^2 = 4.38$, df = 1, P = 0.04). On logistic

Genotypes at position 27 and reported asthma

	No asthma	Reported asthma	Totals for position 27 genotypes
Glutamine 27 homozygote	83	24 (22%)	107
Glutamine and glutamate heterozygote	156	63 (30%)	218
Glutamate 27 homozygote	78	15 (16%)	93

regression analysis and taking other known factors into account (sex, maternal asthma, reported hay fever, and eczema) the glutamine 27 allele conferred an independent increased risk of reported asthma (odds ratio 2.18, confidence interval 1.13 to 4.23, P = 0.02). Conversely, homozygosity for the glutamic acid 27 polymorphism had a lower risk (odds ratio 0.46, (0.24 to 0.89)). Of the 104 children with reported asthma, 47 were also reported to have coexisting hay fever or eczema, or both. When this subpopulation was included in a secondary analysis, the modifying effect of glutamic acid 27 was of a similar order ($\chi^2 = 9.56$, df = 4, P = 0.05).

Comment

The finding that the glutamic acid 27 polymorphism may be associated with a decreased prevalence of reported asthma in childhood is consistent with its effects on IgE concentration and non-specific bronchial reactivity.[3 4] Interestingly, this polymorphism was not associated with asthma in adult populations,[3] in whom IgE may be a less important determinant of the asthma phenotype. Whether the glutamine for glutamic acid polymorphism at position 27 determines the asthma phenotype in children or whether it is in linkage disequilibrium with another gene, perhaps in the nearby T helper 2 cytokine gene cluster on chromosome 5q, remains to be established.

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Parental history of gastric or duodenal ulcer and prevalence of *Helicobacter pylori* infection in preschool children: population based study

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Helicobacter pylori infection is present in almost all patients with duodenal ulcers and 80-90% of patients with gastric ulcers,[1] whereas the prevalence of infection among young adults without a history of ulcer is fairly low in Western countries.[2] To investigate the importance of transmission from parent to child we assessed the relation between a parent's history of gastric or duodenal ulcer and infection with *H pylori* in his or her offspring in a large population of preschool children.

Subjects, methods, and results

A cross sectional study was carried out among 1201 preschool children living in Ulm, a city of about 100 000 inhabitants located in southern Germany. The children had a medical examination before starting school in 1996. Details of the study design are reported elsewhere.[3] In brief, a urea breath test using carbon-13 was conducted to determine whether the children had an active infection of *H pylori*. One to two weeks before their child's examination a standardised questionnaire was sent to the parents to ascertain whether they had had a gastric or duodenal ulcer diagnosed by a doctor. The questionnaire also included detailed information on other potential risk factors for *H pylori* infection, such as housing conditions, family demographics, and socioeconomic factors. The prevalence of *H pylori* infection in the children of parents with a history of gastric or duodenal ulcer was compared with that in children whose parents had no such history. Multiple logistic regression was used to adjust for known or suspected risk factors that might confound the results.[4]

Overall, 945 of the 1201 children participated in the study (response rate 79%). To minimise false negative results from the urea breath test, 82 children were excluded because they had received antibiotic treatment within the preceding 4 weeks. A history of gastric or duodenal ulcer was reported in 22 mothers and 28 fathers (table). Overall, 118 (14%) of the 863 children were infected with *H pylori*. Among children whose mothers had a history of gastric or duodenal ulcer the prevalence of infection was more than double that among those whose mothers had no such history (odds ratio 2.4 (95% confidence interval 0.9 to 6.4)). The association was significant after adjustment for known or suspected risk factors of infection by multiple logistic regression (11.7 (3.8 to 36.2); P < 0.0001) (table). No significant association was seen between a paternal history of ulcer and active infection in children.

Comment

The difference between the prevalence of infection in children whose mothers are infected with *H pylori* and that in children whose mothers are not infected is

Prevalence of *Helicobacter pylori* infection in 863 preschool children according to parental history of duodenal or gastric ulcer

History of ulcer in parent	No of children	No (%) infected with *H pylori*	Odds ratio (95% CI)	
			Crude	Adjusted*
Mother:				
No	841	112 (13)	1.0	1.0
Yes	22	6 (27)	2.4 (0.9 to 6.4)	11.7 (3.8 to 36.2)
P value for comparison			0.07	<0.0001
Father:				
No	835	113 (14)	1.0	1.0
Yes	28	5 (18)	1.4 (0.5 to 3.7)	1.6 (0.4 to 5.5)
P value for comparison			0.51	0.49

*Adjusted for nationality, mother's education, father's education, housing density, birth order, history of breast feeding, attendance at nursery, antibiotic treatment, and history of ulcer in the other parent.

likely to be even larger than the difference shown by the mothers with a history of ulcer in this study.

In theory, the relation between a parent's history of ulcer and *H pylori* infection in his or her offspring may be explained by several mechanisms, including common environmental or genetic factors that influence susceptibility to infection.[5] However, these factors imply that a history of ulcer in the mother or father will be similarly associated with infection in a child. As mothers typically have closer contact with their children, a more plausible explanation for the observed patterns would be transmission between mother and infant. Our results would also be consistent with the hypotheses that the transmission may be influenced by the presence of ulcer or that *H pylori* strains causing peptic ulcer may be more infective than other strains.

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Relation of aplastic anaemia to use of chloramphenicol eye drops in two international case-control studies

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Although the use of chloramphenicol eye drops is thought to cause aplastic anaemia,[1] this side effect has not been studied critically. We examined the use of ocular chloramphenicol in two population based case-control studies conducted with the same methods.[2 3]

Subjects, methods, and results

The data from the international granulocytosis and aplastic anaemia study were collected over varying times from 1980 to 1986 in Israel and in Ulm and Berlin (Germany), Milan (Italy), Budapest (Hungary), Sofia (Bulgaria), and Stockholm and Uppsala (Sweden); the total base population was about 19 million.[2] Data collection continued independently in Sweden until 1992. The Thai study was conducted from 1989 to 1994 in Bangkok and from 1990 to 1994 in Khonkaen and Songkla; the total population was about 21 million.[3]

In both studies patients with aplastic anaemia were identified by regular telephone contacts with all hospitals in the study regions. Cases were patients whose peripheral blood counts and bone marrow histology met accepted diagnostic criteria[2]; each diagnosis was confirmed by a panel of haematologists blinded to drug exposures. Controls matched for age and sex were selected from among patients admitted to the same hospitals within 3 months for reasons judged to be independent of antecedent drug use—for example acute trauma.[2 3] Data on exposure to chloramphenicol were obtained by interview and included detailed histories of all drug use (including topical drugs) in the 6 months before admission; lists of indications for use and trade names of drugs of particular interest were used to help recall. The time of onset of aplastic anaemia could not be determined with precision because some symptoms, such as fatigue, are vague. Therefore, any use in the 5 month period from 6 months to 1 month before admission was judged to be aetiologically relevant.

There were 426 cases and 3118 controls. None of the cases had used chloramphenicol eye drops, but seven of the controls had used them (table[1]). The upper 95% confidence limit for a relative risk of zero[4] was 5.1. Five of the exposed controls (0.2%) had been exposed for ≥3 days.

Comment

We conducted two population based studies using virtually identical protocols representing about 185 million person years of observation in industrialised and developing countries. Among more than 400 cases of aplastic anaemia there was no use of chloramphenicol eye drops. Although there was no evidence of an association the prevalence of use among the controls was low, and the possibility of some increase in risk cannot be excluded.

Bias is unlikely to account for the findings, since associations were found in these data for several other previously suspected drugs.[2 3] Information bias, in particular, is improbable: chloramphenicol has long been suspected as a cause of aplastic anaemia, and the likely result of any such bias would have been an overestimation of the risk. Definition of the appropriate window of exposure for drug induced aplastic anaemia is more problematic. Because of the insidious onset of aplastic anaemia we excluded any drug use that started in the month before admission.

Our data provide no support to the claim that chloramphenicol eye drops increase the risk of aplastic anaemia.[1] The literature lends only weak support for causality, being based on a few single case reports that are often inadequately investigated and have other possible causes. The recommendation that chloramphenicol eye drops should be avoided because of an increased risk of aplastic anaemia[1] is not well founded.

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Exposure to chloramphenicol in seven controls

Control No	Region	Age (years)	Sex	Route	Frequency	Last use before admission	Duration
1	Thailand	9	M	Ocular	Daily	3rd month	2 days
2	Thailand	21	M	Ocular	Daily	4th month	1 day
				Oral	Daily	2nd month	3 days
3	Thailand	63	F	Ocular	Daily	5th month	5 days
4	Thailand	29	F	Ocular	Daily	3rd month	3 days
5	Israel	66	M	Ocular	Daily	1 day	2 months
6	Sweden	34	F	Ocular	Occasional	1 day	5 years
7	Israel	19	M	Ocular	Daily	3rd month	3 days

Risk of serious haematological toxicity with use of chloramphenicol eye drops in a British general practice database

Tim Lancaster, Ann Marie Swart, Hershel Jick

An editorial in the *BMJ* recommended discontinuation of the routine use of chloramphenicol eye drops largely on the basis of case reports suggesting an association between their use and serious haematological toxicity, particularly aplastic anaemia.[1] Although this recommendation has been challenged, the debate has not been informed by reliable estimates of the size of any risk.[2]

Around 400 general practices in the United Kingdom contribute anonymised data to the general practice research database. They record prescriptions and diagnoses from consultations and hospital letters. Use of the data for drug safety studies is well validated.[3] In particular, previous studies have shown that it can be used reliably to detect associations between drug exposure and haematological toxicity.[4] We used the database to describe prescribing patterns of chloramphenicol eye drops and to estimate the risk of aplastic anaemia after their use.

Subjects, methods, and results

We identified all patients who received at least one prescription for chloramphenicol eye drops between January 1988 and April 1995. We reviewed the computer records of patients with a new diagnosis of any of the following conditions occurring up to 90 days after such a prescription: aplastic anaemia, thrombocytopenia, agranulocytosis, leucopenia or neutropenia, unspecified white blood cell disorders, blood dyscrasia (*International Classification of Diseases*, eighth revision, codes 284.9, 287.1, 288.0, 288.1, 288.9, 289.9).

A total of 442 543 patients received 674 148 prescriptions for chloramphenicol eye drops. 314 205 patients (71%) received one prescription; 115 061 (26%) had between two and four prescriptions, and 13 276 (3%) had five or more. Use was higher in the younger age groups. Around 30% of children aged 0-9 years received one or more prescriptions compared with 8% of those aged 10-44 years and 5% of those aged 45 or more.

We identified three patients with serious haematological toxicity and one who developed mild, transient leucopenia that was not considered serious. One of the serious cases, a boy with epilepsy, was admitted to hospital with red cell aplasia 72 days after a prescription for chloramphenicol eye drops. He had received four prescriptions over a five year period, two of them in the three months preceding admission. He had stopped taking lamotrigine six weeks before because he had developed Stevens-Johnson syndrome and had started treatment with phenytoin three weeks before developing red cell aplasia. The patient presented with severe anaemia and bone marrow biopsy confirmed red cell aplasia. Phenytoin was discontinued and he was given a blood transfusion and treated with folic acid. He recovered fully. Clinical opinion was that the lamotrigine or

phenytoin treatment was probably the cause of the aplasia. Thus, a causal association with chloramphenicol seems unlikely. The second serious case was a woman in her 60s with cirrhosis of the liver; she developed pancytopenia 71 days after a single course of chloramphenicol eye drops. She was not admitted to hospital and reported no symptoms. The last serious case was a woman in her 80s who had melaena seven days after a prescription for chloramphenicol eye drops. She was found to have pancytopenia and died from gastrointestinal bleeding 12 weeks later.

Comment

Even in the unlikely event that all three cases were caused by chloramphenicol eye drops, these data indicate that the risk of serious haematological toxicity after treatment with ocular chloramphenicol is in the order of 3 per 442 543 patients or 3 per 674 148 prescriptions.

The risk of serious haematological toxicity attributable to chloramphenicol eye drops is small. Chloramphenicol eye drops are cheap and effective. Their continued use for eye infections seems to be a safe clinical strategy.

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Endpiece
Asherisms

The difference between the maniac and the schizophrenic laugh is—mania and the world laughs with you, schizophrenia and you smile alone.

From *A Sense of Asher*, selected by Ruth Holland (BMA Publications, 1984)