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Outcomes of conduct problems in adolescence: 40 year follow-up of national cohort

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ABSTRACT

Objective To describe long term outcomes associated with externalising behaviour in adolescence, defined in this study as conduct problems reported by a teacher, in a population based sample.

Design Longitudinal study from age 13-53.

Setting The Medical Research Council National Survey of Health and Development (the British 1946 birth cohort).

Participants 3652 survey members assessed by their teachers for symptoms of externalising behaviour at age 13 and 15.

Main outcome measures Mental disorder, alcohol abuse, relationship difficulties, highest level of education, social class, unemployment, and financial difficulties at ages 36-53.

Results 348 adolescents were identified with severe externalising behaviour, 1051 with mild externalising behaviour, and 2253 with no externalising behaviour. All negative outcomes measured in adulthood were more common in those with severe or mild externalising behaviour in adolescence, as rated by teachers, compared with those with no externalising behaviour. Adolescents with severe externalising behaviour were more likely to leave school without any qualifications (65.2%; adjusted odds ratio 4.0, 95% confidence interval 2.9 to 5.5), as were those with mild externalising behaviour (52.2%; 2.3, 1.9 to 2.8), compared with those with no externalising behaviour (30.8%). On a composite measure of global adversity throughout adulthood that included mental health, family life and relationships, and educational and economic problems, those with severe externalising behaviour scored significantly higher (40.1% in top quarter), as did those with mild externalising behaviour (28.3%), compared with those with no externalising behaviour (17.0%).

Conclusions Adolescents who exhibit externalising behaviour experience multiple social and health impairments that adversely affect them, their families, and society throughout adult life.

INTRODUCTION

Behavioural and externalising disorders affect about 7% of those aged 9-15.[1 2] Conduct disorder, a severe form of externalising behaviour, is one of the most common psychiatric disorders among adolescents,[1 2] and causes severe functional impairment.[3] The prevalence of adolescent conduct problems has been increasing over the past 30 years.[4]

Conduct problems in adolescence are associated with leaving school earlier or with fewer qualifications, becoming a parent at a young age, unemployment, divorce or separation, substance abuse, other psychiatric disorders including depression and anxiety, and suicidal behaviour. These individuals create a considerable economic burden to society.[5]

We examined the adult lives of adolescents with mild and severe externalising behaviour as reported by their teachers, using repeat measures of mental health, social, and economic outcomes at ages 36-53 in a national birth cohort. We also identified sex specific differences in the outcomes of adolescent externalising behaviour.

METHODS

Sample

Our sample comprised the Medical Research Council National Survey of Health and Development (NSHD). The survey originally included every child born in England, Scotland, or Wales during one week in March 1946. See bmj.com. We report on 3652 survey members whose behaviour was assessed at ages 13 and 15.

Externalising behaviour in adolescence

Teachers assessed externalising behaviour using questionnaires that were forerunners of the Rutter child measures. From the results of these questionnaires we created a scale score (7-21). Adolescents were grouped into three categories according to this scale: those who scored below the 75th centile at 13 and 15 were considered to have no externalising behaviour, those who scored above the 93rd centile at either age 13 or 15 were considered to have severe externalising behaviour, and all others were considered to have mild externalising behaviour. See bmj.com.

Outcomes

The survey comprised measures of mental health in adulthood, including alcohol consumption, family life in adulthood, including marital status and employment and educational outcomes in adulthood. See bmj.com. A global life adversity measure was created as a composite variable to capture global adversity in adult life. We

followed methods used by others by adding one point for each negative outcome in adulthood: symptoms of depression or anxiety, self reported history of nervous trouble, alcohol abuse, divorce, teenage parenthood, unhappiness with family life, problems in relationships, lack of education qualifications, manual social class, unemployment, and financial difficulties. We report quarters of this summed scale.

Missing data

For the assessment of externalising behaviour we required complete information for the teacher rating questionnaire items at ages 13 and 15. We excluded survey members if they had missing data, leaving a sample of 3652. Sample sizes for each comparison in the analysis depended on the number responding to the survey at various times in adulthood; survey members were permitted to re-enter the study after missing an outcome assessment in adulthood as long as they had the original assessment in adolescence. Of the sample of 3652, there were 2582 (70.7%) respondents at age 36, 2510 (68.7%) at age 43, and 2297 (62.9%) at age 53.

Statistical methods

We compared the three groups (no externalising behaviour, mild externalising behaviour, severe externalising behaviour, as rated by teacher) on several baseline and early childhood measures including sex, father's social class, cognitive ability at age 8 and symptoms of depression and anxiety at age 13 and 15. Within each group, we compared individuals with complete data over follow-up with those with incomplete data using similar tests to assess bias.

We compared adolescents with or without externalising behaviour using regression models with the externalising group defined as a three level categorical variable, adjusted for sex, father's social class, cognitive ability, and depressive and anxious symptoms at age 13 and 15. We studied sex specific outcomes for all outcomes and investigated interactions between sex and externalising behaviour in the regression models for all outcomes.

RESULTS

In the sample, 348 (9.5%) adolescents had severe externalising behaviour, 1051 (28.8%) had mild externalising behaviour, and 2253 (61.7%) had no externalising behaviour. Adolescents with externalising behaviour were more likely to be boys, have a father from a manual social class, and have lower cognitive ability and were slightly more likely to report depressive and anxious symptoms. In all cases, characteristics of those with mild externalising behaviour fell between those with severe externalising behaviour and those with no externalising behaviour.

Adolescents with externalising behaviour were less likely to provide complete data throughout the follow-up (complete data available for 65.5% of those with no externalising behaviour, 59.9% with mild externalising behaviour, 55.2% with severe externalising behaviour; P<0.001). See bmj.com.

Mental health in adulthood—Symptoms of depression and anxiety were more common among those with severe externalising behaviour in adolescence than no externalising behaviour (adjusted odds ratio 1.3, 1.0 to 1.7). Adolescents with severe externalising behaviour were also more likely to report a history of nervous trouble (1.5, 1.0 to 2.2). Adolescents with mild externalising behaviour were more likely to be abusing alcohol than those with no externalising behaviour, though this was not the case for those with severe externalising behaviour.

Family life in adulthood—Adolescents with mild or severe externalising behaviour were more likely to become parents during their teenage years. They were also more likely to get divorced in adulthood compared with those with no externalising behaviour in adolescence and to report that they were unhappy with family life in adulthood. Adolescents with severe externalising behaviour were more likely to report problems in relationships with spouses, children, or friends in adulthood.

Employment and educational outcomes in adulthood—Adolescents with either mild (2.3, 1.9 to 2.8) or severe (4.0, 2.9 to 5.5) externalising behaviour were more likely to leave school with no qualifications than other adolescents (table). They were also more likely to be in manual social classes in adulthood. There were no significant differences between externalising groups with regard to unemployment in adulthood, though adolescents with severe externalising behaviour were more likely to report difficulties with their finances in adulthood (2.1, 1.4 to 3.2).

Global life adversity—The composite measure of global life adversity indicated that adolescents with mild externalising behaviour were more likely to experience adversity in adult life than those with no externalising behaviour (1.9, 1.6 to 2.3). For adolescents with severe externalising behaviour, however, the adjusted odds ratio was 2.9 (2.1 to 4.0), with almost three quarters of adolescents with severe externalising behaviour being in the top half of the life adversity scale (table).

Sex specific outcomes—Interaction terms between externalising behaviour and sex identified few significant differences between men and women for the relation between externalising behaviour in adolescence and outcomes in adulthood. See bmj.com. Notably, there were no significant interactions between sex and externalising behaviour in adolescence with regard to the global life adversity scale, suggesting that men and women with adolescent externalising behaviour are affected equally in adulthood.

DISCUSSION

Findings and similar research

In this population based follow-up of adolescents, those who engaged in externalising behaviour according to their school teachers had a higher likelihood of poor outcomes in numerous domains across a 40 year period. These poor outcomes also extended to those with milder forms of externalising behaviour. The results remained after adjustment for other important predictors of outcomes in adulthood. We created a composite score and found that adolescents who engage in either mild or

Economic, educational, and global adversity outcomes in adulthood according to level of externalising behaviour in adolescence (none, mild, severe). Figures are percentage of survey members with adjusted* odds ratios and 95% confidence intervals

	None	Mild	Severe	Mild *v* none	Severe *v* none
No educational qualifications	30.8	52.2	65.2	2.3 (1.9 to 2.8)‡	4.0 (2.9 to 5.5)‡
Manual social class	29.7	45.6	52.0	1.7 (1.4 to 2.1)‡	2.0 (1.5 to 2.8)‡
Unemployed at least once†	9.5	11.1	11.9	1.2 (0.8 to 1.8)	1.2 (0.7 to 2.2)
Financial difficulties†:					
No problems	75.4	70.1	56.3		
Problems reported once	17.9	22.0	31.9	1.3 (1.0 to 1.7)	2.1 (1.4 to 3.2)‡
Problems reported twice or more	6.8	7.8	11.8		
Global life adversity:					
Least adversity	26.6	16.0	13.4		
2nd quarter	22.9	16.6	12.9		
3rd quarter	33.5	39.2	33.6	1.9 (1.6 to 2.3)‡	2.9 (2.1 to 4.0)‡
Most adversity	17.0	28.3	40.1		

*Adjusted for sex, father's social class, cognitive ability, and depression/anxiety in adolescence.
†Reported at ages 36, 43, and 53.
‡Significant at P<0.05.

severe externalising behaviour experience multiple impairments that persist throughout adult life.

As in other studies of sex differences in outcomes of adolescent antisocial behaviour,[6-8] we did not find consistent patterns of sex specific outcomes. We found that adolescent conduct problems were strongly linked to the presence of symptoms of depression and anxiety in adulthood. Some suggest that the presence of concurrent conduct disorder and depression is less likely to be an example of comorbid disease processes and more likely to be an underlying feature of conduct disorder itself.[9]

Numerous studies have linked conduct problems in adolescence to alcohol abuse in adulthood. Though we found evidence that adolescents with milder externalising behaviour were more likely to abuse alcohol in adulthood, most adolescents with teacher rated externalising behaviour did not abuse alcohol as adults. A population based cohort study in New Zealand also reported that those whose conduct problems did not persist beyond childhood did not have increased rates of alcohol abuse in early adulthood.[10]

Antisocial behaviour in early childhood is associated with the formation of delinquent peer groups[11] and later conduct disorder in adolescence.[12] In turn, conduct disorder in adolescence is associated with further affiliation with delinquent peer groups and involvement in criminal activities.[13]

We found that externalising behaviour was strongly associated with leaving school early. A prospective birth cohort from New Zealand showed that early conduct problems lead to later conduct problems and not that early conduct problems lead to educational underachievement that carries lasting consequences.[6] Our results support this concept. This suggests that adolescent misconduct might adversely affect developing social behaviours and result in pervasive social and mental health difficulties throughout adult life.

Methodological considerations

We used data collected almost 50 years ago to identify children who might be diagnosed with a behavioural disorder today but we could not make clinical diagnoses on the basis of the information collected. We used a dimensional scale to measure conduct problems which is more predictive of future delinquent behaviour than diagnostic categories.[7]

The national survey data contain only teachers' assessments of the children's behaviour. However, these are more strongly associated with the adolescents' functional impairment than assessments based on information from the parents or the children themselves.[14] They also predict future delinquent behaviour better than parents' assessments.

A limitation of this study is the attrition of survey members over the 40 year follow-up period. Those lost to follow-up were also those with the most extreme difficulties, so our results might be conservative estimates of the true picture.

We were unable to differentiate between those whose externalising behaviour began in childhood or in adolescence. People who have childhood onset antisocial behaviour might have more extreme negative outcomes in adulthood.[15] Our findings might underestimate the severity of poor outcomes for those with the most longstanding externalising behaviours.

Our study also has several methodological strengths. Firstly, the national survey is a representative population based sample. Secondly, the sample is large and allowed for follow-up of 348 adolescents with severe externalising behaviour. Thirdly, because the national survey is one of the oldest prospective cohort studies, it provides follow-up data much further into adult life than other studies of adolescent externalising behaviour.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical and high risk samples suggest that adolescents with severe externalising behaviour or conduct disorder are more likely to be depressed or anxious, abuse alcohol, leave school early, struggle to obtain or maintain employment, and get divorced or separated in adulthood

WHAT THIS STUDY ADDS

Adolescents in the general population with severe externalising behaviour experience multiple impairments, including poor mental health, relationship difficulties, and economic problems well into adult life

Adolescents with less severe forms of externalising behaviour also experience poor outcomes as adults

Ethical approval: The National Survey of Health and Development has received ethical approval from the Central Manchester local research ethics committee.
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Does single application of topical chloramphenicol to high risk sutured wounds reduce incidence of wound infection after minor surgery? Prospective randomised placebo controlled double blind trial

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ABSTRACT

Objective To determine the effectiveness of a single application of topical chloramphenicol ointment in preventing wound infection after minor dermatological surgery.

Design Prospective randomised placebo controlled double blind multicentre trial.

Setting Primary care in a regional centre in Queensland, Australia.

Participants 972 minor surgery patients.

Interventions A single topical dose of chloramphenicol (n=488) or paraffin ointment (n=484; placebo).

Main outcome measure Incidence of infection.

Results The incidence of infection in the chloramphenicol group (6.6%; 95% confidence interval 4.9 to 8.8) was significantly lower than that in the control group (11.0%; 7.9 to 15.1) (P=0.010). The absolute reduction in infection rate was 4.4%, the relative reduction was 40%, and the relative risk of wound infection in the control group was 1.7 (95% confidence interval 1.1 to 2.5) times higher than in the intervention group. The number needed to treat was 22.8.

Conclusion Application of a single dose of topical chloramphenicol to high risk sutured wounds after minor surgery produces a moderate absolute reduction in infection rate that is statistically but not clinically significant.

Trial registration Current Controlled Trials ISRCTN73223053.

INTRODUCTION

Chloromycetin ointment consists of 10 mg/g of chloramphenicol in plastibase 30W and soft white and liquid paraffin.[12] Chloramphenicol has a broad spectrum of activity against Gram positive and Gram negative bacteria, rickettsias, and *Chlamydia*.[3]

Box 1 Excision procedure

1 Skin preparation—normal saline or chlorhexidine

2 Usual sterile technique (standard precautions), including sterile gloves

3 Local anaesthetic (type and volume recorded)

4 Suture material—nylon (size recorded)

5 Dressing type—melolin and tape

6 No antibiotics, either topical or oral (if required, or already prescribed, exclude from study); no topical antiseptics, such as betadine or alcohol; no antiseptic washes or medicated soaps

7 Removal of sutures according to body site: back—10 days; all other sites—seven days

Chloramphenicol ointment is indicated for treatment of bacterial conjunctivitis, but little evidence exists for its effectiveness in prophylaxis or treatment of wound infection (see bmj.com). A survey of UK plastic surgeons reported that 66% used chloramphenicol eye ointment in their practice, mainly as prophylaxis against infection.[4] We sought to establish the effectiveness of topical chloramphenicol ointment in preventing wound infection after dermatological surgery.

METHODS

We did the study in three private general practices in Mackay, Queensland, between June 2007 and March 2008. Practice nurses invited consecutive patients presenting for minor skin excisions to take part in the trial.

Eligibility criteria—We excluded patients who were already taking oral antibiotics, for whom oral or topical antibiotics were clinically indicated immediately postoperatively, or who were on immunosuppressive drugs.

Surgical wound management protocol—We ran a workshop for participating general practitioners to develop guidelines to ensure that excisions were managed in a standardised manner. The procedure shown in box 1 was agreed.

Intervention—We could not get information about the exact proportions of the constituents of the base of Chloromycetin ointment from the manufacturer. The principal investigator visited a compounding pharmacist to develop a close match to the vehicle of the Chloromycetin ointment. Immediately after suturing, the doctor applied either paraffin ointment or chloramphenicol ointment to the sutured wounds by using sterile forceps.

Clinical outcomes—The practice nurse or the doctor assessed wounds for infection on the agreed day of removal of sutures or sooner if the patient re-presented with a perceived infection. We adapted our definition of wound infection from standardised surveillance criteria for defining superficial surgical site infections developed by the Centre for Disease Control's National Nosocomial Infection Surveillance System (box 2).[5] We also developed our own wound scale (see bmj.com).

Statistical analysis—We based all analysis on the intention to treat principle. Depending on the distribution, we describe numerical data as mean value and standard deviation or median value and interquartile range.

RESULTS

Practice and study characteristics—Of the total of 1246 patients who attended for skin excisions during the period from June 2007 to March 2008, 232 patients were excluded. Of the remaining 1014 patients, 509 were randomised to the intervention (chloramphenicol) group and 505 to the placebo (paraffin) group. Follow-up was completed in 972 (95.9%) randomised patients.

Comparisons at baseline—Large differences existed between the intervention and the control groups at baseline (see bmj.com). In the intervention group, 71.7% of patients were diagnosed with non-melanoma skin cancer or solar keratosis compared with 65.1% in the control group.

Incidence of infections—Infection occurred in 85 (8.7%) of the 972 excisions. The incidence of infection in the chloramphenicol group (6.6%; 95% confidence interval 4.9 to 8.8) was significantly lower than the incidence in the control group (11.0%; 7.9 to 15.1) (P=0.010; adjusted for cluster sampling). The relative risk of infection was 1.7 times higher in the control group compared with the intervention group (table). The number needed to treat (number of wounds treated for each infection prevented) was 22.8 (488/21.4). We found no significant difference in the wound score between the control and intervention groups (P=0.253), although 5.5% of patients showed erythema greater than 1 cm in the intervention group compared with 9.1% of patients in the control group (table).

Box 2 Definition of surgical site infection

- Infection must be within 30 days of excision
- Purulent discharge from the wound must be present, or

  The general practitioner must diagnose a wound infection, or

  The general practitioner prescribes antibiotics
- Stitch abscess must not be counted as an infection

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DISCUSSION

The results of this study suggest that a single dose of topical chloramphenicol to sutured wounds can produce a relative reduction in infection rate of about 40%. The absolute reduction was 4.4%, which fell short of our pre-determined reduction for clinical relevance (5%), so this was essentially a negative trial. The incidence of infection in our control group (11%) is much higher than reported in the published literature looking at similar cohorts.[6-8] The intervention thus may not produce a worthwhile absolute reduction in infection in low risk settings where infection rates are already low; the number needed to treat in these circumstances would be much higher than our figure of 22.8.

Limitations

Various characteristics influence the occurrence of infections; although we recorded information on as many variables as possible, ensuring that the baseline data were comparable proved difficult. For example, inadequate data were recorded on suture size and occupation, so we could not compare these factors. In addition, the prevalence of diabetes and of other medically important conditions was probably under-recorded, and power to analyse these subgroups was limited. Surgical training and technique of the general practitioners involved is a potential confounder that would be difficult to quantify and was not recorded. However, we adjusted the statistical analysis for the cluster sampling, taking the doctor as the primary sampling unit. The type of skin preparation used by the three participating practices differed, but we found no previously published evidence that this makes any difference to infection rates.[9] A total of 42 participants were lost to follow-up. If all 21 participants who were lost to follow-up in the intervention group had developed an infection, the rates of infection in both groups would have been similar (10.4% and 11.0%); however, we believe that this scenario is extremely unlikely.

Diagnosis of infection—even when guidelines are used—is still subjective, and inter-observer and intra-observer variation may occur.[10] The definition we used is the most widely implemented standard definition of wound infection,[5] and by developing our own wound assessment scale we hoped to reduce the subjectivity of diagnosis of infection. We have no evidence to support the intra-practice and inter-practice reproducibility of measurement and recording procedures.

The study did not have an arm in which no ointment was applied, so we do not know if the ointment itself had any pro-infective or anti-infective properties. The ointment base of Chloromycetin consists of a mixture of soft white paraffin, liquid paraffin, and plastibase 30W, which is a plasticised hydrocarbon gel consisting of 95% mineral oil and 5% polyethylene glycol. Our placebo ointment consisted of 50% soft white paraffin and 50% liquid paraffin and was not completely identical to the ointment base of Chloromycetin as it did not contain plastibase 30W. We cannot determine if this substance has an effect on infection, although we think that this is unlikely. Our trial used only a single dose of chloramphenicol ointment. We have no reason to surmise that repeated doses might lead to a greater reduction in infection rate.

Generalisability

The climate in Mackay is hot and humid, with a mean daily maximum temperature ranging between 24.2°C and 30°C during the summer months and a relative humidity of 75-79%.[11] These tropical conditions could increase sweat production and produce damp dressings, which might reduce the effectiveness of wound dressings as a potential barrier against exogenous bacteria.[12-14] This would make wounds more prone to infection in a tropical environment, so the results may not necessarily be generalisable to a temperate climate, although no published evidence shows that heat and humidity increase infection rates. This might also explain why our infection rates were higher than suggested by previous data from temperate climates.[6-8]

Antibiotic use

Some concern exists about the overuse of topical antibiotics resulting in antibiotic resistance. British and

Incidence of wound infections in intervention (chloramphenicol) and control (paraffin) groups

Infections	Intervention group (n=488)	Control group (n=484)	Combined results (n=972)
No of infections	32	53	85
Incidence of infection	6.6%	11.0%	8.7%
Relative risk (95% CI) of infection	1 (reference category)	1.7 (1.1 to 2.5)	NA
Wound score:	(n=487)	(n=483)	(n=970)
Stitch abscess	14 (2.9%)	14 (2.9%)	28 (2.9%)
<1 cm erythema	67 (13.8%)	62 (12.8%)	129 (13.3%)
>1 cm erythema	27 (5.5%)	44 (9.1%)	71 (7.3%)

NA=not applicable.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A survey of UK plastic surgeons showed that 66% use chloramphenicol ointment in some capacity

A small pilot study suggested that chloramphenicol ointment might reduce the incidence of wound infection

No published studies have been done in a primary care setting

WHAT THIS STUDY ADDS

A single application of topical chloramphenicol to high risk sutured wounds reduced infection by 40%

Australian guidelines suggest that use of topical antibiotics should be restricted because of the capacity of most topical drugs to select resistant micro-organisms and to cause sensitisation. The guidelines also suggest that antimicrobials recommended for topical use should be selected from classes not in use for systemic treatment.[3 15] A contrary argument says that the potential for antimicrobial resistance with topical antibiotics is actually lower than with systemic antibiotics because of the higher local concentration achieved by topical delivery.[16] Patterns of antimicrobial activity and resistance have been examined for other antibiotic ointments.[17 18] However, no evidence exists, over three decades of extensive use worldwide, to show that, with the exception of mupirocin, topical antibiotics administered on an outpatient basis contribute to any emerging resistance pattern.[16] Chloramphenicol eye drops have been shown to be effective in the treatment of meticillin resistant *Staphylococcus aureus* ocular surface infections.[19]

Some concern also exists about the incidence of allergic contact dermatitis with use of topical antibiotics. Contact allergy has been reported with the use of chloramphenicol ointment, but the incidence is thought to be low.[20 21] Although any connection between the use of topical chloramphenicol and aplastic anaemia is unlikely,[22 23] our study was not large enough to fully assess the risk in this setting.

The decision to prescribe antibiotic prophylaxis is complicated; in addition to efficacy, the antibiotic costs, adverse effects, and resistance should be taken into account. However, in some circumstances, topical delivery of antibiotic may be preferable to systemic administration.[3 15] The results of this study could encourage the judicial use of topical antibiotics after minor skin surgery.

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Ethical approval: The study was approved by the James Cook University ethics committee (approval number H2590). All patients provided written informed consent.

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Lung cancer deaths from indoor radon and the cost effectiveness and potential of policies to reduce them

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ABSTRACT

Objective To determine the number of lung cancer deaths related to indoor radon in the home and to explore the cost effectiveness of alternative policies to control indoor radon and their potential to reduce lung cancer mortality.

Design Cost effectiveness analysis.

Setting United Kingdom.

Data sources Epidemiological data on risks from indoor radon and from smoking, vital statistics on deaths from lung cancer, survey information on effectiveness and costs of radon prevention and remediation.

Main outcome measures Estimated number of deaths from lung cancer related to indoor radon, lifetime risks of death from lung cancer before and after various potential interventions to control radon, the cost per quality adjusted life year (QALY) gained from different policies for control of radon, and the potential of those policies to reduce lung cancer mortality.

Results The mean radon concentration in UK homes is 21 becquerels per cubic metre (Bq/m^3). Each year around 1100 deaths from lung cancer (3.3% of all deaths from lung cancer) are related to radon in the home. Over 85% of these arise from radon concentrations below 100 Bq/m^3 and most are caused jointly by radon and active smoking. Current policy requiring basic measures to prevent radon in new homes in selected areas is highly cost effective, and such measures would remain cost effective if extended to the entire UK, with a cost per QALY gained of £11 400 (€12 200; $16 913). Current policy identifying and remediating existing homes with high radon levels was, however, neither cost effective (cost per QALY gained £36 800) nor effective in reducing lung cancer mortality.

Conclusions Policies requiring basic preventive measures against radon in all new homes throughout the UK would be cost effective and could complement existing policies to reduce smoking. Policies involving remedial work on existing homes with high radon levels cannot prevent most radon related deaths, as these are caused by moderate exposure in many homes. These conclusions are likely to apply to most developed countries, many with higher mean radon concentrations than the UK.

INTRODUCTION

In most countries the largest source of exposure to natural ionising radiation is the radioactive gas radon-222, a natural air pollutant arising from radionuclides in the earth's crust. Outdoor concentrations of radon are usually low, but indoor concentrations are higher, especially in houses and other small buildings.

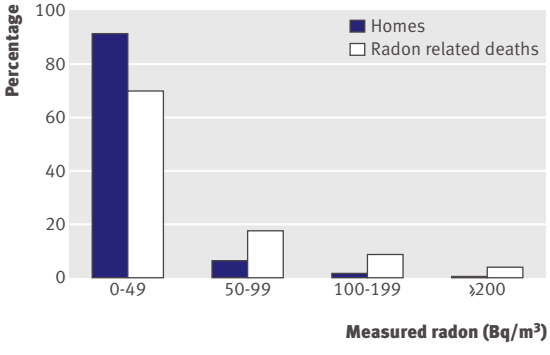
If inhaled, solid short lived radon progeny may deposit on the bronchial epithelium and expose sensitive cells to α irradiation, increasing the risk of lung cancer in proportion to the number of cells exposed. Studies of radon related lung cancer have usually quantified the risk in terms of radon concentration because this can be measured directly. For the same reason policies to control indoor radon are also formulated in terms of radon concentration.

Recently, evidence has become available on the risk of lung cancer from indoor radon in people with well documented smoking histories.[1-3] This confirms a material risk and enables the number of fatal radon related lung cancers to be estimated with greater confidence.

Many countries have policies to control indoor radon.[4 5] These usually focus on the small proportion of buildings where radon concentrations are above an "action level." In the United Kingdom the action level for homes is currently 200 becquerels per cubic metre (Bq/m^3) and current policy is mainly concerned with identifying homes with measurements above this level, although in high radon areas basic preventive measures are also required for all new homes (see bmj.com). We determined the number of radon related fatal lung cancers and the cost effectiveness of policies to control radon and their potential to reduce lung cancer mortality in the UK.

METHODS

We calculated numbers of deaths from radon related lung cancer from data on indoor radon concentrations, epidemiological studies, and official statistics.[2 3 6-9] Quality adjusted life years (QALYs) gained by radon control measures were calculated, and direct costs incurred or saved by homeowners, the Health Protection Agency,



Distributions of measured radon concentrations in UK homes and of deaths from radon related lung cancer

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other government departments, and the United Kingdom's health service were estimated and expressed in 2007 pounds sterling. Cost effectiveness was calculated as the ratio of net change in cost to net change in outcome. The cost effectiveness of various radon control policies was compared with no policy, enabling comparison between them and with other health interventions. The National Institute for Health and Clinical Excellence (NICE) in England and Wales views interventions with cost effectiveness less than £20 000 per QALY gained favourably and interventions with cost per QALY gained of more than £30 000 unfavourably.[10] Hence we take the range £20 000-£30 000 per QALY to indicate the maximum amount that society is currently willing to pay for health gain.

RESULTS

Deaths from radon related lung cancer

The mean indoor radon concentration in UK homes is 21 Bq/m^3. In 2006, 3.3% of deaths from lung cancer in the UK (0.2% of all deaths) were caused by radon indoors. About 1 in 7 of the deaths from radon related lung cancer was caused by radon but not by active smoking, and the remainder were caused by radon and active smoking jointly, with nearly half such deaths occurring in former smokers (table 1).

If radon concentrations were measured in all homes in the UK, 91% of measurements would be <50 (mean 16) Bq/m^3, 6% would be 50-99 (68) Bq/m^3, 2% would be 100-199 (133) Bq/m^3, and 0.4% would be >200 Bq/m^3. Only 4% of deaths from radon related lung cancer are caused by exposure in homes where the measurement would be ≥200 Bq/m^3, with 9% in the range 100-199 Bq/m^3, and 17% in the range 50-99 Bq/m^3. The remaining 70% result from exposure in homes where the radon measurement would be <50 Bq/m^3 (see figure on bmj.com).

The Health Protection Agency has designated areas where more than 1% of measurements exceed 200 Bq/m^3 (that is, mean radon >36 Bq/m^3) as "radon affected,"[11] but 75% of radon related lung cancers arise elsewhere.

Table 1 | Number of deaths from lung cancer in United Kingdom, 2006, by cause

Cause	No (%) of deaths from lung cancer	Deaths from lung cancer	
Not active smoking or indoor radon	4664* (13.6)		
Radon but not active smoking	157† (0.5)	3.3% due to radon§	
Active smoking and radon‡:			86.4% due to active smoking or radon
Current smokers	532 (1.6)	85.9% due to active smoking	
Former smokers	421 (1.2)		
Active smoking but not indoor radon	28 376 (83.1)		
Total No of lung cancer deaths¶	34 150 (100)		

*Including any deaths caused by passive smoking but not by radon.
†Including any deaths caused by passive smoking and radon.
‡Cancers that would have been prevented by avoidance of either indoor radon or smoking.
§Mean indoor concentration of radon in UK is 21 Bq/m^3.
¶Total number of deaths from all causes in UK in 2006 was 572 224. Indoor radon is estimated to cause 1110 (that is, 157+532+421) deaths (1 in 516 or 0.2% of deaths from all causes in UK).

Cost effectiveness of policies for new homes

Current government policy in England requires the installation of basic preventive measures to prevent radon during construction in all new homes in areas where ≥3% of homes have radon measurements >200 Bq/m^3 (that is, areas with mean radon ≥52 Bq/m^3). At 52 Bq/m^3 the cost per QALY gained when considering only radon prevention costs is £3200 and the cost per QALY gained when considering only NHS costs is £4800, making a total of £8000 per QALY gained, well below the maximum usually considered cost effective. Cost effectiveness improves for areas with higher mean radon concentration and deteriorates for areas with lower mean radon concentration. However, even in areas with mean radon as low as 10 Bq/m^3, the total cost per QALY gained is still only £21 400 (table 2). When the entire UK is considered, the total cost per QALY gained is £11 400 (£6600 when considering only radon prevention costs and £4800 when considering only NHS costs), suggesting that a policy requiring basic radon preventive measures in all new UK homes would be highly cost effective. In high radon areas, basic preventive measures at the time of construction could be supplemented by pipework to facilitate installation of underfloor ventilation, with a requirement to measure the radon after the house is occupied and, if appropriate, to install a fan. However, such measures could not be cost effective unless the mean radon in the area was well over 90 Bq/m^3.

Cost effectiveness of policies for existing homes

Current government policy for England comprises offering free radon measurements to existing homes in areas where ≥5% of homes have measured radon levels of >200 Bq/m^3 (that is, areas with mean ≥64 Bq/m^3). Homeowners are advised to remediate, usually at their own expense, if their radon measurement exceeds 200 Bq/m^3. In areas with a mean radon level of 64 Bq/m^3, the total cost per QALY gained of this policy is £36 800 (£32 000 when considering radon measurement and remediation costs only and £4800 when considering NHS costs only), somewhat above the maximum amount typically considered good value for money.

The cost effectiveness of this policy depends on the mean radon level in the area (table 2). Also, in any area the cost per QALY depends on the action level. Reducing the action level to 100 Bq/m^3 might improve the cost per QALY gained for areas with a mean radon level of 64 Bq/m^3 to about £30 000.

Health benefits from radon interventions vary with the number and characteristics of people in the home. For new homes this has little policy relevance. For existing homes, however, policy relevance may be substantial. Cost effectiveness was calculated for remediating existing homes in areas with a mean radon level

of 64 Bq/m^3 and an action level of 100 Bq/m^3, assuming households of average size were occupied entirely by lifelong non-smokers or by current cigarette smokers. Remediation is likely to be highly cost effective (<£14 000 per QALY gained) for current cigarette smokers, but very cost ineffective (>£160 000 per QALY gained) for never smokers. For former smokers, cost effectiveness will be intermediate.

Potential for different radon policies to reduce deaths from lung cancer in the UK

Ten years of the current policy for new homes would avert only five deaths from lung cancer per year across the entire UK, increasing by 0.5 deaths per year for each year of the policy. In contrast, the suggested policy of basic measures in all new homes would avert 44 deaths from lung cancer per year after 10 years of that policy, and this number would increase by 4.4 deaths per year as the policy continued so that a cumulative total of nearly 1000 deaths would be averted by 20 years of policy.

For existing homes, current policy targeted on areas with a mean radon level of ≥64 Bq/m^3 will avert about one death from lung cancer per year if fully implemented. Reducing the action level to 100 Bq/m^3 would approximately double this number at current measurement and remediation rates of 30% and 20%. If these rates could be increased, say to 60% for measurements and 50% for remediation, about 10 deaths would be averted per year after full implementation of the policy.

DISCUSSION

Direct evidence now shows that indoor radon causes lung cancer in the general population even at concentrations <200 Bq/m^3.[2 3] We estimate that in the UK indoor radon is responsible for 3.3% of deaths from lung cancer—that is, 0.2% of all deaths. In many other countries, concentrations are higher[1] and the proportions of deaths attributable to radon will be correspondingly higher. For the 27 European Union countries, the mean indoor radon concentration is around 55 Bq/m^3, suggesting that it causes about 8% of deaths from lung cancer (that is, around 18 000 each year). Indoor radon is therefore a public health issue. In most countries a small proportion of homes have much higher concentrations than the majority. Policy to date has focused on these extreme concentrations,[4 5 11] ignoring the lower levels experienced by most of the population and which cause most radon related lung cancers.

Policy implications of results

Radon concentrations are modifiable by intervention. Radon control policies should therefore be evaluated using methods routinely applied to other health interventions. Our results indicate that current government policy in England requiring basic preventive measures in all new homes in areas with a mean radon level of ≥52 Bq/m^3 is highly cost effective, and would remain so if the policy were extended to the whole UK, thereby reducing lung cancer mortality by a modest but worthwhile amount.

Table 2 | Cost effectiveness of policies to control radon concentrations according to mean indoor radon concentration in local area. For new homes, control policy requires basic radon preventive measures, such as a sealed membrane at ground level, to be installed during construction. For existing homes, control policy consists of offering free radon measurements to all homes in an area, followed by advice to remediate at homeowner's own expense if measurement exceeds action level.

Mean indoor radon concentration in local area (Bq/m^3)	% of national housing stock in areas with mean at or above this value	Cost (£s) per QALY gained (discounted)						
			Existing homes†					
			Action level (Bq/m^3 measured value)					
		New homes*	25 Bq/m^3	50 Bq/m^3	100 Bq/m^3	150 Bq/m^3	200 Bq/m^3	400 Bq/m^3
10	87.5	21 400	295 400‡	1 200 000	9 800 000	43 100 00	136 400 000	3 165 900
20	39.6	13 100	85 200‡	105 600	285 200	744 300	1 682 500	17 840 700
30	16.7	10 300	60 600	56 900‡	86 100	159 700	293 800	2 056 100
40	7.6	8 900	49 300	43 000‡	49 200	71 600	111 500	564 600
50	3.7	8 100	42 200	36 200	36 200‡	44 900	61 200	233 900
52§	3.2	8 000**	41 000	35 100	34 400‡	41 600	55 400	200 200
60	1.9	7 500	37 200	31 900	29 800‡	33 400	41 300	123 300
64¶	1.5	7 400	35 600	30 700	28 200‡	30 700	36 800**	101 100
70	1.0	7 100	33 400	28 900	26 000‡	27 400	31 500	76 100
80	0.6	6 800	30 400	26 600	23 500‡	23 700	25 900	52 500
90	0.4	6 600	27 900	24 700	21 700	21 300‡	22 400	39 200
100	0.2	6 400	25 900	23 200	20 300	19 500‡	20 100	31 200

£1 (€1.1; $1.5).
*Cost effectiveness of requiring basic radon preventive measures in all new homes throughout UK is £11 400.
†Calculations assume that never smokers, current smokers, and former smokers are equally likely to remediate. They also assume that percentage reduction in radon concentration achieved by remediation is independent of pre-remediation concentration.
‡Most cost effective action level for each targeted area.
§Areas with mean indoor radon concentration of 52 Bq/m^3 have 3% of radon measurements >200 Bq/m^3.
¶Areas with mean indoor radon 64 Bq/m^3 have 5% of radon measurements >200 Bq/m^3.
**Limits of current policy in England (that is, for new homes, basic radon preventive measures are required in areas with ≥3% of radon measurements >200 Bq/m^3, and for existing homes offers of free measurements are targeted on areas with ≥5% of radon measurements >200 Bq/m^3 with an action level of 200 Bq/m^3).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Radon gas in ordinary homes increases the risk of lung cancer, particularly for smokers

Current UK policies to control radon in the home focus on radon concentrations >200 Bq/m^3 while neglecting the lower levels experienced by most of the population

Previous economic evaluations of radon control policies have not used modern methodology with recent data

WHAT THIS STUDY ADDS

About 1100 deaths from lung cancer in the UK each year are related to radon, but less than 5% of these arise from radon concentrations >200 Bq/m^3

A policy requiring basic measures to prevent radon in all new homes throughout the UK would be highly cost effective and would contribute to reducing lung cancer mortality

Policies to identify and remediate existing homes with high radon concentrations are unlikely to be cost effective, and have limited potential to reduce lung cancer mortality in the UK

Government policy to identify existing homes with radon measurement >200 Bq/m^3 and recommend remediation has poor cost effectiveness. Lowering the action level from 200 Bq/m^3 to 100 Bq/m^3 might improve cost effectiveness, possibly to about £30 000 per QALY in areas with a mean radon level of 64 Bq/m^3, but only provided that smokers and former smokers remediated as often as never smokers. Cost effectiveness would also improve if the proportion of homeowners remediating when advised to do so increased—for example, through better advice and support. Requiring all homeowners to disclose all radon measurements to potential purchasers when selling the home might also increase remediation rates.

The most common reason for not following advice to remediate is cost.[11] Grants towards radon remediation might increase remediation rates, and could be justified because remediation has health benefits to future as well as current home occupiers. However, a documented low radon concentration might materially benefit homeowners via the house price, especially in areas with high radon levels.

Strengths and limitations of the study

As well as healthcare costs, we also included other direct costs such as those incurred by homeowners, who typically pay for both preventive and remedial action, and by the Health Protection Agency and government departments involved in radon control. Such costs are not usually included by NICE at present, but as it increasingly undertakes evaluation of public health interventions[12] this wider societal perspective may become more common.

About six in seven deaths from radon related lung cancer are caused by radon and active smoking jointly (see bmj.com). Our analyses assume that those in whom lung cancers are averted by radon control have smoking habits, and therefore lung cancer risks, typical of the total population. This is likely to be appropriate for prevention in new homes. For existing homes, however, a recent study has shown that remediation rates among homeowners who are lifelong non-smokers are about twice those of homeowners who are current smokers.[11] If so, cost effectiveness of remediation in existing homes may be even less favourable than indicated by our analyses, possibly by a substantial amount.

Conclusions and policy recommendations

We conclude that requiring basic prevention of radon in new homes throughout the UK would be a highly cost effective public health intervention and could make a modest but worthwhile contribution to reducing the annual number of deaths from lung cancer, alongside existing policies to reduce smoking. UK radon concentrations are lower than those in most other countries so similar policies are likely to be even more cost effective elsewhere. In contrast, the case in the UK for policies to remediate existing homes is less clear and the potential of such policies to reduce deaths from radon related lung cancer is limited.

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Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study

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ABSTRACT

Objectives To investigate the performance of classic risk factors, and of some new biomarkers, in predicting cardiovascular mortality in very old people from the general population with no history of cardiovascular disease.

Design The Leiden 85-plus Study (1997-2004) is an observational prospective cohort study with 5 years of follow-up.

Setting General population of the city of Leiden, the Netherlands.

Participants Population based sample of participants aged 85 years (215 women and 87 men) with no history of cardiovascular disease; no other exclusion criteria.

Main measurements Cause specific mortality was registered during follow-up. All classic risk factors included in the Framingham risk score (sex, systolic blood pressure, total and high density lipoprotein cholesterol, diabetes mellitus, smoking and electrocardiogram based left ventricular hypertrophy), as well as plasma concentrations of the new biomarkers homocysteine, folic acid, C reactive protein, and interleukin 6, were assessed at baseline.

Results During follow-up, 108 of the 302 participants died; 32% (35/108) of deaths were from cardiovascular causes. Classic risk factors did not predict cardiovascular mortality when used in the Framingham risk score (area under receiver operating characteristic curve 0.53, 95% confidence interval 0.42 to 0.63) or in a newly calibrated model (0.53, 0.43 to 0.64). Of the new biomarkers studied, homocysteine had most predictive power (0.65, 0.55 to 0.75). Entering any additional risk factor or combination of factors into the homocysteine prediction model did not increase its discriminative power.

Conclusions In very old people from the general population with no history of cardiovascular disease, concentrations of homocysteine alone can accurately identify those at high risk of cardiovascular mortality, whereas classic risk factors included in the Framingham risk score do not. These preliminary findings warrant validation in a separate cohort.

INTRODUCTION

In primary prevention of cardiovascular disease, patients are identified according to classic risk factors, including age, sex, systolic blood pressure, total and high density lipoprotein cholesterol, diabetes mellitus, smoking, and electrocardiogram based left ventricular hypertrophy.[1-3] The Framingham risk score, which includes these classic risk factors, was originally validated for people aged up to 75 years, but has nevertheless been much used in older populations.[4 5] Observational studies in the oldest people (≥85 years) have shown that the power of classic risk factors to predict cardiovascular disease diminishes with advancing age.[3 6-11]

Several new biomarkers are effective indicators of high risk of cardiovascular disease—namely C reactive protein, folic acid, interleukin 6, homocysteine, fibrinogen, cystatin C, troponin I, various lipoproteins and apolipoproteins, and natriuretic peptides. Their incremental predictive value beyond that of classic risk factors is generally small.[12-22] Their predictive value in older populations has rarely been studied, and findings were mostly inconclusive.[23-26] Recently, however, a study in a cohort of men aged 71 years found that the addition of four new biomarkers to a model with classic risk factors significantly improved prediction of death from cardiovascular causes.[27] Data about the performance of combinations of new biomarkers in isolation from classic risk factors are non-existent.

We assessed the performance of classic risk factors and some new biomarkers as predictors of cardiovascular mortality over five years in people without cardiovascular disease at age 85.

METHODS

Study design, setting and population

The Leiden 85-plus Study is an observational, prospective, population based cohort study of inhabitants of the city of Leiden, the Netherlands. Its general aim is to study determinants of successful ageing in the general population of the oldest people. Between September 1997 and September 1999, 705 people in the 1912-14 birth cohort reached the age of 85 years and were eligible to participate in the study. No exclusion criteria were used. Fourteen people died before enrollment; a total of 599 (87%) people were recruited to the study. All participants underwent face to face interviews, blood sampling, electrocardiography, and functional tests.

We excluded all participants with a history or evidence of cardiovascular disease (n=272 of 599, 45%). A further 25 participants were excluded because of missing data leading to a final sample size of n=302.

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Cardiovascular mortality

Participants were followed up for mortality until age 90 years; none were lost to follow-up. Dates of death were obtained from municipality records. Specific data on causes of death were obtained from Statistics Netherlands, where all national death certificates are coded according to the International Classification of Diseases and Related Disorders, 10th revision.[28] Causes of death were divided into cardiovascular causes and non-cardiovascular causes.

Classic risk factors in participants at age 85 years

At baseline we measured systolic blood pressure and serum concentrations of total cholesterol and high density lipoprotein. Self-reported current and past smokers of cigarettes, cigars, and pipes were judged to have a history of smoking. Diabetes mellitus was assessed by physician reports, non-fasting glucose concentrations and use of diabetes medication. Electrocardiograms were recorded and coded for left ventricular hypertrophy.

New biomarkers in participants at age 85 years

We selected four new biomarkers measured in the Leiden 85-plus Study: homocysteine and folic acid from the methionine-homocysteine pathway, and C reactive protein and interleukin 6 as markers of inflammation.

Data analysis

For every participant, we calculated the Framingham risk score with 5 year cardiovascular mortality as the end point and including all weighted classic risk factors.[5] We assigned participants to high, intermediate, and low risk groups based on tertiles of the calculated risk scores.

We constructed seven new prediction models, using combinations of classic risk factors and new biomarkers: (1) all classic risk factors; (2) homocysteine concentration and sex; (3) folic acid concentration and sex; (4) C reactive protein concentration and sex; (5) interleukin 6 concentration and sex; (6) homocysteine concentration plus all classic risk factors; and (7) all four new biomarkers and sex. We entered each combination of risk factors in a Cox proportional hazards model, and, for each model, noted for each participant their individual predicted risk of cardiovascular mortality during the follow-up period. We assigned participants to a high, intermediate, or low risk group on the basis of tertiles of predicted risk for each model.

We assessed the performance of the different prediction models by comparing the tertiles of Framingham risk scores with the observed 5 year cardiovascular mortality. In addition, using risk scores from each model, receiver operating characteristic curves with corresponding areas under the curves (neutral value 0.50=risk prediction by pure chance) were constructed, using cardiovascular mortality versus non-cardiovascular mortality or survival as the outcome.

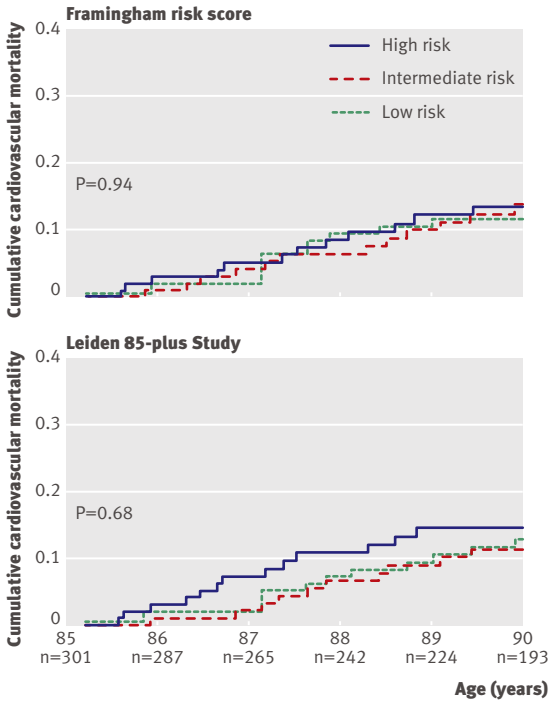

Fig 1 | Cumulative cardiovascular mortality depending on tertiles of risk obtained from prediction models using homocysteine, folic acid, C reactive protein and interleukin 6

RESULTS

The majority of the 302 participants were women, did not live in institutions, and performed well on the mini-mental state examination. Of the 302 participants, 108 (36%) died during follow-up; 35 (32%) of these deaths were caused by cardiovascular disease.

We found no differences in cardiovascular mortality between the risk categories based on the Framingham risk score (risk ratio for high *v* low risk category 1.2, 95% confidence interval 0.51 to 2.6; see bmj.com). When the Framingham risk factors were entered as separate variables in a Cox proportional hazard model to create a prediction model calibrated for very old people, three new risk categories were obtained, but these did not predict the observed 5-year cardiovascular mortality either (risk ratio for high *v* low risk category 1.3, 95% confidence interval 0.57 to 2.7).

Figure 1 shows the performance of the sex adjusted prediction models based on homocysteine, folic acid, C reactive protein, and interleukin 6. Only the model based on homocysteine resulted in significant differences between the risk categories (log rank test, P=0.002); the high risk category had a 3.4-fold (95% confidence interval 1.4 to 8.1) increased risk of cardiovascular mortality compared with the low risk category. Entering additional biomarkers into the homocysteine model did not increase its discriminative power.

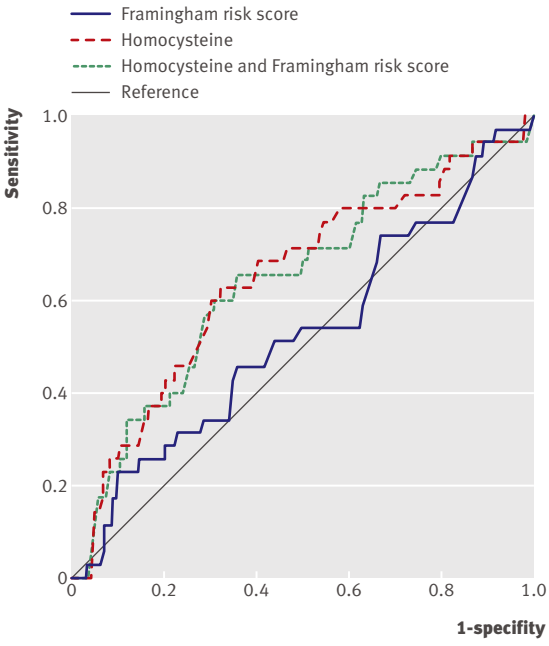

Fig 2 | Receiver operating characteristic curves showing performance of three prediction models for 5 year cardiovascular mortality based on Framingham risk score, homocysteine concentrations only, and homocysteine concentrations plus Framingham risk score

When the predictive value of the Framingham risk score and the risk model based on homocysteine alone were compared by receiver operating characteristic curves (figure 2), the area under the curve for the Framingham risk score was 0.53 (95% confidence interval 0.42 to 0.63) and that for the homocysteine-based model was 0.65 (0.55 to 0.75). Combining the Framingham risk score and the model based on homocysteine did not increase discriminative power (area under the curve 0.65, 95% confidence interval 0.54 to 0.75), nor did the power increase for the model based on a combination of all four new biomarkers (area under the curve 0.65, 95% confidence interval 0.55 to 0.75, receiver operating characteristic curve not shown).

WHAT IS ALREADY KNOWN ON THIS SUBJECT

The Framingham risk score, based on classic risk factors for cardiovascular disease, is still frequently used to estimate risk in older people

The predictive value of these classic risk factors, such as hypercholesterolaemia and systolic hypertension, weakens with age

In the past four decades new biomarkers have been identified that have clear associations with incident cardiovascular disease

WHAT THIS STUDY ADDS

In very old age, classic risk factors as included in the Framingham risk score no longer predict 5 year cardiovascular mortality in people with no history of cardiovascular disease

By contrast, a single homocysteine measurement could accurately identify older individuals who are at high risk of cardiovascular mortality

Plasma concentrations of homocysteine, rather than classic risk factors, could potentially be used to select older people for primary preventive interventions

These findings should be validated in a separate cohort

DISCUSSION

Principal findings

Cardiovascular mortality in people at the age of 85 with no history of cardiovascular disease was not accurately predicted by classic risk factors such as those included in the Framingham risk score. By contrast, a single measurement of homocysteine accurately identified those at high risk of cardiovascular mortality. These results suggest that in this age group, risk identification for primary prevention of cardiovascular disease should be based not on classic risk factors, but on plasma concentrations of homocysteine.

Our study confirms earlier findings of a fall in the predictive abilities of the Framingham risk score in older populations.[3 6]

The strong association between raised concentrations of homocysteine and cardiovascular morbidity and mortality has been described in various populations.[16 18 23 29-31] We have shown that homocysteine remains a potent predictor of risk in older people and is equally robust without classic risk factors being included in the model.

We were unable to replicate in our sample the associations found in younger age groups between cardiovascular disease and concentrations of C reactive protein, interleukin 6, and folic acid.[13 17 20 32] The weakness of these markers of inflammation in predicting cardiovascular mortality in the oldest people is in line with previous findings.[33]

Strengths and weaknesses

The Leiden 85-plus Study is an observational, prospective study of the oldest people, in which 87% of the general population participated and follow-up on mortality was complete. These factors add to the external validity of our results. Another strength of our study is the consistency of the results across statistical methods which supports the validity of our findings.[34-36]

A weakness of our study is the limited number of new biomarkers that we selected to investigate. Other biomarkers might have predictive value equal to that of homocysteine in this population. A second limitation of our study is its relatively small size. We recommend validation of our findings in a larger cohort.

Clinical implications and future research

We studied the best way to identify patients at high risk, not the causes that underlie the observed associations. Although homocysteine accurately predicts cardiovascular mortality in very old age, we do not suggest that lowering homocysteine will be beneficial; in fact, so far this approach has been shown to be ineffective.[37 38] The role of statins in the primary prevention of cardiovascular disease in old age needs

to be explored, since their beneficial effect in secondary prevention is evident.[39 40]

Conclusions

A model based on homocysteine concentration alone was a better predictor of cardiovascular mortality in very old people with no history of cardiovascular disease than were models based on classic risk factors. These preliminary findings call for validation.

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Efficacy of statins in familial hypercholesterolaemia: a long term cohort study

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ABSTRACT

Objective To determine the efficacy of statin treatment on risk of coronary heart disease in patients with familial hypercholesterolaemia.

Design Cohort study with a mean follow-up of 8.5 years.

Setting 27 outpatient lipid clinics.

Subjects 2146 patients with familial hypercholesterolaemia without prevalent coronary heart disease before 1 January 1990.

Main outcome measures Risk of coronary heart disease in treated and "untreated" (delay in starting statin treatment) patients compared with a Cox regression model in which statin use was a time dependent variable.

Results In January 1990, 413 (21%) of the patients had started statin treatment, and during follow-up another 1294 patients (66%) started after a mean delay of 4.3 years. Most patients received simvastatin (n=1167, 33 mg daily) or atorvastatin (n=211, 49 mg daily). We observed an overall risk reduction of 76% (hazard ratio 0.24 (95% confidence interval 0.18 to 0.30), P<0.001). In fact, the risk of myocardial infarction in these statin treated patients was not significantly greater than that in an age matched sample from the general population (hazard ratio 1.44 (0.80 to 2.60), P=0.23).

Conclusion Lower statin doses than those currently advised reduced the risk of coronary heart disease to a greater extent than anticipated in patients with familial hypercholesterolaemia. With statin treatment, such patients no longer have a risk of myocardial infarction significantly different from that of the general population.

INTRODUCTION

Familial hypercholesterolaemia is associated with a greatly increased risk of coronary heart disease, and statins are the first choice treatment for all patients with the condition. Placebo controlled trials were not carried out in these patients when statins were introduced for ethical reasons,[1] and so we lack estimates of the true efficacy of statin treatment in such patients. Two observational studies suggest that statins have roughly halved the risk of coronary heart disease in patients with familial hypercholesterolaemia.[2 3] However, the exact prognosis of treated asymptomatic patients remains unknown, and this lack of hard endpoint data has, for example, limited access to life insurance.[4]

In this study we investigated the effect of statins on the risk of incident coronary heart disease in patients with familial hypercholesterolaemia, using the variation in the time of starting statin treatment to mimic a clinical trial.

METHODS

Study population

During 1989-2002, we recruited a cohort of 2400 patients with familial hypercholesterolaemia from 27 lipid clinics as described previously[5] and recorded extensive phenotypic data for them.[6] We chose 1 January 1990, just after the first statin (simvastatin) became available in the Netherlands, as the start point. We excluded patients who already had coronary heart disease by 1990.

In addition, we compared the risk of incident myocardial infarction in the patients older than 55 years on 1 January 1990 with that in the general population as represented by a selection from the Rotterdam study, a population based, prospective study assessing the disease burden in elderly people since 1990 [7], matched for age and sex.

Outcome measures

We defined coronary heart disease in our study cohort as at least one of the following:

- Myocardial infarction
- Percutaneous coronary intervention or other invasive procedures
- Coronary artery bypass grafting
- Angina pectoris (classic symptoms and a positive test).

In the Rotterdam study, no data on angina were available. We therefore chose to study myocardial infarction as the end point in this analysis. Patients with percutaneous transluminal coronary angioplasty, coronary bypass grafting, or prevalent myocardial infarction were excluded from both the sample of patients from our cohort and the selected population from the Rotterdam study.

See bmj.com for details of the statistical analysis.

RESULTS

Of the 2400 patients recruited, we excluded 254 who already had coronary heart disease by 1990. We excluded a further 188 patients because the type of lipid lowering treatment or the date of starting statin treatment was unknown, leaving 1950 patients. In January 1990, 413 patients were treated with a statin, and a further 1294 patients were prescribed statins

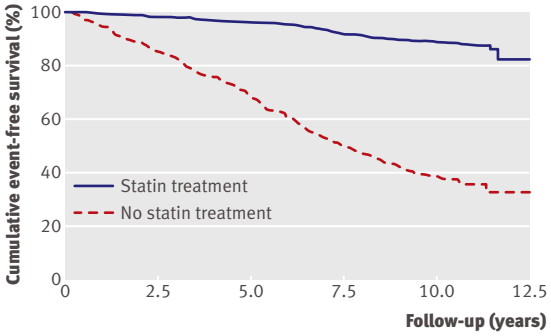

Fig 1 | Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment (P<0.001 for difference)

during follow-up. The mean delay in starting statin use was 4.3 years (SD 3.3 years).

The patients who immediately received statin treatment in 1990 were on average 3.5 years older, had higher total and low density lipoprotein (LDL) cholesterol concentrations (both P<0.001), had lower high density lipoprotein (HDL) cholesterol levels (P=0.02), and were significantly more likely to be hypertensive than the patients who started statin treatment later. Twenty eight patients stopped taking statins for unreported reasons.

The mean follow-up time was 8.5 years (SD 3.1 years). In total, 408 patients had an incident coronary event, of whom 161 had been using statins for an average of 3.4 years (median 2.7 years, range 1 month to 11.6 years). Most patients (n=1167) used simvastatin with a mean dose of 33 mg (SD 20 mg), leading to 44% (SD 16%) lower LDL cholesterol concentrations compared with before they started statin treatment. A further 211 patients used atorvastatin with a mean daily dose of 49 mg providing a reduction in LDL cholesterol level of 49% (SD 15%). Less commonly used statins were pravastatin and fluvastatin. During statin treatment the mean total cholesterol concentration was 5.9 mmol/l (SD 1.2 mmol/l), mean LDL cholesterol was 4.0 mmol/l (SD 1.2), and mean HDL cholesterol was 1.28 mmol/l (SD 0.41).

The absolute risk of first onset of coronary heart disease was 11/1000 person years in statin treated patients compared with 119/1000 person years in untreated patients. Incident coronary heart disease occurred at younger age in untreated patients (48.6 *v* 50.9 years, P=0.05). The treated group had a significantly better event-free survival (P<0.001, fig 1). After adjustment for year of birth, sex, smoking, HDL and LDL cholesterol concentrations, diabetes, and hypertension, statin treated patients had a 82% reduction in risk of coronary heart disease compared with untreated patients (hazard ratio 0.18 (95% confidence interval 0.13 to 0.25), P<0.001).

As expected, men had a 2.5 times greater risk of coronary heart disease than women (95% confidence interval 2.1 to 3.1, P<0.001). We found that women taking statins had a 79% reduction in risk of coronary heart disease compared with women not taking statins (hazard ratio 0.21 (0.13 to 0.34), P<0.001); the men had an 83% risk reduction (hazard ratio 0.17 (0.11 to 0.26), P<0.001).(See table 2 on bmj.com.)

Patients who developed coronary heart disease had higher serum LDL cholesterol concentrations before treatment than did those without coronary heart disease (7.5 mmol/l *v* 7.2 mmol/l, P=0.03). During statin treatment, however, LDL cholesterol levels were identical among patients with and without coronary heart disease (4.1 mmol/l *v* 4.0 mmol/l, P=0.38). Classic risk factors were, as expected, more common in patients with coronary heart disease.

Of all 1288 patients who had ever smoked, 333 had stopped before 1990. A total of 407 statin users never smoked, 388 had stopped before statin treatment was started, and 105 quit within six months of starting statin treatment. To test if lifestyle improvement related to the start of statin treatment could explain why smokers showed a larger risk reduction with statins, we adjusted for smoking cessation within six months of the start of statin treatment, but this did not materially change the effect of statin treatment on coronary heart disease risk (hazard ratio 0.20 (0.15 to 0.26), P<0.001).

A total of 243 patients in our cohort were never treated with statins. We performed an additional analysis adding those patients to the treatment group, as if statin treatment had started on 1 January 1990, to estimate the effect of an intention to treat analysis. The hazard ratio was even lower under these assumptions (data not shown).

We finally compared the risk of myocardial infarction in patients with familial hypercholesterolaemia who were older than 55 years (n=261, 64 men) with that in 1975 people in a subgroup of the participants in the Rotterdam study. The mean age in both subgroups was 61.6 years and both had 24.5% men as a result of stratified selection from the Rotterdam study. The

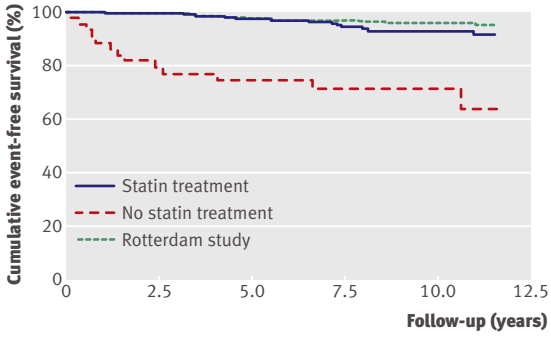

Fig 2 | Kaplan-Meier curve estimates of cumulative myocardial infarct-free survival among patients with familial hypercholesterolaemia older than 55 years according to statin treatment compared with a sample from the general population (Rotterdam study). (P<0.001 for difference between untreated patients and general population; P=0.07 for difference between treated patients and general population)

absolute risk of myocardial infarction was 6.7/1000 person years in our statin treated patients, 60.5/1000 person years in our untreated patients, and 4.1/1000 person years in the sample from the Rotterdam study. Event-free survival of our statin treated patients was not significantly different from that of the Rotterdam study sample (log rank test P=0.07), whereas our untreated patients clearly had a higher risk of coronary heart disease (log rank test P<0.001) (fig 2). After adjustment for year of birth and sex, the point estimate of risk of myocardial infarction in our treated patients with familial hypercholesterolaemia was higher than the risk in the subgroup of the Rotterdam study, but this was not significant (hazard ratio 1.44 (0.80 to 2.60), P=0.23), whereas the risk in our untreated patients was 8.7 times higher (hazard ratio 8.69 (4.77 to 15.82), P<0.001).

DISCUSSION

Relatively modest doses of statins reduced the risk of coronary heart disease by about 80% in patients with familial hypercholesterolaemia, a much more pronounced reduction than was anticipated based on earlier studies.[2 3] Statin treated patients older than 55 years had a risk of myocardial infarction approaching that of the general population, and men and women experienced similar risk reductions in our study.

Strengths and weaknesses of our study

Our follow-up study has a number of limitations. Firstly, it was observational and not a randomised study. Therefore, the patients who started treatment immediately in 1990 may have represented a selected subgroup with more severe risk. If this were so, it would have resulted in a higher risk for the treated group compared with a randomised trial that distributed the risks equally. However, it seems unlikely that we have underestimated the risk reduction as the effect was unexpectedly large.

Secondly, it could be argued that our approach exaggerates the effect of the treatment, because our study was not placebo controlled. Patients might have improved their lifestyle in conjunction with starting statin treatment. However, adjustment for smoking cessation within six months after the start of treatment (as a proxy for lifestyle improvement) did not change the effect of statin treatment.

Thirdly, we analysed statin treatment as a time dependent variable, whereas an intention to treat analysis might have yielded smaller risk reductions. We analysed the 28 patients who stopped statin treatment as if they had stayed on treatment and analysed all patients who were never treated with statins with the treated group as if they had started treatment on 1 January 1990, to estimate the effect that an intention to treat analysis could have had: this showed an even larger effect. The decrease in hazard ratio indicates that our results are not overestimating the effect as a result of deselection of worst cases.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Statins are the first line treatment for familial hypercholesterolaemia, but their efficacy is unknown because hard end points were not studied in placebo controlled trials

WHAT THIS STUDY ADDS

Lower statin doses than currently advised reduced coronary heart disease risk by 80% in patients with familial hypercholesterolaemia

Statin treated patients older than 55 years had a similar risk of myocardial infarction as did a sample from the general population of the same age

Although some of the weaknesses associated with lack of randomisation have been addressed, there is always the danger that unrecognised confounding factors might have affected our results.

Comparison with other studies

The large risk reduction and the overlap of the event-free survival between the treated patients and a sample of the general population (from Rotterdam study) suggest that statin treatment has profoundly improved the prognosis for familial hypercholesterolaemia.

Two previous studies have investigated this issue. A study in the United Kingdom suggested that statins reduced mortality in patients with familial hypercholesterolaemia but that mortality was still higher than in the general population.[2] Exact information about the start date of statin treatment was not available, however, suggesting there might have been an unrecognised delay in statin initiation similar to what we found.

In a much smaller study, 214 statin treated patients with familial hypercholesterolaemia still had increased risk of cardiovascular disease.[3] As suggested by the high frequency of premature cardiovascular disease (45%) in first degree relatives, the patients of this study might have been selected preferentially for severe risk of coronary heart disease. Moreover, statin treatment was not assessed against untreated familial hypercholesterolaemia and not in a time dependent fashion. The latter may have resulted in underestimation of the statin effect because of misclassification of periods without treatment.

Implications of findings

The standard treatment used currently is more aggressive than that used in our study: current regimens use simvastatin and atorvastatin doses up to 80 mg daily.[8 9] It should be emphasised that we excluded all prevalent cases from our study, thereby restricting our study to primary prevention. Our results cannot be extrapolated to secondary prevention, which may require more aggressive treatment.

In previous studies we tested statin treatment of children with familial hypercholesterolaemia and

showed attenuation of progression of carotid intima-media thickness.[10 11] Our present study suggests that starting aggressive treatment during early childhood, as is currently done and advised by the American Academy of Pediatrics, is probably not necessary to reduce coronary heart disease risk.[12] Although atherosclerosis is present in children, this process is to a certain extent reversible.[13] It is probably safe to limit statin treatment of children with heterozygous familial hypercholesterolaemia to those whose first degree relatives have severe premature coronary heart disease.

In conclusion, our data show that lower statin doses than currently advised result in impressive reductions of coronary heart disease risk in patients with familial hypercholesterolaemia. These findings warrant an immediate start of statin treatment after familial hypercholesterolaemia has been diagnosed since such treatment leads to near normalisation of coronary heart disease risk.

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Are you working?

The patient who coauthored this piece, a refugee who is now resident in the UK, is profoundly grateful for the medical help he has received under the NHS, an institution he much admires. But recently he asked me, "Why do doctors ask me if I'm working—it's the first question they ask. Why don't they ask me first about my health problems?" He is currently being investigated and treated for several.

I asked what this question meant to him, and was shamed by the answer, which I summarise here:

"When doctors ask me if I'm working, they look at me, they think 'refugee'; they think of the taxes they are paying, and I'm not working. They imply I don't deserve health care or their attention unless I am working and paying taxes; they are imposing extra barriers because I am not white and British. Do they ask all their patients if they are working? They are stereotyping me as … lazy, having no skills to offer. They think I came here to do nothing, unwilling to make investment in living in the UK.

"It is humiliating. It is not my fault that I cannot work. They know nothing about me, how I have lived, why I am here. They are making moral judgments before they ask medical questions."

It is hard to counter these interpretations. This man's fight for human rights cost him imprisonment and months of torture. He had to leave his country in order to survive and to avert further persecution of himself and his family; he has indefinite leave to remain. He does not expect to be treated as hero or as victim, although he is both and more, but he does expect to be treated with respect.

This patient was by no means the first to raise with me the issue of being asked about work early in a medical interview, nor the only one to sound hurt in describing it. I had rarely followed it up, and never before received such an impassioned answer. It may be that the question about work is intended as an innocuous opener, but it is heard and understood in the setting of increasing political moves to restrict access to health care and to present refugees as undeserving. To introduce it later, and in context, is little to ask, and we ask it on behalf of thousands of refugees in the UK.

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