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Screening men for abdominal aortic aneurysm: 10 year mortality and cost effectiveness results from the randomised Multicentre Aneurysm Screening Study

S G Thompson,[1] H A Ashton,[2] L Gao,[1] R A P Scott,[2] on behalf of the Multicentre Aneurysm Screening Study Group

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[1]MRC Biostatistics Unit, Institute of Public Health, Cambridge CB2 0SR
[2]Scott Research Unit, St Richard's Hospital, Chichester
Correspondence to: S G Thompson
simon.thompson@mrc-bsu.cam.ac.uk

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ABSTRACT

Objectives To assess whether the mortality benefit from screening men aged 65-74 for abdominal aortic aneurysm decreases over time, and to estimate the long term cost effectiveness of screening.

Design Randomised trial with 10 years of follow-up.

Setting Four centres in the UK. Screening and surveillance was delivered mainly in primary care settings, with follow-up and surgery offered in hospitals.

Participants Population based sample of 67 770 men aged 65-74.

Interventions Participants were individually allocated to invitation to ultrasound screening (invited group) or to a control group not offered screening. Patients with an abdominal aortic aneurysm detected at screening underwent surveillance and were offered surgery if they met predefined criteria.

Main outcome measures Mortality and costs related to abdominal aortic aneurysm, and cost per life year gained.

Results Over 10 years 155 deaths related to abdominal aortic aneurysm (absolute risk 0.46%) occurred in the invited group and 296 (0.87%) in the control group (relative risk reduction 48%, 95% confidence interval 37% to 57%). The degree of benefit seen in earlier years of follow-up was maintained in later years. Based on the 10 year trial data, the incremental cost per man invited to screening was £100 (95% confidence interval £82 to £118), leading to an incremental cost effectiveness ratio of £7600 (£5100 to £13 000) per life year gained. However, the incidence of ruptured abdominal aortic aneurysms in those originally screened as normal increased noticeably after eight years.

Conclusions The mortality benefit of screening men aged 65-74 for abdominal aortic aneurysm is maintained up to 10 years and cost effectiveness becomes more favourable over time. To maximise the benefit from a screening programme, emphasis should be placed on achieving a high initial rate of attendance and good adherence to clinical follow-up, preventing delays in undertaking surgery, and maintaining a low operative mortality after elective surgery. On the basis of current evidence, rescreening of those originally screened as normal is not justified.

Trial registration Current Controlled Trials ISRCTN37381646.

INTRODUCTION

England and Scotland have recently introduced national screening programmes for abdominal aortic aneurysm in men aged 65.[1 2] The screening programme is based closely on the protocol and procedures in the Multicentre Aneurysm Screening Study (MASS),[3 4] which has provided most of the randomised evidence for the mortality benefit after ultrasonography for abdominal aortic aneurysm.[5 6]

Uncertainties relating to screening are its long term benefit on mortality and cost effectiveness, whether rescreening those with a normal scan is warranted, and the extent to which incidental detection of aneurysms erodes the benefit of screening over time. MASS, started in 1997, runs more than 10 years ahead of the UK screening programme and is uniquely positioned to tackle these uncertainties and to inform the development of the national programme.

Results from MASS were last published after seven years of follow-up.[4] The only existing evidence from randomised trials after seven years comes from a small trial,[7] in which a possibly substantial increase in ruptured aneurysms among participants screened as normal was noted during later follow-up.[8] Such an increase would reduce the long term benefit from an initial scan. Moreover, long term cost effectiveness has been estimated only through modelling,[9 10] and such models extrapolated from short term data may be misleading.[11 12] We present new information from the 10 years of follow-up now available in MASS.

METHODS

Overall, 67 770 men aged 65-74 were recruited during 1997-9 from four UK centres and randomised to receive an invitation to screening for abdominal aortic aneurysm or not (control group). Among the 33 883 invited men, 27 204 (80%) attended and 1334 aneurysms (≥3.0 cm) were detected. Surveillance within this group involved rescanning: annually for those with aneurysms 3.0-4.4 cm and every three months

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for those with aneurysms 4.5-5.4 cm. Patients were referred for possible elective surgery when the aneurysm reached 5.5 cm, the aneurysm had expanded by 1.0 cm or more in one year, or symptoms attributable to the aneurysm were reported.

We collected additional data from local hospital records on follow-up ultrasonography within medical imaging departments and surgery for abdominal aortic aneurysm. The UK Office for National Statistics notified us of deaths up to 31 March 2008. Follow-up ranged from 8.9 to 11.2 years (mean 10.1 years). The primary outcome of interest—deaths related to abdominal aortic aneurysm—is defined as all deaths within 30 days of any surgery (elective or emergency) for abdominal aortic aneurysm plus all deaths with codes 441.3-441.6 (international classification of diseases, ninth revision).

We used unadjusted Cox regression to compare deaths related to abdominal aortic aneurysm and all cause mortality between the two randomised groups. Life years gained was derived as the area between the Kaplan-Meier curves of deaths related to abdominal aortic aneurysm for the two groups, adjusting for deaths from other causes.[13] We also obtained an unbiased randomisation based estimate for the benefit of attending initial screening,[14] by subtracting from the controls a group that is equivalent to the non-attending group among those invited.

We estimated the cost effectiveness of screening from a UK health service perspective, for follow-up truncated at 10 years. The relevant unit costs[15] are based on a costing exercise at 2000-1 prices[16] uplifted to 2008-9 prices. We applied discounting at 3.5% per year for costs and effects. Incremental costs and the cost effectiveness ratio take into account censoring at the end of follow-up by dividing the follow-up into intervals of six months.[17 18] We used Fieller's method to calculate the confidence interval for the incremental cost effectiveness ratio.[19]

RESULTS

Of the 1334 men with abdominal aortic aneurysm detected at initial scan, 72% (n=963) had complete clinical follow-up to 10 years compared with 76% at seven years. Men with missing data on death (2.7% at 10 years *v* 2.1% at seven years) were censored at the time they were last known to be alive.

Overall, 155 deaths related to abdominal aortic aneurysm (absolute risk 0.46%) occurred in the invited group compared with 296 (0.87%) in the control group, a relative risk reduction of 48% (hazard ratio 0.52, 95% confidence interval 0.43 to 0.63; see bmj.com). The benefit seen in earlier years was maintained in later years, with continued divergence of the cumulative curves of deaths (figure). The mean age at death was similar in the invited and control groups (75.0 *v* 75.4 years). Non-fatal ruptures of aneurysms were about halved in the invited group (see bmj.com). The unbiased estimate of the reduction in deaths related to abdominal aortic aneurysm among men who were screened was 60% (hazard ratio 0.40, 95% confidence interval 0.32 to 0.50).

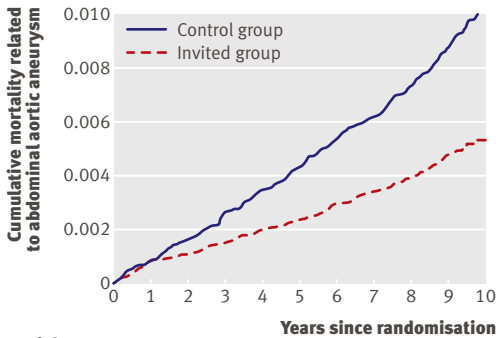
Twenty one men in the invited group died within 30 days of elective surgery, and another six men after more than 30 days. Despite being invited for screening, 170 men subsequently had a ruptured aneurysm. Many of these were excluded from the potential benefit of screening (see bmj.com). Some aneurysms ruptured between recall scans, pending a decision about surgery and while awaiting surgery (see bmj.com). Nineteen of 25 ruptures in men with normal initial scans were fatal. The rate of ruptures increased noticeably after eight years (see bmj.com). In years 8, 9, and 10 there were, respectively, six, six, and three ruptures, with corresponding rupture rates per 10 000 person years of 3.0, 3.8, and 5.7. Time since initial scan was the main determinant of this increased risk.

Over the 10 years, 552 elective operations took place in the invited group and 226 in the control group. The respective 30 day mortality rates of 4% (21/552) and 6% (13/226) were not significantly different (P=0.23). Emergency surgery took place in 62 men in the invited group compared with 141 in the control group. The respective 30 day mortality rates of 29% (18/62) and 36% (50/141) were not significantly different (P=0.37). Nearly all the operations in MASS were open repairs, with endovascular repair occurring only in the later period of follow-up. Two endovascular repairs were undertaken as emergency procedures (both patients died within 30 days) and 68 as elective procedures, representing 9% (68/778) of all elective operations. The 30 day mortality rate for elective endovascular repair was 3% (2/68).

The costs per person were greater in the invited group, by an average of £100 (see bmj.com). The extent of reduction in number of deaths in the invited group led to an estimated incremental cost effectiveness ratio of £7600 (95% confidence interval £5100 to £13 000) per life year gained over the 10 years of the trial.

DISCUSSION

The benefit of inviting men aged 65-74 to screening for abdominal aortic aneurysm remains about the same



Men at risk

Control group	33 887	32 103	29 992	27 664	25 000	13 242
Invited group	33 883	32076	30 101	27 860	25 388	13 385

Cumulative deaths related to abdominal aortic aneurysm, by time since randomisation

WHAT IS ALREADY KNOWN ON THIS TOPIC

Ultrasound screening for abdominal aortic aneurysm in men aged 65 or more reduces mortality in the short term

Rupture of aneurysm in those originally screened as normal, and incidental detection of aneurysms, could reduce the effectiveness of screening over time

WHAT THIS STUDY ADDS

The mortality benefit of one-off screening of men aged 65-74 for abdominal aortic aneurysm is maintained up to 10 years, despite an increase in ruptures among those screened as normal

About half of all aneurysm related deaths should be prevented by a national screening programme

The long term cost effectiveness of screening is highly favourable

7-10 years after screening: the reduction in number of deaths related to abdominal aortic aneurysm in MASS is estimated as 42% at four years,[3] 47% at seven years,[4] and now 48% at 10 years. Being based on a population based sample of UK men, these figures correspond to the expected benefit that will derive from the UK screening programme. About 1900 deaths each year, half of those related to abdominal aortic aneurysm that occur in men aged 65 or more in the UK,[20] should be prevented by screening. Such a programme will never prevent all ruptures but to optimise performance emphasis should be placed on achieving a high initial attendance rate and good adherence to follow-up, preventing delays in surgery, and maintaining a low mortality after elective surgery.

We observed a noticeable increase in ruptures after eight years among those originally screened as normal; although most were fatal the absolute numbers remained small. Deaths due to rupture after a normal scan seem not to have impacted yet on the diverging curves from deaths related to abdominal aortic aneurysm (figure). Rescreening those with an initial normal scan would only become justified if future analyses show a further noticeable increase in ruptures in this group that is not sufficiently offset by the reduction in number of deaths related to abdominal aortic aneurysm for those with an aneurysm detected.

The survival advantage in terms of life years gained continues to increase with time (figure). Because the main costs of the programme (initial screening and elective surgery for those large aneurysms) occur early, whereas the benefit from life years increases over time, cost effectiveness improves when considered over longer time scales. Using the same unit costs and discount rates as in the current analysis, the cost per life year gained is estimated as £41 000 after four years, £14 000 after seven years, and now £7600 after 10 years. The estimate and confidence interval at 10 years is well below the guideline for the NHS of around £25 000 per life year gained.[21] Sensitivity analyses using alternative unit costs[4] did not change this conclusion.

New treatments for abdominal aortic aneurysm may impact on a screening programme and increase its effectiveness. Endovascular repair of aneurysms rather than open repair is now used more widely for elective surgery but was used for only 9% of the elective procedures in MASS. In patients who are fit for open repair, and anatomically suitable for endovascular repair, endovascular repair has lower operative mortality than open repair and fewer deaths related to abdominal aortic aneurysm in the longer term.[22-25] Reliable evidence comparing endovascular repair with open repair is available only up to four years of follow-up, and shows no difference in all cause mortality[25] but a substantial incidence of graft problems and need for reinterventions.[23 24] These incur costs, as does the requirement for surveillance of the graft. Until robust evidence on longer term follow-up is available it may be reasonable to assume that endovascular repair has similar cost effectiveness to open repair, a conclusion supported by recent evidence suggesting roughly equal costs for both repairs over 2.5 years.[26] The overall cost effectiveness of screening for abdominal aortic aneurysm would not be expected to change much if endovascular repair was used, when appropriate, in place of elective open repair.

The inclusion of deaths from aortic aneurysm at an unspecified site may have provided a conservative estimate of the benefit of screening, as codes 441.5 and 441.6 (international classification of diseases, ninth revision) may include some deaths related to thoracic aortic aneurysm. Investigation of inaccuracies in coding showed a minimal impact on study outcomes.[3] The quality of life data collected in the trial around the time of screening showed no clear adverse or beneficial effects of screening or any long term effects after surgery.[3 27] Using general population age specific norms for quality of life,[28] the cost per quality adjusted life year (QALY) in MASS at 10 years was £9400 (95% confidence interval £6300 to £16 000).

Although the loss to follow-up for deaths was small, full follow-up of patients for surgical repair was more problematic. Surgical follow-up was through review of data from local hospitals in each screening area, thus missing data on patients who had moved away or had surgery at other hospitals. An estimate of this problem in one MASS centre showed it to be small (278/4241, 7%), indicating that few people of this age group move away and therefore would be lost to surgical follow-up.

The UK national screening programme for abdominal aortic aneurysm should, in the long term, halve the mortality rate related to abdominal aortic aneurysm in men aged 65 or more, and will be a cost effective programme for the NHS.

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Competing interests: None declared.
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Introductory address (1840)

In the commencement of an undertaking like the present, it is customary to make some prefatory statement, by which those who give it their support may be put in possession of the views and prospects under which it comes before them. The custom is in itself a harmless one, and as some advantages attend a formal introduction and commendation of a work to the regards of the reader, we shall follow in the beaten course, and shall endeavour, on the present occasion, to set forth the main objects for the promotion of which the *Provincial Medical and Surgical Journal* is established.

The most important of these are—1st, to use the words of the Address of the Provincial Medical Association, issued at the institution of that body,—The maintenance of the honour and respectability of the medical profession; 2nd, The affording a special means of communication for the several medical and branch associations which have been formed in various parts of the kingdom; 3rd, The promotion, as far as possible, of the interests of these admirable institutions, and more especially of those of the Provincial Association; 4th, The collecting and recording of the numerous facts observed in every part of the provinces, many of which are now diffused through various channels of information, and too often overlooked from the very causes which should render them of the greatest utility; and 5th, The working out of those rich mines of information and medical instruction—the County Hospitals, Infirmaries, and Dispensaries.

The maintenance of the respectability of the profession, as it will readily be perceived, necessarily involves the contemplation of those great questions of medical reform which are now engaging the attention of medical practitioners. In the consideration of these we shall at once take the highest ground,—that of public utility. The establishment of a system of competent medical education; the securing to the profession a wholesome form of government; the suppression of empiricism; the providing of proper medical attendance for those who are unable to procure it for themselves; and the placing of these and other portions of medical police under the superintendence of those who are the best acquainted with the subject,—are all and each of them but so many modes of advancing the welfare and guarding the interests of the community in general. At the same time, these measures have a direct tendency to maintain medical practitioners, as a class, in that rank of society which, by their intellectual acquirements, by their general moral character, and by the importance of the duties entrusted to them, they are justly entitled to hold.

Introductory address. *Prov Med Surg J* 1840;s1-1:1-4, doi: 10.1136/bmj.s1-1.1.1.

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Analysis of cost effectiveness of screening Danish men aged 65 for abdominal aortic aneurysm

Lars Ehlers,[1] Kim Overvad,[2,3] Jan Sørensen,[4] Søren Christensen,[5] Merete Bech,[5] Mette Kjølby[1,5]

EDITORIAL by Buxton
RESEARCH p 1538

[1]Institute of Public Health, Aarhus University, Vennelyst Boulevard 6, 8000 Aarhus C, Denmark
[2]Department of Cardiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark
[3]Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg, Denmark
[4]Centre for Applied Health Services Research and Technology Assessment, University of Southern Denmark
[5]Health Technology Assessment and Health Services Research, Centre for Public Health, Central Region, Denmark
Correspondence to: L Ehlers
le@folkesundhed.au.dk

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ABSTRACT

Objective To assess the cost effectiveness of screening men aged 65 for abdominal aortic aneurysm.

Design Cost effectiveness analysis based on a probabilistic, enhanced economic decision analytical model from screening to death.

Population and setting Hypothetical population of men aged 65 invited (or not invited) for ultrasound screening in the Danish healthcare system.

Data sources Published results from randomised trials and observational epidemiological studies retrieved from electronic bibliographic databases, and supplementary data obtained from the Danish Vascular Registry.

Data synthesis A hybrid decision tree and Markov model was developed to simulate the short term and long term effects of screening for abdominal aortic aneurysm compared with no systematic screening on clinical and cost effectiveness outcomes. Probabilistic sensitivity analyses using Monte Carlo simulation were carried out. Results were presented in a cost effectiveness acceptability curve and a curve showing the expected (net) number of avoided deaths from abdominal aortic aneurysm over time after the introduction of screening. The model was validated by calibrating base case health outcomes and expected activity levels against evidence from a recent Cochrane review of screening for abdominal aortic aneurysm.

Results The estimated costs per quality adjusted life year (QALY) gained discounted at 3% per year over a lifetime for costs and QALYs was £43 485 (€54 852; $71 160). At a willingness to pay threshold of £30 000 the probability of screening for abdominal aortic aneurysm being cost effective was less than 30%. One way sensitivity analyses showed the incremental cost effectiveness ratio varying from £32 640 to £66 001 per QALY.

Conclusion Screening for abdominal aortic aneurysm does not seem to be cost effective. Further research is needed on long term quality of life outcomes and costs.

INTRODUCTION

Implementation of a national screening programme for abdominal aortic aneurysm in men is on the public health agenda of many western European countries. The scientific case for screening seems established; there is evidence of benefit in men, with a significant reduction in deaths.[1]

The cost effectiveness of screening for abdominal aortic aneurysm may be acceptable.[1] Within trial cost effectiveness reported in the large Multicentre Aneurysm Screening Study (MASS) after four years of follow-up was £28 400 per life year gained. The authors concluded that their result was at the margin of acceptability according to National Health Service thresholds but that cost effectiveness was expected to improve substantially over a longer period.[2] The study did not collect information on quality adjusted life years (QALYs) gained, endovascular repair was not included, and the long term costs of unwanted side effects were not included.

Several health economic decision models of screening for abdominal aortic aneurysm combining data from MASS and other randomised trials with sources of evidence have been published.[3-11] Inconsistencies in the model, together with optimistic assumptions about mortality and quality of life after elective surgery and a focus on short term clinical costs, have made the relevance of these models for decision making unclear.

We determined the cost effectiveness of a screening programme for abdominal aortic aneurysm in men aged 65 on the basis of a probabilistic, enhanced economic decision analytical model from ultrasonography to death. The study was done from a healthcare perspective.

METHODS

We modelled cost effectiveness by combining a decision tree with Markov modelling of long term consequences.[12] The model portrayed a cohort of men aged 65 who could receive an invitation or not to participate in a hypothetical screening programme for abdominal aortic aneurysm (see bmj.com).

Action was determined by the size of the aneurysm: if large (≥5.5 cm) the patient was referred for vascular assessment, and if small (3-4.4 cm) or medium sized (4.5-5.4 cm) the patient was rescanned regularly. In each successive cycle we applied a matrix of transitional probabilities to determine possible transitions from each stage. The risk of rupture depended on the aneurysm's size. Each year the men also risked dying from other causes. We enhanced the model by relaxing the Markov assumption; memory was built into the model using time dependent probabilities of rupture according to an estimated age distribution of men aged 65 or more having emergency surgery. The cycle length was one year.

We made the model probabilistic by applying a relevant distribution for each variable. We used the mean and standard deviation from normal distributions to approximate β distributions for binomial data and Dirichlet distributions for multinomial data. For costs we used "right tailed" γ distributions.[12]

To determine the cost effectiveness ratio of screening for abdominal aortic aneurysm we calculated expected

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costs and health outcomes for the screening alternative compared with the non-screening alternative.

We used Monte Carlo simulations to select values at random from the specified distributions for model variables. We calculated expected costs and health outcomes for the two alternatives over second order uncertainties for a cohort of 10 000 men aged 65.

Data input

Extensive datasets were used for all inputs (see bmj.com). Standard survival analyses were based on Danish data on long term mortality after elective or emergency surgery. We obtained data on incident cases of abdominal aortic aneurysm from the Danish Vascular Registry for 1996-2006 and linked with data on vital status from the Danish Central Office of Civil Registration.[13] From the registry we obtained data on the age distribution of men having emergency surgery during 1996-2006.

We used quality of life weights from a standard population of men—that is, a QALY weight of 0.80 for all hypothetical men aged 65-70 and 0.76 for those aged more than 70. In a sensitivity analysis we used age adjusted quality of life weights from average male smokers of 0.71, and 0.67 for men aged 65-70 and those aged more than 70.[14]

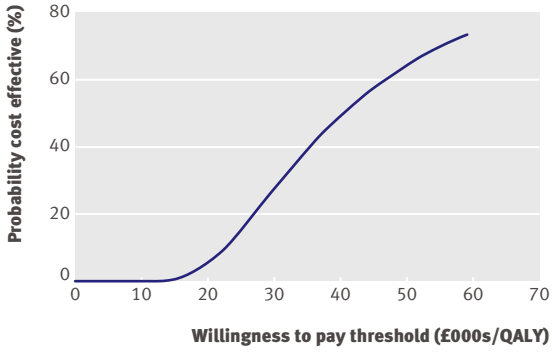
Costs were in 2007 prices (DKK 9.41; £1.00; €1.26; $1.78); we applied the cost to the Danish healthcare system for 2007 as best estimate for surgery cost.[15]

We applied tracker variables to the model and calculated the expected number of deaths avoided and levels of surgery and surveillance under the two alternatives and compared them with data from a recent Cochrane review.[1] We calculated the average age at death from ruptured aneurysm in the different patient pathways and calibrated this against registry and published data.

Analyses

We presented simulation output in a cost effectiveness acceptability curve, showing the probability of screening being cost effective at different threshold ratios.[12] One way sensitivity analyses were done of all model variables and of several additional factors likely to influence cost effectiveness.[16] We discounted cost and effect at 3% to express net present values. Alternative values (0% and 5%) were applied in sensitivity analyses.

We simulated consecutive cohorts of men aged 65 by summing up expected numbers of deaths related to abdominal aortic aneurysm and surgical activity. This was done using two dimensional Monte Carlo simulations averaging 10 000 second order samples of variable values with 10 000 trials for each variable sample. To illustrate the development in the expected (net) number of avoided deaths over time as a result of screening we created curves for the first 15 years of consecutive cohorts of 10 000 men aged 65 at the time of screening. We compared the results of simulating five years of screening with that of one cohort followed throughout life.



Cost effectiveness acceptability curve of screening for abdominal aortic aneurysm in hypothetical population of 10 000 men aged 65

RESULTS

At a discounted rate of 3% the incremental cost effectiveness ratio (base case) was £43 485 per QALY (see bmj.com). The incremental cost effectiveness ratio with one way sensitivity analyses was £32 640-£66 001 per QALY (see bmj.com).

The figure presents the Monte Carlo second order calculation of 10 000 men aged 65. At a willingness to pay threshold of £30 000 the probability of screening being cost effective was less than 30%.

The results of the model simulation of 10 000 men followed through life were consistent with those from published randomised trials.[1,2] Assuming about 250 000-300 000 men aged 65 in England were followed, an expected 675-810 deaths related to abdominal aortic aneurysm would be avoided (see bmj.com), similar to the expectancy of the NHS. Other simulation results for the non-screening alternative, such as estimated mean age at rupture (74 years), were consistent with published data.[17,18]

The expected result five years after the introduction of screening showed an increase of nine deaths related to abdominal aortic aneurysm as a side effect of the increased number of elective operations in the short term, which was increased more than fourfold in the first five years. In the eight years after the introduction of screening there was an increase in the (net) number of avoided deaths, assuming that eight successive cohorts of 10 000 men aged 65 were screened.

DISCUSSION

We constructed a decision analytical model to evaluate the cost effectiveness of screening men aged 65 for abdominal aortic aneurysm. The incremental cost effectiveness ratio (base case) was £43 485 per QALY. At a willingness to pay threshold of £30 000 the probability of screening being cost effective was less than 30%. One way sensitivity analyses showed the incremental cost effectiveness ratio varying from £32 640 to £66 001 per QALY. A screening programme was therefore unlikely to be cost effective.

WHAT IS ALREADY KNOWN ON THIS TOPIC

One time ultrasound screening of men aged 65 or more can significantly reduce mortality from ruptured abdominal aortic aneurysm

It is uncertain whether screening all 65 year old men is cost effective

WHAT THIS STUDY ADDS

Screening men aged 65 for abdominal aortic aneurysm was not cost effective

The incremental cost effectiveness ratio was £43 485 per QALY (range £32 640-£66 001 per QALY)

At a willingness to pay threshold of £30 000 per QALY there was a less than 30% probability of screening being cost effective

Our decision analytical framework was based on best evidence of effectiveness and costs, including registry data for long term mortality after elective and emergency repair of abdominal aortic aneurysm, and age distribution of ruptured aneurysm. The Danish Vascular Registry has been shown to have high validity.[19]

We validated the model by calibrating against key values from a recent Cochrane review.[1] The number of avoided deaths, amount of elective and emergency surgery, and mean age at surgery were consistent with pooled data from randomised trials and clinical data. Estimated age at rupture, death due to rupture, and death after elective surgery in the non-screening alternative were also consistent with published data.

None of the randomised trials of screening for abdominal aortic aneurysm collected information on QALY gains and long term costs; endovascular repair of aortic aneurysm was not used in the trials and therefore not included in the cost calculations in relevant health economic studies. Endovascular repair may be cost effective in patients who are unfit for open repair, but it is used increasingly as a substitute for conventional surgery.[20] Sensitivity analyses showed that including the cost of graft surveillance and secondary procedures after endovascular repair significantly increased the cost per QALY gained.

One limitation of our modelling approach was that it relies on a combination of data from studies in different countries, gross costing, and average QALY weights.[12 16 21] Another limitation was the focus on screening all men aged 65.

Our estimate of the incremental cost effectiveness ratio is comparable to the £28 400 per life year gained (equivalent to about £36 000 per QALY) reported in MASS.[2] The main difference is that the MASS results were presented as a weighted average for men aged 65-74. A lower incremental cost effectiveness ratio was therefore reported. Other reasons are differences in the cost of elective and emergency surgery and the application of different discount rates for costs and health outcomes in MASS.[2]

Conclusion

Screening men aged 65 for abdominal aortic aneurysm was not cost effective; the incremental cost effectiveness ratio was £43 485 per QALY (range £32 640-£66 001 per QALY). At a willingness to pay threshold of £30 000 per QALY the probability of screening for abdominal aortic aneurysm being cost effective was less than 30%.

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Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries

C C Butler,[1] K Hood,[2] T Verheij,[3] P Little,[4] H Melbye,[5] J Nuttall,[2] M J Kelly,[2] S Mölstad,[6] M Godycki-Cwirko,[7] J Almirall,[8] A Torres,[9] D Gillespie,[2] U Rautakorpi,[10] S Coenen,[11,12] H Goossens[13]

[1]Department of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff CF14 4XN, Wales
[2]South East Wales Trials Unit (SEWTU), Department of Primary Care and Public Health, School of Medicine, Cardiff University, Heath Park, Cardiff, Wales
[3]University Medical Centre Utrecht, Julius Center for Health, Sciences and Primary Care, Universiteitsweg 100, Stratenum, 6th Floor, 6.111, 3584 CX Utrecht, Netherlands
[4]University of Southampton, Southampton SO16 5ST
[5]General Practice Research Unit, Institute of Community Medicine, University of Tromso, 9037 Tromso, Norway
[6]Department of Medical and Health Sciences, Linkoping University, and Unit of Research and Development in Primary Care, S-55185 Jonkoping, Sweden
[7]Department of Family and Community Medicine, Medical University of Lodz, U190-153 Lodz.Kopcinskiego 20, Poland
[8]Unitat de Cures Intensives, Hospital de Mataro, Carretera de Cirera s/n, 08304 Mataro (Barcelona), Spain
[9]Servei de Pneumologia i Al·lèrgia Respiratòria, Institut Clínic del Tòrax, Hospital Clínic de Barcelona, CIBERES 06/06/0028, Universitat de Barcelona, Spain
[10]Finnish Office for Health Technology Assessment, FinOHTA, Stakes Tampere Satellite Office, Fin-Medi 3, Biokatu 10, 7. krs, 33520 Tampere, Finland
[11]University of Antwerp-Campus Drie Eiken, Vaccine and Infectious Disease Institute, Centre for General Practice, Antwerp, Belgium
[12]Research Foundation, Flanders, Brussels, Belgium.
[13]University of Antwerp-Campus Drie Eiken, Vaccine and Infectious Disease Institute-Laboratory of Medical Microbiology, Antwerp, Belgium

Correspondence to: CC Butler
ButlerCC@cardiff.ac.uk

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ABSTRACT

Objective To describe variation in antibiotic prescribing for acute cough in contrasting European settings and the impact on recovery.

Design Cross sectional observational study with clinicians from 14 primary care research networks in 13 European countries who recorded symptoms on presentation and management. Patients followed up for 28 days with patient diaries.

Setting Primary care.

Participants Adults with a new or worsening cough or clinical presentation suggestive of lower respiratory tract infection.

Main outcome measures Prescribing of antibiotics by clinicians and total symptom severity scores over time.

Results 3402 patients were recruited (clinicians completed a case report form for 99% (3368) of participants and 80% (2714) returned a symptom diary). Mean symptom severity scores at presentation ranged from 19 (scale range 0 to 100) in networks based in Spain and Italy to 38 in the network based in Sweden. Antibiotic prescribing by networks ranged from 20% to nearly 90% (53% overall), with wide variation in classes of antibiotics prescribed. Amoxicillin was overall the most common antibiotic prescribed, but this ranged from 3% of antibiotics prescribed in the Norwegian network to 83% in the English network. While fluoroquinolones were not prescribed at all in three networks, they were prescribed for 18% in the Milan network. After adjustment for clinical presentation and demographics, considerable differences remained in antibiotic prescribing, ranging from Norway (odds ratio 0.18, 95% confidence interval 0.11 to 0.30) to Slovakia (11.2, 6.20 to 20.27)) compared with the overall mean (proportion prescribed: 0.53). The rate of recovery was similar for patients who were and were not prescribed antibiotics (coefficient −0.01, P<0.01) once clinical presentation was taken into account.

Conclusions Variation in clinical presentation does not explain the considerable variation in antibiotic prescribing for acute cough in Europe. Variation in antibiotic prescribing is not associated with clinically important differences in recovery.

Trial registration Clinicaltrials.gov NCT00353951.

INTRODUCTION

Antibiotic resistance is a growing problem worldwide, with 10% of *Streptococcus pneumoniae* isolates recorded as non-susceptible to penicillin in 30 countries in 2007.[1] There is wide variation in antibiotic prescribing data for ambulant patients in Europe,[2] but we do not know if this variation is explained by differences in presentation of illness or to which conditions it applies. Acute cough is one of the most common reasons for consulting. We examined variation in antibiotic prescribing for acute cough in primary care in Europe and its impact on recovery, controlling for presentation.

METHODS

Networks—The Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infections in Europe (GRACE) (www.grace-lrti.org) Network of Excellence recruited 14 primary care research networks in 13 countries. Networks had access to a minimum of 20 000 patients and had a track record of research.

Study materials and procedures—Study materials and procedures were developed with advice from all networks. National network coordinators and facilitators undertook face to face training in study procedures, and cascaded training to participating general practitioners.

Inclusion criteria—Eligible patients were aged 18 and over who were consulting about an illness where an acute or worsened cough was the main symptom, had a clinical presentation that suggested a lower respiratory tract infection with a duration of up to and including 28 days, were consulting for the first time within this illness episode, were seen within normal consulting hours, and were considered immunocompetent.

Recruitment of patients—Participating general practitioners were asked to recruit consecutive eligible patients in October and November 2006 and from late January to March 2007. The scheduled two month gap enabled us to explore possible temporal variations in cough during the winter.

Data collection—Clinicians recorded aspects of patients' history, symptoms, comorbidities, clinical findings, and management, including antibiotic prescription and other treatments and investigations. They indicated the presence or absence of 14 symptoms (cough, phlegm production, shortness of breath, wheeze, coryza, fever during this illness, chest pain, muscle aching, headache, disturbed sleep, feeling generally unwell, interference with normal activities, confusion/disorientation, and diarrhoea) and then rated them in a four point scale. All data were entered via a remote secure data entry portal onto the GRACE

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online system. From our sample size estimation we required a total sample size of 270 patients per network.

Patient reported follow-up—Patients were given a symptom diary. They were asked to rate 13 symptoms each day until recovery (or for 28 days if symptoms were ongoing) on a seven point scale. Patients rated the same symptoms as the clinicians apart from confusion/disorientation and diarrhoea. In addition they were asked to rate the impact of their illness on their social activities. There were questions about smoking and course of the illness, including subsequent management and contacts with the health service over the next 28 days.

Symptom scores—We converted clinician symptom ratings and patient self reported symptom ratings to scores and scaled these to range between 0 and 100 so that they could be interpreted as a percentage of maximum possible symptom severity. See bmj.com.

Analysis—Differences in clinical presentation were controlled for by using 13 of the 14 symptoms recorded by clinicians (cough was excluded as it was present in 99.8% of cases), sputum type, temperature, age, and comorbidities. Antibiotic prescribing by networks was investigated by using a two level hierarchical logistic model. We fitted a three level hierarchical model to the logged daily symptom scores reported by patients. We controlled for differences in clinical presentation using the same variables as in the previous model, along with smoking status and duration of illness before consulting. See bmj.com.

RESULTS

Patients

A total of 3402 patients were recruited by 387 practitioners. After exclusions there were 3296 (97%) entries in the case report form dataset and 2560 (75%) in the diary dataset. Those who filled in the diary tended to be older than those who did not (median age 45 (interquartile range 33-58) *v* 36 (27-48)), and patients from eastern European networks were most likely to return the symptom diary. Those who did not fill in a diary were no more or less likely to have been prescribed antibiotics than the others. Antibiotics were prescribed for 53% (1776) of included patients for a median of seven days (6-7). Amoxicillin accounted for 29% of prescriptions, ranging from 3% in Tromso to 83% in the Southampton network (fig 1). See bmj.com for details.

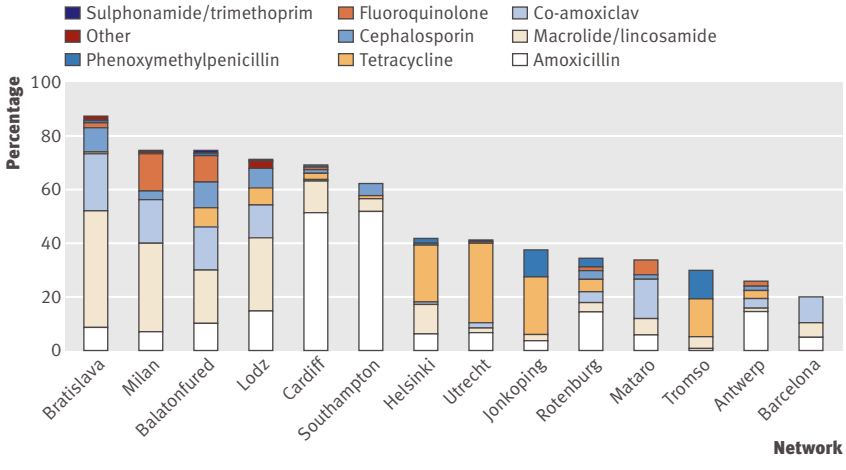

Fig 1 | Choice of antibiotic by network

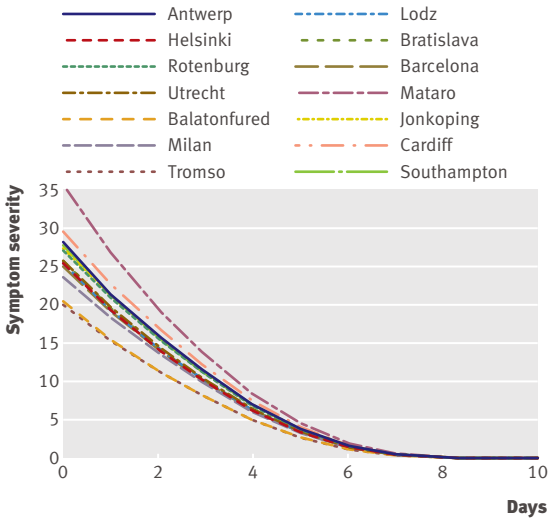

Fig 2 | Predicted recovery curves by network for those prescribed antibiotics from ARMA model

Antibiotic prescribing by networks adjusted for clinical presentation

Significant variation between networks remained after adjustment for clinical presentation (table). There were no significant differences between the two recruitment periods in overall rate of antibiotic prescribing. The model was also fitted to the subsample of patients with usable diary data to check the effect of duration of illness before consultation and smoking status on prescribing. Both variables were significantly associated with receiving a prescription for antibiotics, with a 2% increase in the odds of receiving an antibiotic for each additional day of illness before consulting (odds ratio 1.02, 95% confidence interval 1.01 to 1.04) and a 38% increase in the odds for smokers (1.38, 1.09 to 1.76). Adjustment for these factors, however, had no effect on the magnitude or significance of the variation between networks and therefore we have presented the model with the larger sample.

Patients' recovery

There was considerable variation between networks in the rate of recovery after presentation, as shown by the median symptom trajectory plots. The median time to patients reporting feeling recovered (single item) was 11 days. The median time for patients' symptom severity scores to drop to 0 was 15 days. Respiratory comorbidity was associated with initial higher symptom severity scores. Those who waited longer before presenting had higher initial symptom severity scores.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Acute cough is a major reason for antibiotic prescribing in primary care, with many prescriptions resulting in no clinical benefit

There is considerable variation in antibiotic prescribing to ambulatory patients across Europe

There are inadequate patient level data to determine whether this variation is justified by variation in clinical presentation.

WHAT THIS STUDY ADDS

Considerable variation in antibiotic prescribing for acute cough remains throughout Europe even after adjustment for illness severity, comorbidity, temperature, age, duration of illness before to consultation, and smoking status

Recovery is not meaningfully influenced by variation in antibiotic prescribing

Significant variation in outcome remained across networks after adjustment for clinical presentation, with two of the networks (Balatonfured and Mataro) reporting differences in patients' reported symptom severity at baseline compared with the overall mean, and three of the networks (Cardiff, Milan, and Jonkoping) reporting significantly slower recovery rates and three networks (Mataro, Balatonfured, Antwerp) reporting significantly faster recovery. While there were significant differences in the symptom trajectories across the networks, differences were not clinically important. Almost all the symptom trajectories converged after a week (fig 2). Being prescribed antibiotics was associated with a faster reduction in symptom severity scores, as indicated by the significant interaction between prescribing antibiotics and day. This association, however, was small.

Two level logistic regression model* of odds of being prescribed antibiotic in each network (3296 patients from 384 clinicians). Figures are odds ratios (95% confidence intervals)

Network	OR (95% CI)	P value
Antwerp	0.22 (0.12 to 0.38)	<0.001
Balatonfured	5.69 (2.88 to 11.26)	<0.001
Barcelona	0.29 (0.16 to 0.51)	<0.001
Bratislava	11.2 (6.20 to 20.27)	<0.001
Cardiff	2.44 (1.42 to 4.19)	<0.01
Helsinki	0.58 (0.31 to 1.09)	0.09
Jonkoping	0.25 (0.16 to 0.38)	<0.001
Lodz	4.14 (2.4 to 7.16)	<0.001
Mataro	0.66 (0.37 to 1.18)	0.16
Milan	6.81 (3.49 to 13.27)	<0.001
Rotenberg	0.5 (0.27 to 0.92)	0.03
Southampton	0.84 (0.47 to 1.5)	0.55
Tromso	0.18 (0.11 to 0.30)	<0.001
Utrecht	0.5 (0.29 to 0.85)	0.01

*Model controls for clinician rated symptom scores and clinical presentation. Clinician level variance component was 23.3%, using $\pi^2/3$ estimator.

The impact of antibiotic prescribing, while statistically significant, represents a tenth of a single percentage difference in symptom severity score, and therefore it is reasonable to consider it clinically unimportant. Such a small effect is entirely consistent with a placebo effect.

Hospital admission

Overall, 1.1% (28) of patients were admitted to hospital after inclusion. For individual networks this ranged between from none to 4.3% (9).

DISCUSSION

Main findings

In this prospective study of the management of acute cough among adults in primary care we found considerable variation in the 13 countries studied. Major differences in the decision whether or not to prescribe an antibiotic in these settings remained, even after we adjusted for clinical presentation. We also identified marked differences between networks in choice of antibiotic. These differences might be attributable to different guidelines and habits in different countries.

There were two main findings regarding patients' recovery. Firstly, there were significant differences between networks in both severity of symptoms on day one and the recovery rate. Differences in the recovery rate, however, were small and patients recovered at a similar rate regardless of network. Secondly, whether a patient was prescribed antibiotics or not was statistically associated with outcome, but was not clinically relevant.

Strengths and limitations

We prospectively described antibiotic prescribing for a well defined population of patients in a large number of countries recruited at the same time. Recruitment was for two periods and over a single winter. The clinicians who participated (and therefore their patients) were all affiliated to a research network and so might not have been representative.

Bias

As the study spanned 13 European countries, there is no guarantee that perceptions of health and reporting of symptoms were consistent. We do not know how cultural differences influenced our results. We are exploring these issues in a qualitative study.

Comparison with previous studies

A study of antibiotic treatment by general practitioners for lower respiratory tract infection in five European countries over 10 years ago found that overall 83% of cases were prescribed antibiotics,[3] but was limited by retrospective data collection. In a two country comparison, general practitioners in Spain and Denmark recorded their management of respiratory tract infections. Spanish general practitioners prescribed more antibiotics but there was no adjustment for severity and duration of illness or smoking.[4]

Implications for practice and research

We identified marked differences in whether and what antibiotics are prescribed for acute cough throughout Europe. We also found that large differences in antibiotic prescribing did not translate to clinically important differences in patients' recovery; management of acute cough is an issue that is appropriate for standardised international care pathways promoting conservative antibiotic prescribing.

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Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study

C McCowan,[1] B Kidd,[2] T Fahey[1,3]

[1]Division of Community Health Sciences, University of Dundee, Dundee DD2 4BF
[2]Section of Psychiatry and Behavioural Sciences, Division of Pathology and Neuroscience, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY
[3]Department of General Practice and Family Medicine, Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin 2, Ireland
Correspondence to: T Fahey tomfahey@rcsi.ie

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ABSTRACT

Objective To assess predictors of mortality in a population of people prescribed methadone.
Design Retrospective cohort study.
Setting Geographically defined population in Tayside, Scotland.
Participants 2378 people prescribed and dispensed liquid methadone between January 1993 and February 2004.
Main outcome measures All cause mortality (primary outcome) and drug dependent cause specific mortality (secondary outcome) by means of Cox proportional hazards models during 12 years of follow-up.
Results Overall, 181 (8%) people died. Overuse of methadone (adjusted hazard ratio 1.67, 95% confidence interval 1.05 to 2.67), history of psychiatric admission (2.47, 1.67 to 3.66), and increasing comorbidity measured as Charlson index ≥3 (1.20, 1.15 to 1.26) were all associated with an increase in all cause mortality. Longer duration of use (adjusted hazard ratio 0.95, 0.94 to 0.96), history of having urine tested (0.33, 0.22 to 0.49), and increasing time since last filled prescription were protective in relation to all cause mortality. Drug dependence was identified as the principal cause of death in 60 (33%) people. History of psychiatric admission was significantly associated with drug dependent death (adjusted hazard ratio 2.41, 1.25 to 4.64), as was history of prescription of benzodiazepines (4.35, 1.32 to 14.30).
Conclusions Important elements of care in provision of methadone maintenance treatment are likely to influence, or be a marker for, a person's risk of death.

INTRODUCTION

Methadone maintenance programmes have been started on the basis of evidence that methadone decreases illicit drug use, reduces injecting behaviour, reduces the risk of opioid related deaths, improves physical and mental health, and is associated with a decrease in criminal activity.[1-3] In the United Kingdom, methadone treatment for heroin addiction is largely provided by general practitioners, and prescribing of methadone in primary care substantially increased throughout the 1990s.[4 5] The central ethos of this approach is one of harm minimisation, and other countries are expanding provision of methadone treatment into primary care.[6 7]

However, treatment with methadone in primary care has been described as a "double edged sword" because methadone itself is associated with drug related deaths.[8] A confidential inquiry carried out in Scotland found that of 56 drug related deaths in 2000, methadone was cited on the death certificate in 30 (54%) cases.[9] Methadone related deaths seem to be due to an interaction of patient related and organisational factors: drug dosing, concurrent use of other drugs, and deficiencies in the monitoring and delivery of methadone care programmes.[3 10]

In this study, we aimed to examine the interaction of patient related factors and prescribing factors at the individual level and assess their independent impact on the risk of both all cause mortality and drug dependent cause specific mortality in a primary care setting.

METHODS

Study design and patients

We identified people resident in Tayside, Scotland, who were registered with a general practitioner and were prescribed and dispensed liquid methadone between January 1993 and February 2004. We used the unique Community Health Index number used in all encounters with the NHS, to link detailed clinical data at the level of the individual patient.

Procedures

We collected data on age, sex, and postcode for each patient who was dispensed a liquid methadone prescription. We linked these records to all dispensed prescribing and to standard morbidity register records for admission to hospital or to a psychiatric unit. We made linkages to General Register Office mortality data and to laboratory datasets relating to urine testing for opiates and other drugs. We used census data to calculate socioeconomic status.[11] We derived a Charlson comorbidity index from each person's standard morbidity register record in the hospital admission records.[12 13] We categorised Charlson index scores into three groups with low (0), medium (1-2), and high (≥3) morbidity.

From prescription records, we calculated the length of methadone treatment, the mean dose of methadone, and the total amount prescribed. We categorised people as overusing methadone if the length of treatment was shorter than the total coverage of the prescribed prescriptions. We categorised people who were below, within, and above the recommended methadone maintenance range of 60 mg to 120 mg daily and fitted this as a binary variable with ≥60 mg as the cut-off point.[14] We examined prescribing records for other drugs and recorded any patient who was prescribed benzodiazepines, antipsychotics, antidepressants and opioid analgesics. Our main outcome measure was all cause mortality.

Table 1 | Univariable and multivariable associations between covariates and all cause mortality

Cohort characteristic	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Male sex	1.06 (0.77 to 1.45)	NA
Age (per year)	1.04 (1.02 to 1.05)*	1.00 (0.98 to 1.01)
Social class (Carstairs):		
1 (reference category)	1.0	1.0
2	0.16 (0.04 to 0.73)*	0.18 (0.04 to 0.82)*
3	0.48 (0.16 to 1.40)	0.52 (0.17 to 1.54)
4	0.49 (0.16 to 1.49)	0.45 (0.15 to 1.41)
5	0.41 (0.14 to 1.17)	0.36 (0.12 to 1.04)
6	0.62 (0.22 to 1.70)	0.46 (0.16 to 1.28)
7	0.54 (0.19 to 1.51)	0.52 (0.18 to 1.76)
Comorbidity (Charlson index):		
0 (reference category)	1.0	1.0
1-2	2.85 (1.86 to 4.37)*	1.08 (1.02 to 1.14)*†
≥3	6.58 (4.72 to 9.19)*	1.20 (1.15 to 1.26)*†
Mean methadone dose ≥60 mg	1.54 (1.07 to 2.23)*	0.93 (0.62 to 1.39)
Overusing methadone	3.12 (2.09 to 4.64)*	1.67 (1.05 to 2.67)*
Methadone breaks	0.58 (0.50 to 0.67)*	0.93 (0.78 to 1.10)
Duration of methadone treatment (years)	0.78 (0.75 to 0.82)*	0.95 (0.94 to 0.96)*†
Time since last methadone prescription filled (months):		
≤1 (reference category)	1.0	1.0
2-3	0.77 (0.49 to 1.22)	0.97 (0.91 to 1.02) †
4-6	0.66 (0.33 to 0.1.30)	0.91 (0.84 to 0.99)* †
›6	0.45 (0.32 to 0.62)*	0.70 (0.66 to 0.73)* †
Psychiatric admission	2.46 (1.74 to 3.49)*	2.47 (1.67 to 3.66)*
Having urine tested	0.31 (0.23 to 0.41)*	0.33 (0.22 to 0.49)*
Co-prescribing:		
Benzodiazepines	1.18 (0.74 to 1.86)	NA
Antipsychotics	0.77 (0.53 to 1.12)	0.85 (0.56 to 1.29)
Antidepressants	0.76 (0.56 to 1.01)	0.80 (0.57 to 1.44)
Opioid analgesics	1.33 (0.99 to 1.79)	1.17 (0.84 to 1.64)

Final regression model mutually adjusted for all significant covariates; male sex, use of benzodiazepines, and volume of methadone prescribing by practice were assessed unadjusted but had no significant influence (P>0.2) and so were excluded from final model.
NA=not applicable.
*P<0.05.
†Variable treated as time varying coefficient in Cox regression model and hazard ratio reported at median follow-up of 4.38 years.

Statistical analysis

We used Cox proportional hazards models to estimate hazard ratios for each unadjusted and adjusted covariate in relation to all cause mortality and cause specific mortality. We included covariates in the multivariate model if we deemed them to be of clinical significance or if they had a univariable P value below 0.2. We followed up patients until time of death or the end of the study period.

RESULTS

Descriptive statistics

A cohort of 2378 people were prescribed and dispensed methadone during the 12 year study, with a median follow-up of 4.38 (interquartile range 1.92-8.12) years. Sixty five per cent were aged under 30 years, and more than half were from the lowest socioeconomic groups. More than 40% of patients were prescribed methadone for more than three years.

Almost half of the cohort had a record of psychiatric admission, and co-prescription of benzodiazepines, antipsychotics, antidepressants, and opioid analgesics was high. Almost four fifths of the patients had at least one urine test. The mean dose of methadone was lower than the recommended adequate maintenance range of 60-120 mg daily for 2023 (85%) people, within this range for 349 (15%) people, and above 120 mg for six people. The median individual mean dose was 40 (interquartile range 28-51) mg.

Cause of death and methadone prescriptions over time

During the 12 year study period, 181 (8%) people died. The number of deaths remained constant despite the increase in methadone prescription items from 5852 in 1993 to 16 379 in 2003. Cause of death was available in 166 (92%) of these people. Codes that relate to "drug dependence" were recorded as the principal cause in 60 (33%) people.

Univariable and multivariable associations with all cause mortality

After adjustment for significant covariates, increasing comorbidity, overuse of methadone, and history of psychiatric admission were all associated with an increase in all cause mortality (table 1). Longer duration of methadone use, increasing time since last methadone prescription was filled, and history of having urine testing were protective in relation to all cause mortality, but "breaks" in receiving methadone and co-prescription of drugs were not associated once fitted to the multivariable model (table 1).

Univariable and multivariable associations with cause specific mortality

When we assessed the 60 (33%) people who had a "drug related" death, the same explanatory variables that were protective in relation to all cause mortality persisted—namely, longer duration of methadone use, increasing time since last methadone prescription was filled, and history of having urine testing (table 2). Similarly, history of psychiatric admission remained independently associated with increased risk of drug dependent cause specific mortality. Of note, co-prescribing of benzodiazepines was now strongly associated, whereas prescription of antidepressants and antipsychotics seemed to be protective in relation to drug related death (table 2).

Table 2 | Univariable and multivariable associations between covariates and drug dependent cause specific mortality

Cohort characteristic	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Male sex	1.24 (0.70 to 2.21)	NA
Age (per year)	0.98 (0.95 to 1.01)	1.00 (0.98 to 1.01)
Social class (Carstairs):		
1-4 (reference category)	1.0	NA
5-7	1.12 (0.63 to 2.02)	NA
Mean methadone dose ≥60 mg	0.68 (0.29 to 1.58)	NA
Overusing methadone	4.52 (2.47 to 8.26)*	1.85 (0.91 to 3.80)
Methadone breaks	0.51 (0.39 to 0.68)*	1.01 (0.74 to 1.40)
Duration of methadone treatment (years)	0.76 (0.69 to 0.83)*	0.93 (0.92 to 0.95)*†
Time since last methadone prescription filled (months):		
≤1 (reference category)	1.0	1.0
2-3	0.52 (0.22 to 1.24)	0.64 (0.26 to 1.04)
4-6	0.40 (0.10 to 1.67)	0.24 (0.06 to 1.01)
>6	0.34 (0.19 to 0.62)*	0.02 (0.00 to 0.05)*
Psychiatric admission	2.23 (1.22 to 4.07)*	2.41 (1.25 to 4.64)*
Having urine tested	0.27 (0.16 to 0.45)*	0.52 (0.26 to 1.04)
Co-prescribing:		
Benzodiazepines	2.73 (0.85 to 8.76)	4.35 (1.32 to 14.30)*
Antipsychotics	0.18 (0.056 to 0.58)*	0.27 (0.08 to 0.89)*
Antidepressants	0.29 (0.16 to 0.53)*	0.51 (0.30 to 0.98)*
Opioid analgesics	0.65 (0.39 to 1.10)	0.72 (0.41 to 1.26)

Final regression model mutually adjusted for all significant covariates; male sex, comorbidity (Charlson index), social class, mean methadone dose (≥60 mg daily), and volume of methadone prescribing by practice were assessed unadjusted but had no significant influence on cause specific mortality (P>0.2) and so were excluded from final model.
NA=not applicable.
*P<0.05.
†Variable treated as time varying coefficient in Cox regression model and hazard ratio reported at median follow-up of 4.38 years.

DISCUSSION

Clear signals emerge in relation to safe prescribing and monitoring of methadone maintenance treatment in primary care, but caution is needed in that these associations may not be causal because of the nature of this observational study.[15] Although only a relatively small proportion of the people used a higher than recommended dose of methadone, their relative risk of death was more than one and a half times that of people who took the correct dosage. In terms of protective factors, longer duration of treatment, increasing time since last methadone prescription, and a history of involvement in urine testing programmes were associated with a reduced risk of all cause mortality. These are likely to be markers of people who are stabilised on maintenance treatment and engaged in monitoring procedures or who have successfully completed a methadone treatment reduction programme.

We found substantial under-dosing with methadone; 84% of the cohort were receiving a mean dose that was less than the recommended 60-120 mg.[14 16] Evidence from randomised controlled trials comparing different methadone dosages supports use of higher doses in terms of retention and reduction of heroin usage. However, the findings in relation to mortality from overdose are based on a very small number of deaths.[17] More research is needed in relation to the risks and benefits of a low dose versus high dose approach in terms of retention and risk of overdose.

More than a third of the cohort who died had a principal cause of death attributed to a drug related cause. Co-prescription of benzodiazepines had the strongest association with drug dependent death, history of psychiatric admission remained an independent risk factor, and co-prescribing of antipsychotics and antidepressants was independently protective. Markers of stability with methadone or cessation of methadone remain protective—history of urine testing and time since last methadone prescription was filled (table 2).

Our evidence suggests that improvements that have taken place in terms of the delivery of methadone maintenance programmes in the UK are likely to reduce the risk of death in this vulnerable group of people.[4 18] This study also provides evidence about subgroups of people, particularly those with a history of psychiatric admission, who have a higher risk of death. Similarly, for general practitioners who are prescribing methadone, monitoring of urine and avoidance of co-prescribing of benziodiazepines should be implemented. People at higher risk (history of psychiatric illness, poor engagement with services including urine testing) might be more appropriately managed in a specialist, rather than a generalist, environment.

Context of other studies

Our findings in relation to all cause mortality are consistent with the high mortality described in the drug

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised controlled trials have shown that methadone maintenance is an effective intervention, decreasing illicit drug use, reducing injecting behaviour, and reducing opioid related deaths

Concern exists about the safety of prescribing methadone in community settings, as methadone itself is associated with drug related deaths

WHAT THIS STUDY ADDS

Overuse of methadone, history of psychiatric admission, and increased comorbidity were associated with all cause mortality; drug dependent deaths were associated with co-prescription of benzodiazepines and history of psychiatric admission

History of urine testing, longer duration of use of methadone, and increasing time since last filled prescription were all associated with a reduced risk of death

Important elements in the process of care when providing methadone maintenance in the community may influence each person's risk of death.

outcomes research in Scotland (DORIS) study.[19] Although a relatively small proportion of the Tayside population were prescribed methadone, the proportion who died during the follow-up period was substantial. The applicability of our findings is therefore likely to be robust. Co-prescribing of benzodiazepines was associated with drug related death, which supports findings that these substances, along with alcohol, are commonly found in subsequent toxicological reports of drug related deaths.[20]

Limitations of study

The significant association of overuse of methadone with all cause mortality could be attributed to factors other than excessive use of methadone itself—for instance, it could be a marker for more chaotic drug using behaviour or dispersion of methadone. In observational studies of this sort, the possibility of residual confounding may remain a problem; caution is needed when interpreting the association of organisational and prescribing factors with all cause and drug dependent cause specific mortality. Other shortcomings of the study relate to the limited details of practice arrangements regarding initial assessment, supervised consumption, and counselling arrangements.

Implications for methadone programmes

This cohort did not have a record of patient centred indices of wellbeing. The interaction of psychological wellbeing, history of psychiatric admission, and the impact of psychosocial support alongside methadone prescribing and monitoring needs further study. In terms of improving the delivery of methadone maintenance programmes in primary care, paper based guidance may no longer be sufficient. Health information technology systems have been shown to improve quality of care by increasing adherence to guideline based recommendations, enhancing surveillance and monitoring, and decreasing the incidence of drug errors.[21]

Conclusions

Prescribing of methadone could be improved, particularly as regards dosage, co-prescribing of benzodiazepines, and monitoring. Further research is needed into health information technology systems that provide structure to the planning, coordination, and monitoring needed for an effective methadone maintenance programme in primary care.[21]

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Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study

Lesley M E McCowan,[1] Gustaaf A Dekker,[6] Eliza Chan,[1] Alistair Stewart,[2] Lucy C Chappell,[4] Misty Hunter,[1] Rona Moss-Morris,[5] Robyn A North,[3] on behalf of the SCOPE consortium

EDITORIAL
by Campbell and Murphy

[1]Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, School of Population Health, University of Auckland, Auckland, New Zealand
[2]Department of Epidemiology and Biostatistics, Faculty of Medical and Health Sciences, University of Auckland
[3]Discipline of Obstetrics and Gynaecology, School of Paediatrics and Reproductive Health, University of Adelaide, Australia
[4]Division of Reproduction and Endocrinology, King's College London
[5]School of Psychology, University of Southampton
[6]Women and Children's Division, Lyell McEwin Hospital, University of Adelaide
Correspondence to:
L M E McCowan
l.mccowan@auckland.ac.nz

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STUDY QUESTIONS What are the relative risks of spontaneous preterm birth and of having a small for gestational age baby among pregnant women who stop smoking by 15 weeks' gestation?

SUMMARY ANSWER There were no differences in these adverse pregnancy outcomes between women who stopped smoking by 15 weeks' gestation and non smokers, but women who continued to smoke had a 3.2-fold increase in spontaneous preterm birth and a 1.8-fold increase in small for gestational age babies.

Participants and setting

Between November 2004 and July 2007, 2504 healthy nulliparous women were recruited to the Screening for Pregnancy Endpoints (SCOPE) study in Auckland, New Zealand, and Adelaide, Australia.

Design, size, and duration

After recruitment to this prospective multicentre cohort study at 15 weeks' gestation, participants were divided into three groups according to self reported smoking status—"non-smokers," who did not smoke at all during pregnancy; "stopped smokers," who had smoked at some time during pregnancy but who stopped before the 15 week interview; and "current smokers," who still smoked at the time of the interview. Small infant size for gestational age was defined as birth weight <10th customised centile, and spontaneous preterm birth was spontaneous labour or rupture of the membranes resulting in birth at <37 weeks' gestation. We compared the odds of these outcomes between stopped smokers and the other groups using logistic regression, adjusting for demographic and clinical risk factors

Main results and the role of chance

Of the participants, 1992 (80%) were non-smokers, 261 (10%) were stopped smokers, and 251 (10%) were current smokers. We found no differences between non-smokers and stopped smokers in rates of spontaneous preterm birth (4% *v* 4%, adjusted odds ratio 1.03 (95% CI 0.49 to 2.18), P=0.66) or small for gestational age infants (10% *v* 10%, 1.06 (0.67 to 1.68), P=0.8). Current smokers, however, had higher rates of spontaneous preterm birth than stopped smokers (10% *v* 4%, 3.21 (1.42 to 7.23), P=0.006) and higher rates of small for gestational age infants (17% *v* 10%, 1.76 (1.03 to 3.02), P=0.03).

Bias, confounding, and other reasons for caution

Participants' smoking status was not validated by biochemical measures, but, given the similarities in pregnancy outcomes between stopped smokers and non-smokers, it is unlikely that many women who continued to smoke falsely claimed to have stopped smoking. Of the women who had stopped smoking by the 15 week interview, 94% had already stopped by 12 weeks' gestation. It is therefore possible that the benefits we observed were due to stopping smoking in the first trimester.

Generalisability to other populations

As has been found in other studies, the women who continued to smoke were heavier smokers before pregnancy, younger, less well educated, less likely to be employed, and reported higher rates of alcohol use than the other participants. Those who stopped smoking by 15 weeks' gestation had intermediate values for these characteristics. Our results are therefore likely to be generalisable to other pregnant women.

Study funding/potential competing interests

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PREGNANCY OUTCOMES BY MATERNAL SMOKING STATUS

	Non-smokers	Stopped smokers	Mean difference (95% CI)*	Current smokers	Mean difference (95% CI)†
Spontaneous preterm births	4% (88/1992)	4% (10/261)	-0.6% (-2.6% to 2.6%)	10% (25/251)	6.1% (1.7% to 10.8%)
Small for gestational age	10% (195/1992)	10% (27/261)	-0.5% (-5.0% to 2.9%)	17% (42/251)	6.4% (0.4% to 12.4%)
Mean (SD) birth weight (g)	3409 (592)	3479 (560)	-70 (-146 to 6)	3139 (751)	270 (190 to 350)
Uncomplicated pregnancies	60% (1192/1992)	62% (162/261)	-2.2% (-8.3% to 4.2%)	44% (111/251)	-17.8% (-26.1% to -9.2%)

*Stopped smokers *v* non-smokers †Stopped smokers *v* current smokers

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Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data

Katy J L Bell,[1] Andrew Hayen,[1] Petra Macaskill,[1] Les Irwig,[1] Jonathan C Craig,[1] Kristine Ensrud,[2] Douglas C Bauer[3]

EDITORIAL by Compston

[1]Screening and Test Evaluation Program, School of Public Health, Edward Ford Building (A27), University of Sydney, NSW 2006, Australia
[2]University of Minnesota Medical School, Veterans Affairs Medical Center, One Veterans Drive (111-0), Minneapolis, MN 55417, USA
[3]Box 0560, 185 Berry Street 5700, University of California, San Francisco, CA 94143–0560, USA
Correspondence to: K J L Bell
katyb@health.usyd.edu.au

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STUDY QUESTION Do the effects of alendronate differ between individuals enough to warrant routine monitoring of bone mineral density?

SUMMARY ANSWER Between-person differences in the effects of alendronate on bone mineral density were small compared with background within-person variation in bone density measurements, and treatment was estimated to be beneficial for the vast majority of patients. Monitoring bone mineral density in the first three years after starting bisphosphonate treatment in postmenopausal women is unnecessary and may be misleading.

Participants and setting

The Fracture Intervention Trial was a randomised controlled trial conducted at 11 clinical centres around the United States that compared the effects of alendronate with placebo in 6459 postmenopausal women with low bone mineral density.

Design

For this secondary analysis of the trial data, bone density measurements of hip and spine were obtained from four time points (before treatment and at one, two, and three years after treatment was started). Mixed models were used to estimate the mean and between-person variation in treatment effects as well as background within-person variation.

Primary outcomes

Between-person (treatment related) variation and within-person (measurement related) variation in hip and spine bone mineral density.

Main results and the role of chance

The table shows the actual treatment effects (estimated from the mixed models, for alendronate compared with placebo) and the apparent treatment effects (estimated from the observed changes, alendronate only) after three years. The mean actual treatment effect on hip bone mineral density was an increase of 0.030 g/cm^2 (P<0.001). There was strong evidence of between-person variation in actual treatment effects, with a standard deviation of 0.0055 g/ cm^2 (P=0.008), but only weak evidence of additional between-person variation in actual treatment effects after one year (P=0.07). After three years, the 95% distribution for the actual effects of treatment did not overlap zero, ranging from an increase of 0.019 g/cm^2 (2.5th centile) to 0.041 g/cm^2 (97.5th centile). Within-person variation was several times greater than the between-person variation in treatment effects, so that observations on individuals often showed apparent decreases of bone mineral density. The apparent 95% distribution of change after three years of treatment ranged from a decrease of 0.031 (2.5th centile) to an increase of 0.075 (97.5th centile).

TREATMENT EFFECTS ON HIP BONE MINERAL DENSITY AFTER 3 YEARS OF ALENDRONATE

Variable	Estimated effect on hip bone mineral density (g/cm^2)		
	Mean	Between-person standard deviation	95% distribution‡
Actual effect (alendronate *v* placebo)*	0.030	0.0055	0.019 to 0.041
Apparent effect (alendronate only)†	0.022	0.027	-0.031 to 0.075

*Data from final mixed model—adjusted for baseline hip bone mineral density, age, body mass index, and self rated health status
†Based on changes observed in alendronate group
‡95% distribution of treatment effects estimated from mean ± standard deviation

Bias, confounding, and other reasons for caution

The large within-person variation in bone density is likely to be an underestimate, as bone density measurements made in clinical trials probably have considerably less within-person variation than measurements made in clinical practice, strengthening still further the argument against monitoring. The participants in this study had no other major medical problems. Most were asked to take daily supplements of calcium and vitamin D in addition to trial medication.

Generalisability to other populations

Our results may be generalised to the effects of other potent oral bisphosphonates of roughly equivalent dose in postmenopausal women. Further work is needed to generalise beyond this group of drugs to other treatments, such as intravenous bisphosphonates and non-bisphosphonate drugs such as oestrogen, oestrogen agonist/antagonists, parathyroid hormone, and strontium ranelate.

Study funding/potential competing interests

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