Open Access: free full text available online
For the full versions of these articles see bmj.com

RESEARCH

Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial

Alastair D Hay,[1] Céire Costelloe,[1] Niamh M Redmond,[1] Alan A Montgomery,[1] Margaret Fletcher,[2] Sandra Hollinghurst,[1] Tim J Peters[1]

EDITORIAL by Harnden
RESEARCH, p 734

[1]Academic Unit of Primary Health Care, NIHR National School for Primary Care Research, Department of Community Based Medicine, University of Bristol, Bristol BS8 2AA
[2]Faculty of Health and Social Care, University of West England, Bristol
Correspondence to: A D Hay
alastair.hay@bristol.ac.uk

Cite this as: *BMJ* 2008;337:a1302
doi:10.1136/bmj.a1302

ABSTRACT

Objective To investigate whether paracetamol (acetaminophen) plus ibuprofen are superior to either drug alone for increasing time without fever and the relief of fever associated discomfort in febrile children managed at home.

Design Individually randomised, blinded, three arm trial.

Setting Primary care and households in England.

Participants Children aged between 6 months and 6 years with axillary temperatures of at least 37.8°C and up to 41.0°C.

Intervention Advice on physical measures to reduce temperature and the provision of, and advice to give, paracetamol plus ibuprofen, paracetamol alone, or ibuprofen alone.

Main outcome measures Primary outcomes were the time without fever (<37.2°C) in the first four hours after the first dose was given and the proportion of children reported as being normal on the discomfort scale at 48 hours. Secondary outcomes were time to first occurrence of normal temperature (fever clearance), time without fever over 24 hours, fever associated symptoms, and adverse effects.

Results On an intention to treat basis, paracetamol plus ibuprofen were superior to paracetamol for less time with fever in the first four hours (adjusted difference 55 minutes, 95% confidence interval 33 to 77; P<0.001) and may have been as good as ibuprofen (16 minutes, −7 to 39; P=0.2). For less time with fever over 24 hours, paracetamol plus ibuprofen were superior to paracetamol (4.4 hours, 2.4 to 6.3; P<0.001) and to ibuprofen (2.5 hours, 0.6 to 4.4; P=0.008). Combined therapy cleared fever 23 minutes (2 to 45; P=0.025) faster than paracetamol alone but no faster than ibuprofen alone (−3 minutes, 18 to −24; P=0.8). No benefit was found for discomfort or other symptoms, although power was low for these outcomes. Adverse effects did not differ between groups.

Conclusion Parents, nurses, pharmacists and doctors wanting to use medicines to supplement physical measures to maximise the time that children spend without fever should use ibuprofen first and consider the relative benefits and risks of using paracetamol plus ibuprofen over 24 hours.

Trial registration Current Controlled Trials ISRCTN26362730.

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008;337:a1302

INTRODUCTION

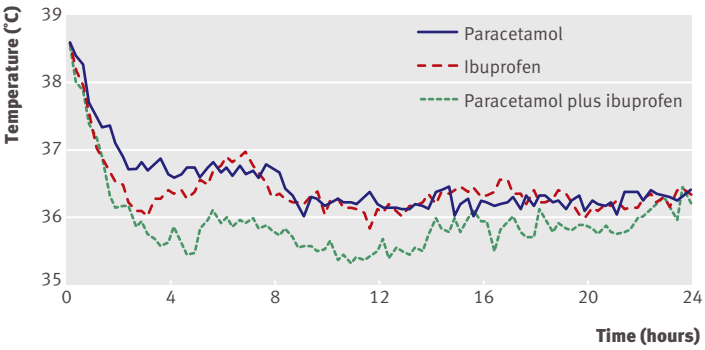
Paracetamol (acetaminophen) and ibuprofen have been shown to be superior to placebo[1-3] and ibuprofen superior to paracetamol[4] for the relief of fever (see bmj.com). As the drugs have different mechanisms of action[5] they might be more effective when used together than alone. Five previous trials[6-10] mostly tested the effects of single doses at selected time points, were largely done in secondary care, and reached conflicting conclusions. We carried out a community based, three arm, blinded, randomised controlled trial to compare the effectiveness of multiple doses of paracetamol plus ibuprofen compared with either drug alone. Our investigation into the relative cost effectiveness will be reported later.[11]

METHODS

We recruited and followed up children between January 2005 and May 2007 (see bmj.com). We invited all NHS organisations providing primary care services in Bristol to assist with recruitment. We included children if they were aged between 6 months and 6 years and were unwell with a temperature of at least 37.8°C and up to 41.0°C as a result of illnesses that could be managed at home. After a baseline questionnaire had been completed, we randomised children using minimisation to one of three trial arms (paracetamol plus ibuprofen, paracetamol alone, ibuprofen alone; see bmj.com).[12]

Intervention

The intervention was the provision of, and advice to give, the study drugs for up to 48 hours: paracetamol every 4-6 hours (maximum of four doses in 24 hours) and ibuprofen every 6-8 hours (maximum of three doses in 24 hours). Parents, research nurses, and investigators were blinded to treatment allocation by using identically matched placebo drugs. Parents received two medicine bottles; one or both with active drugs, the other placebo. The dose of drug was determined by the child's weight (paracetamol



	Percentage of children with recorded temperatures >37.2°C at different time points (hours)												
	0*	2	4	6	8	10	12	14	16	18	20	22	24
Paracetamol	81*	36	29	25	19	25	19	19	17	15	14	12	12
Ibuprofen	85*	15	15	29	12	13	10	12	15	6	8	12	13
Paracetamol plus ibuprofen	73*	9	2	10	13	5	6	12	6	8	2	6	10

Mean temperature over first 24 hours after randomisation, by treatment group. *All children had temperatures greater than 37.2°C at baseline eligibility assessment, as measured by standard digital axillary thermometry. Temperature measured using a data logger was less than 37.2°C for 19 children because of delays between digital thermometry measure and drug dosing (median eight minutes for paracetamol plus ibuprofen and nine minutes for paracetamol and ibuprofen) and differences between digital and data logger thermometry methods

15 mg/kg per dose and ibuprofen 10 mg/kg per dose) measured at the baseline visit.

The first doses were given in the presence of the research nurse and were timed to coincide with the child's next due dose of drug. The order in which the first drug was given was determined randomly. Time zero was the time that the drugs were swallowed. The first four hours was regarded as the "efficacy period." We asked the parents to give the drugs regularly from four to 24 hours (see bmj.com) and to give the drugs between 24 and 48 hours in response to their child's symptoms. At 48 hours we retrieved the drugs and advised the parents to use over the counter preparations as required until day 5.

Outcomes

The primary outcomes were the number of minutes without fever (<37.2°C) in the first four hours and the proportion of children reported as being normal on the discomfort scale at 48 hours. Secondary outcomes were collected at three time points. In the first 24 hours we recorded fever clearance (time to the temperature first falling below 37.2°C), the time spent without fever over 24 hours, and the proportion of children without fever associated symptoms: discomfort, reduced activity, reduced appetite, and disturbed sleep. At 48 hours and day 5 we obtained data on fever associated symptoms and temperature measured by parents. At all time points we asked parents about adverse effects.

Using a data logger (OM-CP-RTDTEMP110; Omega Engineering, Stamford, CT) connected to an axillary temperature probe, we measured and recorded temperature every 30 seconds for 24 hours. The parents recorded fever associated symptoms, axillary temperature (measured with standard digital thermometers), and adverse effects in symptom diaries.

Statistical analyses

The sample size calculation is on bmj.com. Comparative analyses were done in Stata 9 on an intention to treat basis using linear or logistic regression and adjusting for minimisation variables. Primary comparisons were between paracetamol plus ibuprofen and either drug alone, and secondary comparisons were between paracetamol and ibuprofen, using Dunnett's and Tukey's adjustments for multiple comparisons.[13] In regression models we used the proportion of valid time under the fever threshold and we weighted these according to the amount of valid data (see bmj.com). Secondary analyses included additional adjustment for factors showing possible imbalance at baseline and preplanned exploratory analyses for differential effects of paracetamol plus ibuprofen compared with paracetamol or ibuprofen for baseline age, temperature, discomfort, antibiotic use, and presence of otitis media (affected children might experience enhanced effects for both fever and pain).

RESULTS

Thirty five primary care sites in Bristol agreed to take part in the trial (see bmj.com). Overall, 156 children participated. In four children, clinicians and parents but not research staff were unblinded to treatment allocation.

The groups were comparable at baseline, although potentially influential differences existed for sex, method of recruitment, and activity (see bmj.com). Additional adjustment for these variables had negligible effects in all analyses; only minimisation variables are adjusted for in the comparative analyses. Nearly all the children were unwell, with more than 90% experiencing discomfort, reduced activity, abnormal appetite, or abnormal sleep (see bmj.com).

For time without fever in the first four hours (and the corresponding secondary outcome within 24 hours), children receiving paracetamol plus ibuprofen spent more time without fever than those given ibuprofen and, in turn, those given paracetamol (table and bmj.com). Fever clearance was faster in children given paracetamol plus ibuprofen than in those given paracetamol but was similar for those given ibuprofen. Children given paracetamol plus ibuprofen spent less time with fever over 24 hours than those given either drug. A suggestion was that more fever associated symptoms had normalised in children given ibuprofen than the other treatments at 24 and 48 hours, but by day 5 these trends had largely disappeared.

Comparative analyses

Strong evidence suggested that children given paracetamol plus ibuprofen spent 55 extra minutes without fever in the first four hours compared with those given paracetamol, and likewise for children given ibuprofen, an extra 39 minutes compared with those given paracetamol (see bmj.com). The confidence interval and P value suggest little difference between giving paracetamol plus ibuprofen and giving ibuprofen alone.

Strong evidence suggested that paracetamol plus ibuprofen cleared the fever 23 minutes faster than paracetamol alone, and ibuprofen 26 minutes faster than paracetamol (see bmj.com). Giving paracetamol plus ibuprofen over 24 hours increased time without fever by 4.4 hours compared with paracetamol and by 2.5 hours compared with ibuprofen.

No consistent evidence of effect for fever associated symptoms from 24 hours to day 5 was seen, but odds ratios tended to favour ibuprofen more than the other treatments at 24 and 48 hours (data not shown).

Descriptive statistics of outcomes (time without fever and no discomfort) at selected times. Values are numbers (percentages) unless stated otherwise

Outcomes	Paracetamol (n=52)	Ibuprofen (n=52)	Paracetamol plus ibuprofen (n=52)
Primary outcomes			
Mean (SD) time without fever in first 4 hours (minutes)*	116.2 (65.0)	156.0 (57.6)	171.1 (40.8)
No discomfort at 48 hours†	34 (65)	37 (71)	36 (69)
Secondary outcomes:			
Outcomes at 24 hours:			
Mean (SD) time until first fever clearance (minutes)‡	71.0 (69.1)	42.2 (33.5)	45.5 (34.3)
Mean (SD) time without fever in first 24 hours (minutes)*	940.3 (362.9)	1055.2 (329.7)	1217.4 (237.6)
No discomfort†	22 (44)	36 (69)	29 (56)
Normal activity†	20 (40)	20 (58)	23 (48)
Normal appetite†	10 (21)	14 (27)	14 (29)
Normal sleep†	17 (37)	13 (50)	20 (37)
Outcomes at 48 hours:			
Mean (SD) temperature (°C)§	36.4 (0.89)	36.4 (0.85)	36.6 (1.01)
Normal activity†	31 (60)	37 (73)	28 (54)
Normal appetite†	21 (41)	22 (44)	21(41)
Normal sleep†	27 (52)	31 (61)	25 (48)
Outcomes at day 5:			
Mean (SD) temperature (°C)**	36.2 (0.93)	36.1 (0.78)	36.0 (0.66)
No discomfort†	43 (88)	38 (81)	38 (76)
Normal activity†	44 (90)	39 (85)	37 (73)
Normal appetite†	29 (58)	29 (59)	32 (62)
Normal sleep†	31 (62)	25 (50)	27 (53)

*Time spent with temperature less than 37.2°C in first four hours after first dose of drug, using number of valid (see bmj.com) 30 second interval points from data logger; unknown for zero, one, and two children in three groups, respectively, by four hours, and zero, two, and two, respectively by 24 hours. Time without fever over first four hours was 48 minutes for paracetamol, 65 minutes for ibuprofen, and 71 minutes for paracetamol plus ibuprofen and for time without fever in first 24 hours was 65 minutes for paracetamol, 73 minutes for ibuprofen, and 84 minutes for paracetamol plus ibuprofen.
†Children reported at relevant time to be "normal" (see table 1 on bmj.com); denominators may vary owing to missing data (in most cases fewer than four children).
‡Time from baseline until temperature first falls below 37.2°C; unknown for five children (zero, two, and three, respectively) and right censored at 240 minutes for three children.
§Measured by research nurse; unknown for one, five, and two children, respectively.
**Measured by parent; unknown for four, seven, and three children, respectively.

Mean temperature by treatment group

The figure shows the mean temperature every 15 minutes by treatment group with the proportion of children febrile at corresponding two hourly time points. Ibuprofen and paracetamol plus ibuprofen reduced children's temperatures faster and for longer than paracetamol in the first four hours, and paracetamol plus ibuprofen was superior to either drug in reducing mean temperatures over 24 hours. A rise in mean temperature was seen for children in the ibuprofen group, which then fell just after six hours, coinciding with the earliest time that parents were advised that a second dose of ibuprofen could be given. This rise may have been prevented in the other groups by paracetamol, which could have been given at four hours.

The mean temperatures are lower than might be expected biologically. This could be explained by the choice of axillary thermometry, which is known to record temperatures around 0.8°C lower than rectal digital thermometers,[14] or by the liberal definition of valid temperature used in the present study (see bmj.com).

Relation between discomfort and temperature

A repeated measure analysis explored the relation between all discomfort measures recorded across up to eight time points to 48 hours and their coinciding mean digital axillary thermometer measures. The mean temperatures were 36.4°C for children who scored normal on the discomfort scale, 37.2°C for those who scored not quite normal, 38.1°C for those who scored some pain or distress, and 38.3°C for those who scored crying or very distressed.

Adverse effects

The most common adverse effects were diarrhoea and vomiting, which were equally distributed between groups (see bmj.com). The overall number of children experiencing adverse events was, however, too small to make meaningful comparisons between treatments.

Dosing of study drugs

All 52 children in each of the three groups were given, as per protocol, their first dose of study drug under nurse supervision (see bmj.com). The recommended maximum four doses of paracetamol in the first 24 hours were received by 65% of children given paracetamol, 46% given ibuprofen, and 42% given paracetamol plus ibuprofen, with this recommended maximum exceeded by 12%, 6%, and 8%, respectively. The corresponding percentages receiving the recommended maximum three doses of ibuprofen or placebo in 24 hours were 73%, 75%, and 71% and those exceeding this recommended maximum were 13%, 12%, and 13%. All percentages were much lower at 48 hours.

Blinding

At 48 hours parents were asked to guess treatment allocation. Taking "I don't know" responses as failure to guess correctly, allocation was guessed correctly by 16 (31%) parents in the paracetamol group, 17 (33%) in the ibuprofen group, and 9 (17%) in the paracetamol plus ibuprofen group, compared with the 33% expected by chance.

DISCUSSION

In febrile children we found strong evidence of faster time to fever clearance and more prolonged time without fever in the first four hours favouring paracetamol plus ibuprofen and ibuprofen over paracetamol, but no evidence of any difference between paracetamol plus ibuprofen and ibuprofen alone. In the first 24 hours strong evidence suggested more time without fever favouring paracetamol plus ibuprofen over either drug. We found no evidence of differences in fever associated discomfort at 48 hours. The frequency of adverse effects did not seem to differ between groups.

Comparison with existing literature

Using continuous thermometry we compared the effects of two antipyretics combined with either drug alone using maximum licensed, repeated doses in children at home. Previous studies have recruited from secondary care,[6 7 9 10] investigated the effects of single doses,[7 9] and did not use continuous thermometry. The finding that ibuprofen was found to be more effective than paracetamol in the first four hours is consistent with the literature.[4]

Strengths and limitations of the study

One strength of the study was its internal validity: randomisation was concealed, nurses and investigators were blinded to allocation, and attrition was minimal. In addition, the intervention and follow-up periods were long enough to enable a fair comparison between multiple doses of antipyretics with differing times to maximum effect[15]and we used continuous thermometry to generate the objective and intuitive outcome of time without fever. Finally, we recruited and followed up children in the community, where most cases of fever are managed.

We are aware of five possible weaknesses of the study. Firstly, because we had no placebo only group our data cannot inform the decision on whether to use antipyretics. This was a deliberate decision as we thought parents would not have participated if there had been a placebo only group and good evidence already exists showing the superiority of single drugs over placebo (see bmj.com). Secondly, although the recruited sample did not give sufficient power to detect plausible differences in discomfort, research has suggested that two drugs combined confer additional benefit on symptoms than one drug alone [8] and we did show a relation between increasing discomfort and worsening fever. Thirdly, an axillary temperature of 37.8°C might not be regarded as denoting fever. Since no agreed definition of fever or how to measure temperature exists,[16] to a limited extent its selection was arbitrary. The mean temperature at baseline was 38.5°C, a temperature at which 90% of doctors and 70% of nurses would recommend treatment,[17] and most of the children were unwell with the illness. Fourthly, the success of blinding was assessed at 48 hours by asking parents to guess which drugs were active. Overall, the 153 parents who responded were not able to guess treatment, but the 83 who expressed an opinion did identify allocation more often than would be expected by chance (see bmj.com). Finally, our sample might not be representative of the general population. The most common reason for ineligibility was insufficient fever, a factor we think is unlikely to be associated with any other physiological marker of response to drugs.

Implications of this research

It is good practice for parents, nurses, and doctors to use the minimum number of drugs possible to treat young, unwell children with fever.[18] Although other studies have shown that paracetamol is superior to placebo,[1-3] our study suggests that those wanting faster and more prolonged fever relief in the first four hours should use ibuprofen in preference to paracetamol. Similarly, where symptoms are expected to last at least 24 hours, those wanting to maximise the time without fever should probably start with ibuprofen but also consider paracetamol plus ibuprofen. The decision on whether to start with ibuprofen or paracetamol plus ibuprofen, however, should also be influenced by an assessment of the benefits (an additional 2.5 hours without fever) compared with the risk of unintentionally exceeding the maximum recommended dose owing to the complexity of using two drugs; even in the context of this supervised trial, between 6% and 13% of parents exceeded the maximum number of recommended doses in the first 24 hours.

In the community paracetamol and ibuprofen are usually dosed by age, and we recognise that calculating doses by weight means the results may inform primary and secondary care practice more than practice at home. We decided against a dose by age regimen for two reasons. Given the recommendation of the children's national service framework to dose by weight[19] and the dose by weight presentations in the British national formulary for children,[20] we believe that in the future more medicines for children will be given by weight. Also, we wanted to ensure that heavier children for their age received a therapeutic dose and to avoid exceeding the maximum recommended dose for children who were light for their age.

Recent case reports have highlighted the concern about renal toxicity in dehydrated children given ibuprofen.[21 22] Although this serious effect is rare, we excluded children with dehydration from our trial and believe that ibuprofen should not routinely be given to children with, or at risk of, dehydration. Good evidence shows, however, that ibuprofen is as safe as

WHAT IS ALREADY KNOWN ON THIS TOPIC

Paracetamol plus ibuprofen are being increasingly used at home and in primary and secondary care for the relief of fever and its associated symptoms

Five previous trials of combined therapy mostly tested single doses for children in secondary care and reached conflicting conclusions

WHAT THIS STUDY ADDS

In the first four hours, temperature is reduced faster and for longer in children given ibuprofen than in those given paracetamol

In the first 24 hours, children given both drugs spent 4.4 hours less time with fever than those given paracetamol and 2.5 hours less time with fever than those given ibuprofen.

Parents and healthcare professionals should consider ibuprofen first and the relative benefits and risks of using combined therapy over 24 hours

paracetamol for children with asthma, where there is no evidence of sensitivity to non-steroidal anti-inflammatory drugs.[23]

We agree with the guidelines for fever from the National Institute for Health and Clinical Excellence (NICE) that antipyretics should be used only when children have fever associated with other symptoms.[18] However, we believe that the guidance on the use of two drugs combined need not be so cautious now that good evidence supports the superiority of both drugs combined over one drug alone for increasing time without fever over 24 hours.

Doctors, nurses, pharmacists, and parents wanting to use medicines to treat young, unwell children with fever should be advised to use ibuprofen first and to consider the relative benefits and risks of using paracetamol plus ibuprofen over 24 hours.

We thank Avon, Gloucestershire, and Wiltshire NHS Direct; the Bristol general practitioner practices; the south Bristol walk-in centre; the emergency department of the Bristol Royal Hospital for Children; the children and parents who participated; the South West Medicines for Children Local Research Network; the research nurse team W Horseman, J Farrimond, R Powell, S Shatford, P Richards; the South West Medicines for Children Local Research Network nurse V Payne; W Patterson (trial coordinator); S Doohan and S Burke (project administrators); K Schroeder, M Weiss, and A Emond (co-applicants); Sara Whitburn (proof and background reading); K Pitcher (data entry and quality); the trial steering committee (AL Kinmonth, C Butler, J Peacock, M Blythe, and P Denyer); and the data monitoring and safety committee (R Bragonier, S Kerry, and J Chudleigh).

Contributors: See bmj.com.

Funding: National Institute for Health Research health technology assessment programme (project No 03/09/01). The final study design, data collection and analysis, interpretation of results, and paper writing was the sole responsibility of the authors. For the duration of the trial, ADH held a postdoctoral award from the National Coordinating Centre for Research Capacity Development, Department of Health. The views and opinions expressed in this paper do not necessarily reflect those of the funding bodies. The active drugs and placebos were purchased from Pfizer and DHP Investigational Medicinal Products, respectively. Neither had any other role in the design, conduct, analysis, or reporting of the trial.

Competing interests: None declared.

Ethical approval: Bath research ethics committee (reference No 04/Q2001/197).

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Wilson JT, Brown RD, Kearns GL, Eichler VF, Johnson VA, Bertrand KM, et al. Single-dose, placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children. *J Pediatr* 1991;119:803-11.
2 Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther* 1989;46:9-17.
3 Brewer EJ Jr. A comparative evaluation of indomethacin, acetaminophen and placebo as antipyretic agents in children. *Arthritis Rheum* 1968;11:645-51.
4 Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. *Arch Pediatr Adolesc Med* 2004;158:521-6.
5 Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. [Review]. *Am J Med* 2001;111:304-15.
6 Lal A, Gomber S, Talukdar B. Antipyretic effects of nimesulide, paracetamol and ibuprofen-paracetamol. *Indian J Pediatr* 2000;67:865-70.
7 Erlewyn-Lajeunesse MDS, Coppens K, Hunt LP, Chinnick PJ, Davies P, Higginson IM, et al. Randomised controlled trial of combined paracetamol and ibuprofen for fever. *Arch Dis Child* 2006;91:414-6.
8 Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. *Arch Pediatr Adolesc Med* 2006;160:197-202.
9 Nabulsi MM, Tamim H, Mahfoud Z, Itani M, Sabra R, Chamseddine F, et al. Alternating ibuprofen and acetaminophen in the treatment of febrile children: a pilot study. *BMC Med* 2006;4:4.
10 Kramer LC, Richards PA, Thompson AM, Harper DP, Fairchok MP. Alternating antipyretics: antipyretic efficacy of acetaminophen versus acetaminophen alternated with ibuprofen in children. *Clin Pediatr (Phila)* 2008 Jun 16 [ePub ahead of print].
11 Hollinghurst S, Redmond N, Costelloe C, Montgomery AA, Fletcher M, Peters TJ, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): economic evaluation of the randomised controlled trial. *BMJ* 2008;337:a1490.
12 Treasure T, MacRae KD. Minimisation: the platinum standard for trials? Randomisation doesn't guarantee similarity of groups; minimisation does [editorial] [see comments]. *BMJ* 1998;317:362-3.
13 Zar J. *Biostatistical analysis*. 2 ed. Englewood Cliffs, NJ: Prentice-Hall, 1994.
14 Craig JV, Lancaster GA, Williamson PR, Smyth RL. Temperature measured at the axilla compared with rectum in children and young people: systematic review. *BMJ* 2000;320:1174-8.
15 Kelley MT, Walson PD, Edge JH, Cox S, Mortensen ME. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. *Clin Pharmacol Ther* 1992;52:181-9.
16 Michael MS, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. *Vaccine* 2004;22:551-6.
17 Sarrell M, Cohen HA, Kahan E. Physicians', nurses', and parents' attitudes to and knowledge about fever in early childhood. *Patient Educ Couns* 2002;46:61-5.
18 National Institute for Health and Clinical Excellence. *Feverish illness in children. Assessment and initial management in children younger than 5 years*. London: NICE, 2007.
19 Department of Health. *National service framework for children, young people and maternity services*. London: Her Majesty's Stationery Office, 2004.
20 British Medical Association, Royal Pharmaceutical Society of Great Britain, Royal College of Paediatrics and Child Health. *BNF for children*. London: BMJ Publishing Group, RPS, RCPCH, 2007.
21 Mathews John C, Shukla R, Jones CA. Using NSAID in volume depleted children can precipitate acute renal failure. *Arch Dis Child* 2007;92:524-6.
22 Moghal NE, Hegde S, Eastham KM. Ibuprofen and acute renal failure in a toddler. *Arch Dis Child* 2004;89:276-7.
23 Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children.[see comment]. *Pediatrics* 2002;109:E20.

Accepted: 4 July 2008

Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): economic evaluation of a randomised controlled trial

Sandra Hollinghurst,[1] Niamh Redmond,[1] Céire Costelloe,[1] Alan Montgomery,[1] Margaret Fletcher,[2] Tim J Peters,[1] Alastair D Hay[1]

EDITORIAL by Harnden
RESEARCH, p 729

[1]Academic Unit of Primary Health Care, NIHR National School for Primary Care Research, Department of Community Based Medicine, University of Bristol, Bristol BS8 2AA
[2]Faculty of Health and Social Care, University of the West of England, Bristol BS16 1QY
Correspondence to: S Hollinghurst
s.p.hollinghurst@bristol.ac.uk

Cite this as: *BMJ* 2008;337:a1490
doi:10.1136/bmj.a1490

ABSTRACT

Objective To estimate the cost to the NHS and to parents and carers of treating febrile preschool children with paracetamol, ibuprofen, or both, and to compare these costs with the benefits of each treatment regimen.

Design Cost consequences analysis and cost effectiveness analysis conducted as part of a three arm, randomised controlled trial.

Participants Children between the ages of 6 months and 6 years recruited from primary care and the community with axillary temperatures ≥37.8°C and ≤41°C.

Interventions Paracetamol, ibuprofen, or both drugs.

Main outcome measures Costs to the NHS and to parents and carers. Cost consequences analysis at 48 hours and 5 days comparing cost with children's temperature, discomfort, activity, appetite, and sleep; cost effectiveness analysis at 48 hours comparing cost with percentage of children "recovered."

Results Difficulties in recruiting children to the trial lowered the precision of the estimates of cost and some outcomes. At 48 hours, cost to the NHS was £11.33 for paracetamol, £8.49 for ibuprofen, and £8.16 for both drugs. By day 5 these costs rose to £19.63, £18.36, and £13.92 respectively. For parents and carers, the 48 hour costs were £23.86 for paracetamol, £20.60 for ibuprofen, and £25.07 for both, and the day 5 costs were £26.35, £29.90, and £24.02 respectively. Outcomes measured at 48 hours and 5 days were inconclusive because of lack of power; the cost effectiveness analysis at 48 hours provided little evidence that one treatment choice was significantly more cost effective than another. At 4 hours ibuprofen and the combined treatment were superior to paracetamol in terms of the trial primary outcome of time without fever; at 24 hours the combined treatment performed best on this outcome.

Conclusions There is no strong evidence of a difference in cost between the treatments, but clinical and cost data indicate that using both drugs together may be most cost effective over the course of the illness. This treatment option performs best and is no more expensive because of less use of healthcare resources, resulting in lower costs to the NHS and to parents.

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008;337:a1490

INTRODUCTION

Paracetamol and ibuprofen are increasingly used together for the relief of fever and its associated symptoms, though it is not known whether a combination of both is superior to either single drug. To our knowledge, the cost implications have not been previously investigated. In 2004 prescriptions for oral suspensions of paracetamol and ibuprofen cost about £3.5m (€4.4m; $6.1m) in England alone.[1]

The aim of this study was to estimate the cost to the NHS and to parents and carers of treating preschool children with a fever with paracetamol, ibuprofen, or both drugs. These costs were compared with the benefits of each treatment regimen.

METHODS

This evaluation forms part of a randomised controlled trial.[2] Children between the ages of six months and six years with a temperature of at least 37.8°C and no higher than 41°C were recruited to the study between January 2005 and May 2007 by one of three methods: local and remote recruitment (from general practices, out of hours cooperatives, NHS Direct, a walk-in centre, and the emergency department of a children's hospital) and direct recruitment from the community. Participants were randomised to one of three treatments: paracetamol alone, ibuprofen alone, or a combination of both. Placebo drugs were used to blind parents and researchers to the allocated treatment. The drugs were administered regularly for the first 24 hours, at the maximum dose appropriate for the child's weight.[2] Between 24 and 48 hours parents gave the drugs as required, depending on the child's symptoms.

The primary outcomes of "time without fever" and discomfort were measured in the first four hours and at 48 hours respectively. Additional secondary outcomes including temperature, activity, appetite, and sleep were measured at different time points across the five day follow-up period.

Study design

The economic evaluation was conducted from the perspectives of the NHS and of parents and carers. We included all relevant resource use during the five days after randomisation, excluding the consultation at which recruitment took place (table 1).

Cost consequences analysis

We carried out a cost consequences analysis at 48 hours and five days from baseline for the NHS and for parents and carers. We recorded a range of benefits at both time points, including the child's temperature, discomfort, activity, appetite, and sleep. These were treated as individual outcomes and also combined to provide an indication of whether the child had "fully recovered."

This was based on parents reporting that the child was "normal" for him or her with respect to discomfort, activity, appetite, and sleep and on the child having a temperature <37.2°C. Thus "fully recovered" is in effect "returned to normal for that child."

Cost effectiveness analysis

We used the combined outcome of "fully recovered" in a cost effectiveness analysis at 48 hours to estimate the cost per extra child returning to "normal for that child" and to indicate the relative efficiency of each treatment at a point before it was anticipated that most children would have recovered fully.

Data collection and unit costs

A research nurse collected data from parents and carers on resource use and out of pocket expenses by means of a face to face questionnaire at 48 hours and by telephone at day 5. Table 1 shows the source of costing and unit costs.

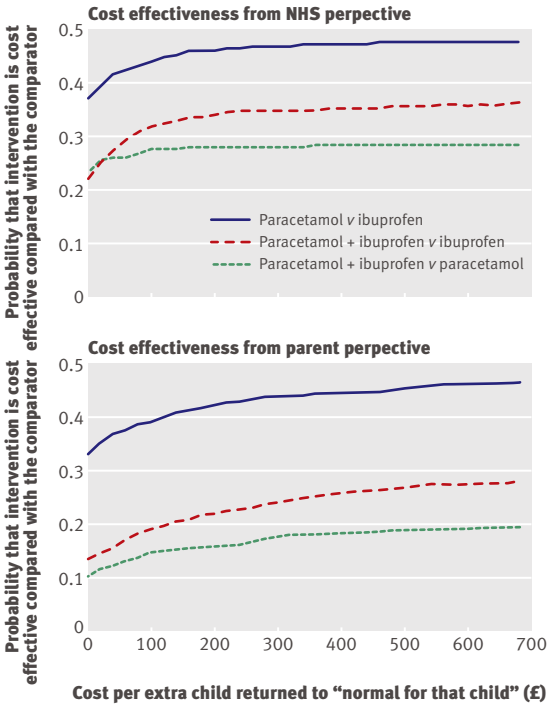
Data analysis

We estimated frequencies of resource use by the patients in each treatment arm, and mean cost per patient in each arm. Bootstrapping (1000 replicates) was used to estimate cost effectiveness planes and cost effectiveness acceptability curves to indicate the level of uncertainty around the point estimates of the incremental cost effectiveness ratios.

Table 1 | Resources (and their unit costs) considered in economic analysis of treating febrile preschool children with paracetamol, ibuprofen, or both

Resource	Unit cost (£)
Primary care[3]:	
General practitioner at surgery	21.00
General practitioner by telephone	23.00
Practice nurse	8.00
Health visitor	24.83
Out of hours[4]:	
Nurse telephone	12.00
Doctor telephone*	34.50
Doctor face to face†	31.50
Walk-in centre[5]	29.81
NHS Direct[6]	18.55
Accident and emergency department[7]	71.00
Inpatient stays[7]:	
Pneumonia	1063.00
Bronchiolitis	942.00
Upper respiratory tract infection	550.00
Ambulance[8]	132.90
Study drugs‡:	
Paracetamol (100 ml)	2.48
Ibuprofen (100 ml)	4.13
Study drugs for sensitivity analysis§:	
Paracetamol (100 ml)	0.42
Ibuprofen (100 ml)	2.69
Travel costs (per mile)[10]	0.49
Lost income per day[11]	94.80

*Based on a 10 minute consultation.
†Based on a 10.8 minute consultation.
‡Mean cost reported by parents buying these over the counter between 48 hours and five days after baseline.
§Cost if prescribed (from *British National Formulary*[9]).



Cost effectiveness acceptability curves from NHS and parent perspectives of treating fever in preschool children at 48 hours

Sensitivity analysis

We tested the robustness of our results against three possible areas of subjectivity. Firstly, we re-estimated the cost per patient from both perspectives if the study drugs had been prescribed rather than purchased over the counter. Secondly, we investigated the effect on the results if dosing had been by age rather than weight. Thirdly, we estimated the cost of hospitalisations.

RESULTS

A total of 156 children were recruited to the study—45 (29%) through local recruitment, 84 (54%) by the remote method, and 27 (17%) directly from the community. Most (64%) had a non-specific viral illness or a respiratory tract infection, 16% had otitis media, and the remaining 20% were assigned a variety of other diagnoses.

Data on NHS costs were complete for 154 (99%) children at 48 hours and 150 (96%) at five days. Personal costs were reported by 143 (92%) parents at 48 hours and 130 (83%) at day 5.

Resource use

The mean resource use per child over the five day follow-up is shown on bmj.com. Sixty per cent of children (93) used no extra NHS resources after the consultation at which they were recruited to the study and 71% (109) had no contact with their general practitioner. Most (52%)

primary care contacts were face to face at the surgery. Children receiving paracetamol had fewest face to face consultations, though most consultations overall, but there was no significant difference in total use of primary care resources among the three groups.

Thirty six prescriptions were issued (excluding two for drugs that had been provided in the study). Most (81%) were for antibiotics. Of the 113 over the counter preparations that were purchased (for 46 children), 62 (55%) were for paracetamol or ibuprofen, and 29 (47%) of these were bought in the first 48 hours (when study drugs were provided) and 24 (83%) of these were for the active ingredient being provided.

Five children spent some time in hospital. Ninety two days of work were lost among 48 (31%) parents because of their child's illness, and 21 (44%) of these reported a direct loss of earnings. Nine (6%) parents incurred out of pocket expenses for sibling or other dependent care because of the child's illness.

Cost analysis

Table 2 shows the mean cost per patient, by treatment group. About 60% of all NHS costs are accounted for by general practitioner appointments. Personal costs were dominated by loss of income.

Cost consequences analysis: 48 hours and 5 days

From the perspective of the NHS, the combined drug treatment was cheapest at both 48 hours and 5 days (see bmj.com). Paracetamol only was the most expensive. Ibuprofen only was cheapest to parents at 48 hours, but by day 5 the combined treatment had become less expensive because the greater parental spending on drugs was offset by lower travel costs (because of less health service use) and less time off work.

Cost effectiveness analysis at 48 hours

From the NHS perspective, the combined treatment is cheaper but (slightly) less effective than either of the two monotherapies, paracetamol alone is more expensive and marginally more effective than ibuprofen alone. See details on bmj.com.

From the parental perspective, paracetamol and ibuprofen together is more expensive and less effective than either of the single treatments. Ibuprofen alone is cheaper but less effective than paracetamol alone. There is little evidence that any treatment choice is significantly more cost effective than any other, and the cost effectiveness acceptability curves in the figure show that none of the probabilities of one treatment being more cost effective than another reaches 50%.

Sensitivity analysis

The results of the three sensitivity analyses for different scenarios are shown on bmj.com. The combined treatment remains the most attractive choice for the NHS and for parents.

DISCUSSION

Over the course of five days the mean cost of care for a preschool child with fever was estimated to be £27 to parents and carers and £17 to the NHS, excluding the cost of any index consultation. Two thirds of the NHS costs were due to consultations with general practitioners. Taken together, the results of our present study and those reported in our trial[12] suggest that paracetamol and ibuprofen given in combination is more effective at 24 hours than either drug given alone and possibly cheaper over a five day period.

Table 2 | Costs (£) associated with treating febrile preschool children with paracetamol, ibuprofen, or both. Values are mean (SD) cost per child by treatment group

	0-48 hours (intervention period)			0-5 days (total follow-up)		
Cost item	Paracetamol	Ibuprofen	Paracetamol + ibuprofen	Paracetamol	Ibuprofen	Paracetamol + ibuprofen
NHS costs	**(n=51)**	**(n=52)**	**(n=51)**	**(n=50)**	**(n=49)**	**(n=51)**
Primary care doctor consultations	6.15 (15.41)	3.99 (10.67)	6.48 (13.36)	12.10 (28.30)	10.38 (18.17)	10.23 (14.67)
Primary care nurse consultations	0	0.15 (1.11)	0	0.58 (4.09)	0.16 (1.14)	0
Other primary care consultations	2.03 (7.29)	0	0	3.55 (9.37)	0	0.36 (2.60)
Total primary care cost	8.18 (17.26)	4.14 (11.16)	6.48 (13.36)	16.23 (34.11)	10.54 (18.42)	10.59 (15.16)
A&E	2.78 (13.92)	4.10 (21.84)	1.39 (9.94)	2.84 (14.05)	7.24 (29.86)	2.78 (13.92)
Prescribed drugs	0.37 (1.00)	0.25 (0.85)	0.29 (0.86)	0.56 (1.27)	0.58 (1.43)	0.55 (1.63)
Total NHS cost	11.33 (23.18)	8.49 (29.13)	8.16 (16.36)	19.63 (38.11)	18.36 (40.26)	13.92 (23.17)
Parental costs	**(n=47)**	**(n=49)**	**(n=47)**	**(n=45)**	**(n=42)**	**(n=43)**
Travel cost	0.31 (1.04)	0.02 (0.08)	0.21 (0.74)	0.70 (1.56)	0.29 (0.77)	0.35 (0.89)
Over the counter drugs*	2.52 (0.29)	4.13 (0.00)	6.75 (0.68)	3.69 (1.61)	4.74 (1.44)	7.96 (2.29)
Other expenditure	21.03 (62.18)	16.44 (58.50)	18.10 (51.64)	21.97 (63.41)	24.83 (90.81)	15.64 (46.74)
Total parental costs	23.86 (62.20)	20.60 (58.52)	25.07 (51.60)	26.35 (63.37)	29.90 (90.68)	24.02 (46.36)

A&E=Accident and emergency department.
*Includes cost of study drugs as if parents had bought over the counter.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Fever is a common symptom of many childhood illnesses

Paracetamol and ibuprofen are often used, separately or together, to reduce temperature and relieve symptoms, but the optimal treatment regimen in terms of cost and outcomes is unclear

WHAT THIS STUDY ADDS

Cost of care of children with a fever is largely borne by parents and the primary care sector

Over the course of five days, using paracetamol and ibuprofen together may lead to less use of healthcare resources than either drug alone, making the combined treatment the best value option

Strengths and weaknesses of the study

This evaluation benefited from being part of a randomised controlled trial. Data collection and entry were thorough and rigorously checked; and data quality was enhanced by our method of collection.

Because of recruitment problems, we were unable to achieve our original target sample size.[12] This affected interpretation of the cost data, and some of the outcome data as the study was eventually powered to detect clinical differences solely in the time spent without fever. This outcome was measured at 4 hours and 24 hours, but cost data were not collected for this short time period. We were underpowered with respect to the outcomes measured or reported at 48 hours and five days, when cost data were collected.

The cost effectiveness analysis at 48 hours was affected by the lack of power. None of the comparisons showed evidence of differences between the treatments in terms of cost effectiveness, and it is therefore difficult to draw strong conclusions from this part of the analysis.

We chose a five day follow-up period because we expected that most children would have recovered by this time, but only 36% children had recovered, mainly because their appetite and sleep had not returned to normal. A further limitation is lack of evidence about any long term adverse effects and costs.

Finally, although we were able to estimate the direct cost to parents of time off work, we were not able to estimate the monetary value to society of that lost productivity.

Comparison with other literature

Our results are similar to those of one study which reported lower resource use in children receiving paracetamol and ibuprofen together compared with those receiving either drug on its own.[12] We have found no published economic evaluations comparing single and dual treatment for childhood fever. A recent cost of illness analysis estimated the cost of an episode of childhood cough to be £25 to the NHS and £15 to parents,[13] which is similar to our mean cost of an episode of illness over five days: £38 to the NHS (allowing for the cost of the initial consultation), and £27 to parents and carers.

Meaning of the study

The results show that, over the course of the whole illness, treating children with both drugs may lead to less use of other healthcare resources than does either of the drugs alone. This would result in lower costs to the NHS and to parents because of less travel and time off work.

We thank the Avon, Gloucestershire and Wiltshire NHS Direct, the Bristol general practices, the South Bristol Walk-In Centre, the Bristol Royal Hospital for Children's Emergency Department, and the children and parents whose participation made this study possible. We thank the South West Medicines for Children Local Research Network (MCRN); the research nurse team W Horseman, J Farrimond, R Powell, S Shatford, P Richards, and MCRN nurse V Payne; W Patterson (trial coordinator); S Doohan and S Burke (project administrators); K Schroeder, M Weiss, and A Emond (co-applicants); and K Pitcher (data entry/quality). We thank the Trial Steering Committee (AL Kinmonth, C Butler, J Peacock, M Blythe, and P Denyer) and Data Monitoring and Safety Committee (R Bragonier, S Kerry, and J Chudleigh) for their support.

Contributors: See bmj.com.

Funding: The study was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (project number 03/09/01). The final study design, data collection and analysis, interpretation of results and paper writing was the sole responsibility of the authors. For the duration of the trial, AH held a postdoctoral award from the National Coordinating Centre for Research Capacity Development (NCCRCD), Department of Health. The views and opinions expressed in this paper do not necessarily reflect those of the NI HR HTA, NCCRCD, or Department of Health. The active drugs and matched placebos were purchased from Pfizer and DHP Investigational Medicinal Products respectively. Neither had any other role in the design, conduct, analysis, or reporting of the trial.

Competing interests: None declared.

Ethical approval: The study was approved by the Bath Research Ethics Committee, UK (reference number 04/Q2001/197).

1 Department of Health. Prescription cost analysis: England 2004. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4107504 (accessed 31 Jul 2008).
2 Hay AD, Costelloe C, Redmond N, Montgomery AA, Fletcher M, Hollinghurst S, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. *BMJ* 2008;337:a1302.
3 Curtis L, Netten A. *Unit costs of health and social care 2006*. Canterbury: PSSRU University of Kent, 2007.
4 Beale N, Hollinghurst S, Taylor G, Gwynne M, Peart C, Straker-Cook D. The costs of care in general practice: patients compared by the council tax valuation band of their home address. *Fam Pract* 2005;22:317-22.
5 Salisbury C, Chalder M, Manku-Scott T, Nicholas R, Deave T, Noble S, et al. *The national evaluation of NHS walk-in centres. Final report*. Bristol: University of Bristol, 2002.
6 Munro J, Nicholl J, O'Cathain A, Knowles E, Morgan A. Evaluation of NHS Direct first wave sites: Final report of the phase 1 research. Sheffield: Medical Care Research Unit University of Sheffield, 2001.
7 Department of Health. National tariff 2006/07. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4127649 (accessed 31 Jul 2008).
8 Department of Health. Reference cost index 2004. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4105545 (accessed 31 Jul 2008).
9 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British national formulary*. London: BMA, RPS, 2008. www bnf org/bnf/ (accessed 8 Feb 2008).
10 Automobile Association. The AA schedule of motoring costs. www.theaa.com/motoring_advice/motoring_costs.html (accessed 31 Jul 2008).
11 UK Statistics Authority. Population estimates for England and Wales. www.statistics.gov.uk/ (accessed 31 Jul 2008).
12 Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. *Arch Pediatr Adolesc Med* 2006;160:197-202.
13 Hollinghurst S, Gorst C, Fahey T, Hay AD. Measuring the financial burden of acute cough in pre-school children: a cost of illness study. *BMC Fam Pract* 2008;9:10.

Accepted: 21 August 2008

Diagnostic evaluation of people with hypertension in low income country: cohort study of "essential" method of risk stratification

Gregorio Montalvo,[1] Fausto Avanzini,[2] Mariella Anselmi,[1,3] Rosanna Prandi,[1] Samuel Ibarra,[4] Monica Marquez,[1] Daniela Armani,[1] Juan-Martín Moreira,[1] Cynthia Caicedo,[1,4] Maria Carla Roncaglioni,[2] Fabio Colombo,[2] Paola Camisasca,[2] Valentina Milani,[5] Simon Quimì,[4] Felix Gonzabay,[4] Gianni Tognoni[6]

[1]Centro de Epidemiología Comunitaria y Medicina Tropical (CECOMET), Esmeraldas, Ecuador
[2]Laboratorio di Ricerca in Medicina Generale, Istituto di Ricerche Farmacologiche Mario Negri, 20156 Milan, Italy
[3]Centro Malattie Tropicali, Ospedale S. Cuore, 37034 Negrar, Verona, Italy
[4]Sistema Local de Salud, Ministerio de Salud Pública, Borbón, Ecuador
[5]Laboratorio di Statistica Medica, Istituto di Ricerche Farmacologiche Mario Negri, Milan
[6]Consorzio Mario Negri Sud, 66030 Santa Maria Imbaro, Chieti, Italy

Correspondence to: F Avanzini, Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa 19, 20156 Milan, Italy
avanzini@marionegri.it

Cite this as: *BMJ* 2008;337:a1387
doi:10.1136/bmj.a1387

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008;337:a1387

ABSTRACT

Objectives To explore the predictive power of a risk stratification method for people with hypertension based on "essential" procedures (that is, available in economically less developed areas of the world), comparing it in the same population with the results given by the method suggested by the 1999 World Health Organization-International Society of Hypertension (WHO-ISH) guidelines.

Design Prospective cohort study of outcomes according to cardiovascular risk profile at baseline.

Setting Primary care in a poor rural area of the Ecuadorian forest.

Participants 504 people with hypertension prospectively monitored for a mean of 6.7 (SD 2.3) years.

Interventions Essential data included blood pressure, medical history, smoking, age, sex, and diagnosis of diabetes; the WHO-ISH methods additionally included measurement of fasting blood glucose, total cholesterol, and creatinine, urinalysis, and electrocardiography.

Main outcome measures Cardiovascular events and total deaths.

Results With both methods there was a highly significant association between the level of predicted risk and the incidence of cardiovascular events and of total deaths: up to three quarters of all cardiovascular events and two thirds of all deaths were reported among people classified as at high or very high risk with either method. The predictive discrimination of the essential method is comparable with the WHO-ISH with C statistics (95% confidence interval) of 0.788 (0.721 to 0.855) and 0.744 (0.673 to 0.815), respectively, for cardiovascular events and 0.747 (0.678 to 0.816) and 0.705 (0.632 to 0.778) for total mortality.

Conclusions The risk stratification of patients with hypertension with an essential package of variables (that is, available and practicable even in the economically less developed areas of the world) serves at least as well as the more comprehensive method proposed by WHO-ISH.

INTRODUCTION

Studies in low income countries which assess cardiovascular risk factors are still rare,[1] and strategies to deal with these risk factors derive mostly from studies produced in more developed countries. Countries with restricted resources need a cost effective cardiovascular preventive strategy[2] that can prioritise those at higher risk of complications.[3-5]

We explored the predictive power of a risk stratification method for hypertension based on "essential" procedures (that is, available in good community practice even in the economically less developed areas of the world), comparing it in the same population with the results given by the method suggested by the World Health Organization-International Society of Hypertension (WHO-ISH) guidelines.[6] This was in an area that could be described as a model of epidemiological transition[7] and where hypertension has been documented as the major component of a high cardiovascular risk profile.[8]

METHODS

The health district of Borbón in Ecuador is an area of about 5000 km^2 almost completely covered by equatorial forest. The population of about 25 000 people, 85% black, 10% Amerindian Indios, and 5% white, is scattered in 129 villages along three rivers. Most (84%) of the population is classified as poor and 34% extremely poor, and one third of the adults are illiterate. The area is served by one hospital with 20 beds in Borbón, 12 health centres along the rivers managed by non-specialised nursing staff, and a network of 50 voluntary health "promotors" ("promotores de salud"), with the occasional supervision from a rural medical doctor. Monthly meetings of all the district health team workers allow close monitoring of the quality of delivered care.

Screening for hypertension and diagnostic investigation

Between 1995 and 2001 a screening programme of the population aged 18 and over was set up to assess the size and impact of the risk of hypertension. The results have been reported elsewhere.[8] The cohort of 1643 people with hypertension (systolic blood pressure ≥140 mm Hg or diastolic ≥90 mm Hg, or both, at the screening and the next day, or taking antihypertensive drugs) was prospectively monitored, and all causes of death and major cardiovascular events (stroke, transient ischaemic attack, myocardial infarction, heart or renal failure, and vascular disease) were recorded. The rural medical doctors diagnosed non-lethal cardiovascular events during their periodic visits to the communities. All deaths were included in a registry based on an immediate postmortem form. Rural medical doctors subsequently defined cause of deaths with verbal autopsies.

With the resources provided by an international donation, between 1998 and 2001 a subset of

	Blood pressure (mm Hg)			
	‹140/90	140-159/ 90-99	160-179/ 100-109	›180/110
WHO-ISH method				
No other risk factor or history of disease	Very low risk	Low risk	Medium risk	High risk
1-2 risk factors*	Low risk	Medium risk	Medium risk	Very high risk
›3 risk factors* or target organ damage† or diabetes	Medium risk	High risk	High risk	Very high risk
Associated clinical conditions‡	High risk	Very high risk	Very high risk	Very high risk
Essential method				
No other risk factor or history of disease	Very low risk	Low risk	Medium risk	High risk
Ageing§ or smoking	Low risk	Medium risk	Medium risk	Very high risk
Diabetes	Medium risk	High risk	High risk	Very high risk
Associated clinical conditions‡	High risk	Very high risk	Very high risk	Very high risk

Age (men ›55 and women ›65), smoking, total cholesterol ›6.47 mmol/l
†Evidence of left ventricular hypertrophy on electrocardiogram, proteinuria, or raised plasma creatinine (106.08–176.80 µmol/l)
‡Past or current symptoms of coronary disease, heart failure, cerebrovascular disease, vascular disease, renal disease
§Men ›55 and women ›65

Fig 1 | Stratification of cardiovascular risk to quantify prognosis: WHO-ISH and essential methods

participants with hypertension underwent all the laboratory and instrumental investigations recommended by the World Health Organization (WHO) and the International Society of Hypertension (ISH).[6 9] Tests included fasting blood glucose, total cholesterol, and creatinine concentrations; urinalysis; and electrocardiography. The local hospital laboratory could not measure plasma potassium concentrations. Participants in the subset lived in the more accessible villages because, in the absence of electricity, blood samples had to be stored in a portable refrigerator and transferred as soon as possible to the hospital at Borbón. Complete laboratory data were available for 504 of the 714 participants evaluated.

The results of the laboratory tests, clinical history, physical examination, and blood pressure, served to estimate each participant's future absolute risk of major cardiovascular events, as suggested by WHO-ISH guidelines.[6] These estimates are based on blood pressure and the presence of other risk factors and history of diseases (fig 1). The rural medical doctors diagnosed associated clinical conditions (cerebrovascular or coronary diseases, heart and renal failure, vascular disease) on the basis of clinical history, physical examination, and, when available, clinical record, as suggested by the WHO-ISH 1999 guidelines.[6] We could not evaluate hypertensive retinopathy because of the lack of equipment and technical competence, and a family history of premature cardiovascular disease could not be assumed to be retrievable information.

In the same population we studied the predictive power of a simplified risk stratification method based only on the data available in this poor region of the equatorial forest. In addition to blood pressure, this essential method includes age, smoking, diabetes (which in this population is usually self diagnosed by tasting urine), and associated clinical conditions (fig 1).

We compared the two risk prediction methods using cardiovascular events (the first non-lethal cardiovascular event or cardiovascular death) as the primary outcome and total mortality as secondary outcome.

Statistical analysis

We measured concordance between the two methods in individual risk stratification by the weighted κ statistic. Differences in the rate of events according to risk categories were evaluated with the Mantel-Haenszel test for linear association. Plots of the Kaplan-Meier estimate of the survival curves according to the cardiovascular risk categories of the two methods were drawn for cardiovascular events and total deaths. We constructed two multivariable Cox proportional hazards models for cardiovascular events for each method, adjusting for four classes of blood pressure and four categories of other risk factors and history of disease. To compare the predictivity of the two stratification methods we used receiver operating characteristic (ROC) curves. To assess the diagnostic

Sensitivity and specificity (95% confidence interval) of two stratification methods at various cardiovascular risk thresholds

	Risk level		
	≥ Medium	≥ High	Very high
Cardiovascular events			
Sensitivity:			
WHO-ISH	91.0 (84.2 to 97.9)	76.1 (65.9 to 86.3)	55.2 (43.3 to 67.1)
Essential	91.0 (84.2 to 97.9)	74.6 (64.2 to 85.0)	53.7 (41.8 to 65.7)
Specificity:			
WHO-ISH	27.7 (23.5 to 31.9)	62.0 (57.5 to 66.6)	82.2 (78.6 to 85.7)
Essential	32.0 (27.7 to 36.4)	65.5 (61.0 to 69.9)	86.0 (82.8 to 89.3)
Total deaths			
Sensitivity:			
WHO-ISH	90.0 (83.0 to 97.0)	67.2 (56.1 to 78.1)	45.7 (34.0 to 57.4)
Essential	88.6 (81.1 to 96.0)	65.7 (54.6 to 76.8)	44.3 (32.7 to 55.9)
Specificity:			
WHO-ISH	27.7 (23.4 to 31.9)	60.8 (56.2 to 65.4)	80.9 (77.2 to 84.6)
Essential	31.8 (27.4 to 36.2)	64.3 (59.8 to 68.8)	84.8 (81.4 to 88.2)

performance of the two methods of risk stratification we compared predicted cardiovascular risk with observed outcomes, calculating the sensitivity and specificity. See bmj.com.

RESULTS

The main baseline characteristics of the 504 participants with hypertension are shown on bmj.com. Most had known about their hypertension for many years (5-10 years for 172 (34%) and >10 years for 119 (24%)).

Stratification by absolute level of cardiovascular risk

As expected, laboratory investigations increased the proportion of participants identified with three or more associated cardiovascular risk factors, target organ damage, or diabetes. In 433 patients (86%), however, the two methods were concordant in weighting the "other risk factors and disease history" with a weighted κ value of 0.764. In 450 patients (89%), the two methods agreed in stratifying total cardiovascular risk with a weighted κ value of 0.902. In only 16 patients out of 217 (7%) did the essential method not confirm the high or very high risk defined by the WHO-ISH method.

Incidence of cardiovascular events during follow-up according to risk prediction

On 31 December 2007 we examined the rates of cardiovascular events and total deaths for all 504 patients with hypertension. During a mean follow-up of 6.7 (SD 2.3) years (range 12 days-9.7 years), 76 (15%) had a cardiovascular event and 74 (15%) died.

The proportion of participants with cardiovascular events was significantly associated with baseline blood pressure: respectively 7%, 11%, 10%, and 25% in those with normal blood pressure (<140/90 mm Hg), mild (140-159/90-99 mm Hg), moderate (160-179/100-109 mm Hg), and severe (≥180/110 mm Hg) hypertension (P<0.001 for trend). The proportion with cardiovascular events was also significantly associated with the four categories of other risk factors and history of disease considered in the WHO-ISH method (7%, 19%, 15%, and 68%, P<0.001 for trend) and the essential method (6%, 21%, 24%, and 68%, P<0.001 for trend).

Multivariate Cox analyses confirmed that in this population the criteria adopted by both methods were significantly associated with the incidence of cardiovascular events. Kaplan-Meier survival curves in patients at very low, low, medium, high, and very high cardiovascular risk according to both methods indicated a highly significant association between the level of predicted risk with both methods and the incidence of cardiovascular events (log rank test, P<0.001). The ROC curves show that the predictive discrimination of the essential method was comparable with that of the WHO-ISH method with C statistics 0.788 (95% confidence interval 0.721 to 0.855) and 0.744 (0.673 to 0.815), respectively (fig 2).

There were no significant differences between the sensitivity and specificity of the two methods at any risk threshold for all cardiovascular events (table) .

The results did not change substantially when we restricted the analyses to the 357 patients with blood pressure ≥140/90 mm Hg who were not taking antihypertensive drugs at baseline.

Total mortality during follow-up according to risk prediction

The percentages of all deaths in patients at very low, low, medium, high, and very high cardiovascular risk were 3%, 6%, 10%, 16%, and 30% according to the WHO-ISH method and 4%, 6%, 10%, 15%, and 35% according to the essential method. As for cardiovascular events, even with total deaths as outcome, both stratification methods showed a significant association between the level of predicted risk and mortality (log rank test, P<0.001); similar predictive discrimination with C statistic 0.705 (0.632 to 0.778) for

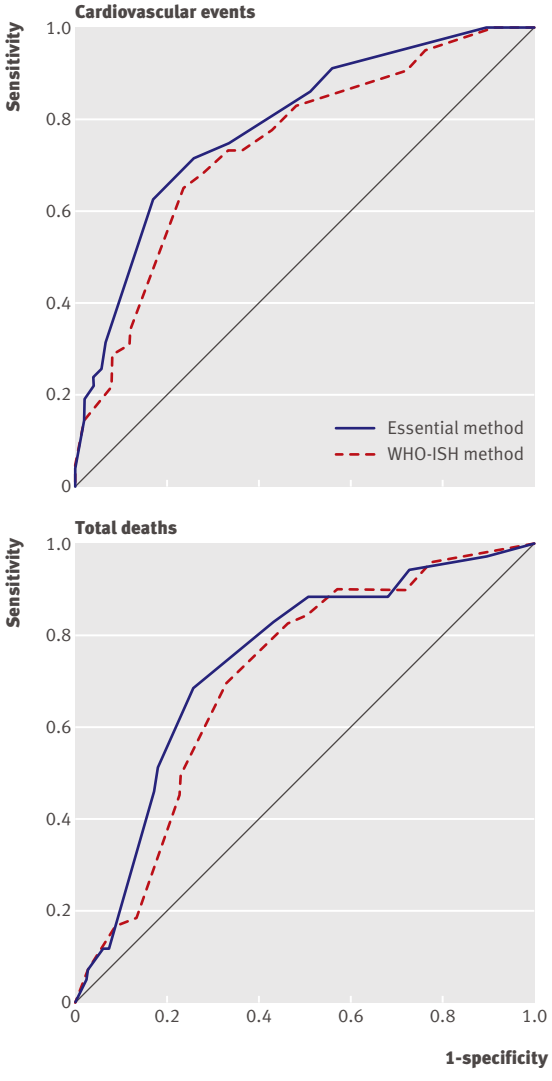


Fig 2 | ROC curves for prediction of cardiovascular events and of total deaths according to WHO-ISH and essential methods

WHAT IS ALREADY KNOWN ON THIS TOPIC

The critical role of arterial hypertension in the increasing burden of cardiovascular diseases in economically less developed areas of the world is clearly recognised, but it is usually addressed on the basis of data and strategies reflecting findings and projections produced in contexts that make them hardly transferable to the real settings of low income countries

WHAT THIS STUDY ADDS

The risk stratification of hypertensive patients with an "essential" package of variables (that is, available and practicable even in the economically less developed areas of the world) serves at least as well as a more comprehensive method with laboratory and instrumental investigations

the WHO-ISH method and 0.747 (0.678 to 0.816) for the essential method (fig 2); and comparable sensitivity and specificity (table).

DISCUSSION

A simplified method for risk stratification of patients with hypertension based on variables that can be classified as essential (because of their affordability, applicability, and reliability even in economically less developed areas of the world) performs at least as well as the more comprehensive method recommended by WHO-ISH guidelines.[6] Among high risk patients identified without any laboratory or instrumental examination we recorded three quarters of all the cardiovascular events occurring during a seven year follow-up (sensitivity 75% *v* 76% for the WHO-ISH method). The specificity of the simplified method was also close to that of the WHO-ISH criteria.

Strengths and limitations

Our findings reflect real life conditions, although we might have underestimated the overall rate of cardiovascular events because of the difficulties of doing instrumental and laboratory tests. A better classification of cardiovascular events, however, should not have influenced the results of the comparison between the two risk stratification approaches. Also, to overcome this possible limitation, we included total deaths in the evaluation of the prognostic power of the two methods.

The problems described here are likely to be representative of the logistic and economic barriers in many other low income countries. The feasibility and predictive accuracy of the proposed simplified method for stratifying cardiovascular risk should be easily transferable and applicable in other settings at a similar stage of the epidemiological transition.

Implications

From the public health point of view, our data do not support the idea of a direct relation between more sophisticated and costly approaches and better care. The resources needed for the diagnostic evaluation of people with hypertension could be drastically reduced, thus allowing broader coverage of the population as well as closer care of those at highest risk or those already disabled. For example, nowadays in the district of Borbón the cost to a patient for the laboratory tests recommended by WHO-ISH is equivalent to the cost of almost two years' treatment with antihypertensive drugs.

We thank Mauricio Espinel and Javier Corrales, medical directors of the health district of Borbón during the screening; the medical team of the health district (Bolivar Jalca, Javier Zambrano); the nurses of the district (Margarita Padilla, Daniel Tiller, Alba Chumo, Neida Mina, Juana Valencia, Hilda Guerrero, María Quiñonez, Angel Añapa, Demetrio Tapuyo, Elsa Arroyo, Lindon Corozo, Feliza Caicedo, Magda Lisley Corozo, Veronica Borja); the network of the voluntary health promoters "Asociaciòn de promotores de salud del area Borbón-APSA" (Heroína Arboleda, Sobeida Arroyo, Oberliza Caicedo, Gonzalo Medina, Amelia Preciado, Santo Mina, Adalín Valencia, Jorge Peralta, María Corozo, Ramona Sabando, Lucrecia Palacios, Erenni Cuero, Blanca Vega, Estela Arroyo, Marcos Borja, Juliana Mina, Pastor Mercado, María Arroyo, Julio Valdez, María Ayoví, Carmen Ayoví, Verónica Borja, Heriberto De la Cruz, Màrtires Ortiz, Hernán Tapuyo, Pedro Añapa, Pedro Luis Añapa, Edgar Añapa); and the local people who participated with enthusiasm in the programmes. We also thank Simona Barlera for statistical support and Fiorenza Clerici, Angela Palumbo, and Guya Sgaroni for secretarial assistance. English editing was kindly done by J D Baggott.

Contributors: See bmj.com.

Funding: CEI (Conferenza Episcopale Italiana), Associazione Amici del terzo mondo di Marsala, Associazione "Cuore batti cuore" di Bergamo, Movimento Laici America Latina/Dipartimento della Cooperazione of the Ministero Affari Esteri, Italia project MAE 2347 Esmeraldas/Equador.

Competing interests: None declared.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Yusuf S, Vaz M, Pais P. Tackling the challenge of cardiovascular disease burden in developing countries. *Am Heart J* 2004;148:1-4.
2 *Integrated management of cardiovascular risk: report of a WHO meeting*. Geneva: World Health Organization, 2002. http://whqlibdoc.who.int/publications/9241562242.pdf
3 Gaziano TA, Steyn K, Cohen DJ, Weinstein MC, Opie LH. Cost-effectiveness analysis of hypertension guidelines in South Africa. Absolute risk versus blood pressure level. *Circulation* 2005;112:3569-76.
4 Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, Rodgers A, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;361:717-25.
5 Rodgers A, Lawes CMM, Gaziano T, Vos T. The growing burden of risk from high blood pressure, cholesterol, and bodyweight. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al, eds. *Disease control priorities in developing countries*. 2nd ed. New York: World Bank/Oxford University Press, 2006.
6 Guidelines Subcommittee. World Health Organization-International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 1999;17:151-83.
7 Yusuf S, Reddy S, Ôunpuu S, Anand S. Global burden of cardiovascular diseases. Part I: general considerations, the epidemiological transition, risk factors, and the impact of urbanization. *Circulation* 2001;104:2746-53.
8 Anselmi M, Avanzini F, Moreira J-M, Montalvo G, Armani D, Prandi R, et al. Treatment and control of arterial hypertension in a rural community in Ecuador. *Lancet* 2003;361:1186-7.
9 WHO Expert Committee. Hypertension control. *World Health Organ Tech Rep Ser* 1996;862:1-83.

Accepted: 7 July 2008

Combined impact of lifestyle factors on mortality: prospective cohort study in US women

Rob M van Dam,[1,2] Tricia Li,[1] Donna Spiegelman,[3,4] Oscar H Franco,[5] Frank B Hu[1,2,3]

[1]Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115, USA
[2]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston MA 02115
[3]Department of Epidemiology, Harvard School of Public Health
[4]Department of Biostatistics, Harvard School of Public Health
[5]Unilever Corporate Research, Sharnbrook, Bedfordshire MK44 1LQ

Correspondence to: R van Dam
rvandam@hsph.harvard.edu

Cite this as: *BMJ* 2008;337:a1440
doi:10.1136/bmj.a1440

ABSTRACT

Objective To evaluate the impact of combinations of lifestyle factors on mortality in middle aged women.

Design Prospective cohort study.

Setting Nurses' health study, United States.

Participants 77 782 women aged 34 to 59 years and free from cardiovascular disease and cancer in 1980.

Main outcome measure Relative risk of mortality during 24 years of follow-up in relation to five lifestyle factors (cigarette smoking, being overweight, taking little moderate to vigorous physical activity, no light to moderate alcohol intake, and low diet quality score).

Results 8882 deaths were documented, including 1790 from cardiovascular disease and 4527 from cancer. Each lifestyle factor independently and significantly predicted mortality. Relative risks for five compared with zero lifestyle risk factors were 3.26 (95% confidence interval 2.45 to 4.34) for cancer mortality, 8.17 (4.96 to 13.47) for cardiovascular mortality, and 4.31 (3.51 to 5.31) for all cause mortality. A total of 28% (25% to 31%) of deaths during follow-up could be attributed to smoking and 55% (47% to 62%) to the combination of smoking, being overweight, lack of physical activity, and a low diet quality. Additionally considering alcohol intake did not substantially change this estimate.

Conclusions These results indicate that adherence to lifestyle guidelines is associated with markedly lower mortality in middle aged women. Both efforts to eradicate cigarette smoking and those to stimulate regular physical activity and a healthy diet should be intensified.

INTRODUCTION

Diet, physical activity, adiposity, alcohol consumption, and cigarette smoking have been associated with risk of chronic diseases. However, to identify priorities for clinical and public health efforts, understanding the magnitude of effects of risk factors, individually and in combination, on overall health is fundamental. The proportion of deaths that is attributable to lifestyle factors has been estimated by using data on relative risks and the prevalence of risk factors from multiple sources and in a small cohort study of elderly, mostly male participants.[1-3] We examined combinations of lifestyle factors in relation to cancer, cardiovascular, and all cause mortality during 24 years of follow-up among middle aged women who participated in the nurses' health study.

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008;337:a1440

METHODS

Study population

The nurses' health study is a prospective cohort study that was established in 1976 when 121 700 female registered US nurses, aged 30 to 55 years, completed a mailed questionnaire on known and suspected risk factors for chronic diseases. Since then, participants have been sent biennial follow-up questionnaires to update information on lifestyle and health conditions. For the current analysis, we began follow-up in 1980, the first year when diet was assessed; 98 462 women, aged 34 to 59 years, completed the questionnaire. After exclusions (see bmj.com), 77 782 women remained for the current analysis.

Assessment of risk factors

Diet was assessed with a 61 item food frequency questionnaire in 1980 and an expanded questionnaire including approximately 120 food items, every two to four years. Nutrient intakes were calculated by summing the nutrient content of a unit of each food multiplied by a weight proportional to the frequency of its use. Validation studies indicated that the food frequency questionnaire estimated dietary intakes with reasonably good accuracy.

Information on disease history and cigarette smoking was assessed on each biennial questionnaire. Frequency of physical activity during the previous year was assessed in 1980, and this information was updated every two to four years. Height was assessed in 1976 and weight in 1980, and the body mass index was calculated (kg/m^2). Father's occupation when the participant was 16 years of age was assessed in 1976. In 1992, we also asked about the degrees the participant had received and, for women who were married or widowed, the highest level of education that their husband completed.

Classification of low risk categories

For adiposity, we defined low risk as a body mass index between 18.5 and 25.0. For physical activity, we defined low risk as an average of at least 30 minutes a day of activity of at least moderate intensity (requiring ≥3 metabolic equivalents an hour, including brisk walking). For cigarette smoking, we defined low risk as never smoking. For alcohol consumption, we defined low risk as light to moderate consumption (≥1 and

<15 g/day—that is, up to approximately one drink a day).

To quantify the healthiness of the diet, we used the previously designed alternative healthy eating score, assigning a score between 0 (least healthy) and 10 (recommended intake) for each of the seven included items and considering participants with a healthy diet score in the upper two fifths (highest 40%) to be in the low risk category for diet.

Ascertainment of mortality

Deaths were reported by next of kin, the postal authorities, or both or were ascertained through searching for non-responders in the National Death Index. Follow-up for deaths in the National Death Index has been estimated to be 98% complete for this cohort.[4] From medical records and death certificates, we distinguished deaths due to cancer and cardiovascular diseases.

Statistical analysis

Women contributed follow-up time from the date of return of the baseline questionnaire to the date of death or 1 June 2004, whichever came first. We used pooled logistic regression analysis stratified by two year calendar time periods to estimate multivariate relative risks. We calculated population attributable risks, which are estimates of the percentage of deaths during follow-up that would not have occurred if all women had been in the low risk category for lifestyle factors, assuming that the observed associations represent causal effects (see bmj.com).

RESULTS

During 1 759 408 person years of follow-up we documented 8882 deaths, including 1790 from cardiovascular disease and 4527 from cancer. The multivariate adjusted relative risks for lifestyle factors and death during follow-up showed that cigarette smoking, higher body mass index, less physical activity, and a lower healthy diet score were all associated with increased cardiovascular, cancer, and all cause mortality. Alcohol consumption was associated with a lower risk of cardiovascular mortality than alcohol abstinence. However, heavy alcohol consumption was associated with an increased risk of cancer mortality. Light to moderate alcohol consumption was associated with the lowest all cause mortality.

Comparing the high risk with the low risk category of lifestyle factors, the estimated population attributable risks were 28% for cigarette smoking, 14% for being overweight, 17% for lack of physical activity, 13% for low diet quality, and 7% for not having light to moderate alcohol consumption. Population attributable risks were higher for cardiovascular

Risk of mortality during 24 years of follow-up according to combinations of lifestyle risk factors*

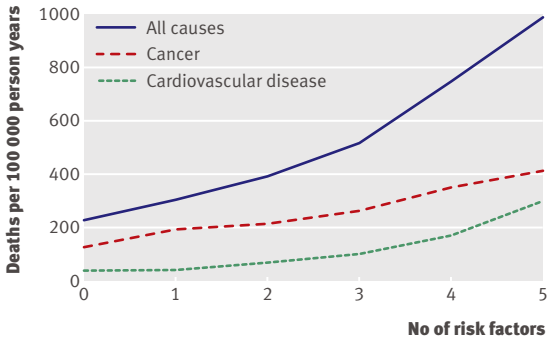
	Death from any cause	Cardiovascular death	Cancer death
Four risk factors: smoking, overweight, low diet quality, low physical activity†			
Relative risk (95% CI):			
No risk factors (3.4%)‡	1.00	1.00	1.00
One risk factor (16%)	1.30 (1.10 to 1.53)	1.43 (0.91 to 2.24)	1.32 (1.06 to 1.63)
Two risk factors (33%)	1.75 (1.49 to 2.05)	2.42 (1.58 to 3.71)	1.61 (1.231 to 1.98)
Three risk factors (34%)	2.52 (2.15 to 2.95)	3.98 (2.60 to 6.08)	2.12 (1.73 to 2.60)
Four risk factors (13%)	3.41 (2.90 to 4.00)	6.91 (4.50 to 10.63)	2.65 (2.14 to 3.28)
Population attributable risk (%) for having any of the four risk factors (95% CI)	54.8 (46.7 to 61.9)	72.0 (58.6 to 81.6)	44.3 (31.2 to 55.8)
Five risk factors: above four and alcohol abstinence or heavy drinking§			
Relative risk (95% CI):			
No risk factors (2.4%)‡	1.00	1.00	1.00
One risk factor (12%)	1.34 (1.09 to 1.64)	1.13 (0.67 to 1.89)	1.55 (1.18 to 2.02)
Two risk factors (27%)	1.70 (1.40 to 2.07)	1.88 (1.15 to 3.05)	1.71 (1.32 to 2.22)
Three risk factors (34%)	2.25 (1.85 to 2.72)	2.80 (1.73 to 4.54)	2.07 (1.60 to 2.68)
Four risk factors (21%)	3.27 (2.70 to 3.97)	4.77 (2.94 to 7.72)	2.79 (2.15 to 3.62)
Five risk factors (4.2%)	4.31 (3.51 to 5.31)	8.17 (4.96 to 13.47)	3.26 (2.45 to 4.34)
Population attributable risk (%) for having any of the five risk factors (95% CI)	58.1 (49.3 to 65.7)	75.2 (60.9 to 84.7)	46.0 (31.7 to 58.3)

*Relative risks and population attributable risks adjusted for age (5 year age categories) and time period (four periods); additionally adjusted for alcohol consumption (0, 1-4, 5-14, 15-29, ≥30 g/d) for "four risk factor" model.
†Overweight: body mass index ≥25; low diet quality: healthy diet score in lower three fifths; low physical activity: <30 min/day.
‡Prevalence in 1990.
§0 or ≥15 g/day alcohol.

mortality than for cancer mortality. Among never smokers, the relative risk of mortality for being overweight was higher than that for the whole study population (1.55, 95% confidence interval 1.44 to 1.66), resulting in a higher population attributable risk (22%, 18% to 27%).

We also evaluated combinations of lifestyle risk factors in relation to mortality. As shown in the figure, cardiovascular, cancer, and all cause mortality increased with an increasing number of risk factors. The table shows the relative risk and population attributable risk for combining risk factors.

Results among never smokers were consistent with those for the whole study population The population attributable risk for all cause mortality for the five risk factors combined was 51% (30% to 67%) for younger women (<60 years) and 63% (52% to 72%) for older women (≥60 years). We examined potential confounding by measures of socioeconomic status. Adjustment for these variables did not materially alter the association between any of the lifestyle factors and mortality during follow-up.



Age standardised all cause, cancer, and cardiovascular mortality during 24 years of follow-up by number of lifestyle risk factors. Lifestyle risk factors included cigarette smoking (ever), lack of physical activity (<30 min/day moderate to vigorous intensity activity), low diet quality (lowest three fifths of healthy diet score), alcohol intake of 0 or ≥15 g/day, and overweight (body mass index ≥25)

DISCUSSION

In this study of 77 782 middle aged US women, never smoking, engaging in regular physical activity, eating a healthy diet, and avoiding becoming overweight were each associated with a markedly lower mortality during 24 years of follow-up. We estimated that 55% of all cause mortality, 44% of cancer mortality, and 72% of cardiovascular mortality during follow-up could have been avoided by adherence to these four lifestyle guidelines. Light to moderate alcohol consumption (up to one drink a day) was also associated with a lower risk of all cause mortality during follow-up.

Results in relation to other studies

Smoking, overweight, physical activity, and quality of diet have consistently been associated with risk of chronic diseases and mortality in prospective cohort studies.[3 5-10] Randomised controlled trials support the protective effect of a prudent Mediterranean-style diet and substitution of polyunsaturated for saturated fat for coronary heart disease[11 12]; of the combination of physical activity, a healthy diet, and moderate weight loss for type 2 diabetes[13]; and of smoking cessation for premature mortality.[14] In addition, randomised controlled trials have shown beneficial effects of moderate alcohol consumption, reduced *trans*-fat intake, high fruit and vegetable intake, and whole grain intake on biological markers of cardiovascular risk.[15-18]

Few previous studies have examined combinations of lifestyle factors in relation to mortality.[1-3 10 19] Our results are consistent with these previous cohort studies and suggest that the population attributable risk estimates from studies using an indirect approach may be conservative for the demographic group that we studied.

Heavy alcohol consumption was associated with higher cancer mortality in our study and light to moderate alcohol consumption was associated with lower cardiovascular mortality. For individual people, the balance of risks and benefits of moderate alcohol consumption may depend on other characteristics; possible benefits may exist for older women with cardiovascular risk factors,[20] and a greater likelihood of adverse effects may exist for women with a personal or family history of alcoholism, alcohol related cancers, or risk factors for these conditions.[21 22]

Strengths and limitations

Strengths of our study include the large sample size, the prospective design with 24 years of follow-up and high response rates, and the repeated collection of detailed information on lifestyle. Some measurement error is inevitable and is likely to have weakened the associations seen. We would probably have seen a lower mortality if we had used more restrictive criteria for the low risk group. However, our results indicate that even modest differences in lifestyle can have a substantial impact on reducing mortality. Because incomplete adjustment for smoking habits can weaken the association between overweight and mortality,[7] our estimates for the association between overweight and mortality in never smokers may be more accurate than those for

WHAT IS ALREADY KNOWN ON THIS TOPIC

Many studies have shown that individual lifestyle factors are associated with risk of chronic diseases

Few studies have evaluated the effects of combinations of lifestyle factors on mortality

WHAT THIS STUDY ADDS

Most deaths during 24 years of follow-up in middle aged women could have been avoided by a combination of not smoking, maintaining a healthy weight, regular physical activity, and a healthy diet

These findings underscore the importance of intensifying both efforts to eradicate cigarette smoking and those aimed at improving diet and physical activity

the total study population. Variation in socioeconomic status in our study of registered nurses was more limited than in the general population. Consistent with results from a British study,[19] adjustment for various measures of socioeconomic status did not appreciably affect associations between lifestyle factors and mortality during follow-up. In analyses with mortality as an end point, confounding by poor health that precedes death and affects lifestyle habits is of particular concern, so we excluded women with conditions that may reflect this poor health status at baseline. Also, our findings were consistent with results in analyses of lifestyle factors and risk of incidence of chronic diseases that are less likely to be affected by this type of confounding.

Because population attributable risks depend on both relative risks and the prevalence of risk factors (the higher the prevalence, the higher the population attributable risk) the prevalence of risk factors has to be considered when generalising our findings to other populations. We believe that our overall conclusions are generally applicable to middle aged women in high income countries. However, our participants were predominantly white and confirmation in other ethnic groups is warranted.

We thank the participants of the nurses' health study for their continued participation, Ellen Hertzmark for expert programming help, and Walter Willett and Meir Stampfer for their valuable comments on the manuscript. The article adheres to the STROBE guidelines (www.strobe-statement.org/).

Contributors: See bmj.com.

Funding: This research was supported by National Institutes of Health (NIH) grants CA87969 and HL60712. RMvD was partly supported by an unrestricted research grant from the Peanut Foundation. The funding sources had no role in the collection, management, analysis, or interpretation of the data and had no role in the preparation, review, or approval of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Competing interests: None declared.

Ethical approval: The institutional review board at Brigham and Women's Hospital approved this study.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA* 2004;291:1238-45. [Correction in *JAMA* 2005;293:293-4.]

2 Ezzati M, Vander Hoorn S, Lopez AD, Danaei G, Rodgers A, Mathers CD, et al. Comparative quantification of mortality and burden of disease attributable to selected risk factors. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, eds. *Global burden of disease and risk factors*. New York: Oxford University Press, 2006:241-68.

3 Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA* 2004;292:1433-9.

4 Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax nationwide death search. *Am J Epidemiol* 1994;140:1016-9.

5 Key TJ, Schatzkin A, Willett WC, Allen NE, Spencer EA, Travis RC. Diet, nutrition and the prevention of cancer. *Public Health Nutr* 2004;7:187-200.

6 Vineis P, Alavanja M, Buffler P, Fontham E, Franceschi S, Gao YT, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst* 2004;96:99-106.

7 Manson JE, Stampfer MJ, Hennekens CH, Willett WC. Body weight and longevity: a reassessment. *JAMA* 1987;257:353-8.

8 Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;273:402-7.

9 McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. *Am J Clin Nutr* 2002;76:1261-71.

10 Khaw KT, Wareham N, Bingham S, Welch A, Luben R, Day N. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. *PLoS Med* 2008;5:e12.

11 De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454-9.

12 Sacks FM, Katan M. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. *Am J Med* 2002;113(suppl 9B):13-24S.

13 Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.

14 Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;142:233-9.

15 Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;319:1523-8.

16 Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003;77:1146-55.

17 Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;336:1117-24.

18 Pereira MA, Jacobs DR Jr, Pins JJ, Raatz SK, Gross MD, Slavin JL, et al. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am J Clin Nutr* 2002;75:848-55.

19 Wannamethee SG, Shaper AG, Walker M, Ebrahim S. Lifestyle and 15-year survival free of heart attack, stroke, and diabetes in middle-aged British men. *Arch Intern Med* 1998;158:2433-40.

20 Fuchs CS, Stampfer MJ, Colditz GA, Giovannucci EL, Manson JE, Kawachi I, et al. Alcohol consumption and mortality among women. *N Engl J Med* 1995;332:1245-50.

21 Rehm J, Gmel G, Sempos CT, Trevisan M. Alcohol-related morbidity and mortality. *Alcohol Res Health* 2003;27:39-51.

22 Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998;279:535-40.

Accepted: 22 July 2008