Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease

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Abstract

Objective: To assess the effectiveness of multiple risk factor intervention in reducing cardiovascular risk factors, total mortality, and mortality from coronary heart disease among adults.

Design: Systematic review and meta-analysis of randomised controlled trials in workforces and in primary care in which subjects were randomly allocated to more than one of six interventions (stopping smoking, exercise, dietary advice, weight control, antihypertensive drugs, and cholesterol lowering drugs) and followed up for at least six months.

Subjects: Adults aged 17-73 years. 903 000 person years of observation were included in nine trials with clinical event outcomes and 303 000 person years in five trials with risk factor outcomes alone.

Main outcome measures: Changes in systolic and diastolic blood pressure, smoking rates, blood cholesterol concentrations, total mortality, and mortality from coronary heart disease.

Results: Net decreases in systolic and diastolic blood pressure, smoking prevalence, and blood cholesterol were 4.2 mm Hg (SE 0.19 mm Hg), 2.7 mm Hg (0.09 mm Hg), 4.2% (0.3%), and 0.14 mmol/l (0.01 mmol/l) respectively. In the nine trials with clinical event end points the pooled odds ratios for total and coronary heart disease mortality were 0.97 (95% confidence interval 0.92 to 1.02) and 0.96 (0.88 to 1.04) respectively. Statistical heterogeneity between the studies with respect to changes in mortality and risk factors was due to trials focusing on hypertensive participants and those using considerable amounts of drug treatment, with only these trials showing significant reductions in mortality.

Conclusions: The pooled effects of multiple risk factor intervention on mortality were insignificant and a small, but potentially important, benefit of treatment (about a 10% reduction in mortality) may have been missed. Changes in risk factors were modest, were related to the amount of pharmacological treatment used, and in some cases may have been overestimated because of regression to the mean, lack of intention to treat analyses, habituation to blood pressure measurement, and use of self reports of smoking. Interventions using personal or family counselling and education with or without pharmacological treatments seem to be more effective at reducing risk factors and therefore mortality in high risk hypertensive populations. The evidence suggests that such interventions implemented through standard health education methods have limited use in the general population. Health protection through fiscal and legislative measures may be more effective.

Introduction

Primary prevention programmes in many countries attempt to reduce mortality and morbidity due to coronary heart disease through modifying risk factors.[1 2] Randomised controlled trials of the efficacy of multiple risk factor intervention using counselling and education in addition to, or instead of, pharmacological treatments to modify major cardiovascular risk factors have been carried out in primary care and in the workplace. The findings of these trials have been equivocal; efficacy in reducing the incidence of disease seems to be associated with the degree of control achieved.[3 4] Given the evidence from quasi-experimental studies, such as the North Karelia project[5 6] and the Stanford heart disease prevention programme,[7-9] multiple risk factor intervention using counselling and educational methods is widely believed to be efficacious and cost effective and worthy of expansion.

Such beliefs have been associated with the development of health promotion as a supposed specialty,[10] the routine collection of data on cardiovascular risk factors in British primary care, and primary prevention policy—for example, the health of the nation strategy in England.[11] More recent trials examining changes in risk factors have cast considerable doubt on the effectiveness of these multiple risk factor interventions[12 13] and even interventions against smoking,[14 15] prompting a review of the reasons for the frequent failure of such community experiments.[16]

Two previous reviews of multiple risk factor intervention using counselling and education with or without pharmacological treatments were conducted before the publication of more recent trials, were not systematic in their coverage, and did not formally aggregate the findings through meta-analysis.[17 18] Consequently, we carried out a formal systematic review

and meta-analysis examining the published randomised controlled trials and obtaining supplementary information when possible.

Methods

Search methods

Randomised controlled trials of coronary heart disease prevention by specific interventions and multiple risk factor intervention were identified by a systematic Medline search strategy from 1966 to April 1995. The strategy used a series of terms to identify randomised controlled trials and then used topic terms to define the diseases of interest: coronary heart disease and stroke. Text word searches using the terms "prevention" and "multiple risk factor" were applied, and specific interventions of interest were searched for, comprising smoking cessation, dietary change, exercise, weight loss, blood pressure control, and cholesterol lowering. (A full search strategy is available from us.) This was supplemented by examining the reference lists of each of the randomised controlled trials identified, consulting with experts in the subject, and checking citations. The chief investigator of each trial was written to requesting relevant data not included in the published reports. A database of references was compiled using reference manager software.[19]

Randomised controlled trials of primary prevention of coronary heart disease by means of multiple (more than one) risk factor interventions using counselling and education with or without pharmacological treatments in general populations, occupational groups, and in high risk groups were included in the systematic review. Studies of children or only adults under 40 were excluded. Trials of secondary prevention were excluded. As primary prevention requires sustained changes in behaviour studies with follow up of less than 26 weeks were also excluded.

Statistical methods

Odds ratios were used to summarise clinical event treatment effects and logistic regression by EGRET[20] was used to provide pooled estimates for groups of trials. Risk factor effects were assessed as net changes—that is, the difference in the intervention group minus that in the control group—as this makes allowance for secular trends, measurement habituation effects, and regression to the mean. Net changes for continuous variables were pooled by using the standard deviations and sample sizes of intervention and control groups as weights, as described by Fleiss.[21] Changes in smoking were expressed as net changes in prevalence of smoking, and pooled estimates were calculated by weighting using the inverse of the variance for each study, with the pooled standard error calculated as the square root of the inverse of the sum of the weights.[21] Fixed and random effects analyses were carried out. Random effect analysis tends to provide more conservative estimates of the precision of estimates of effect size.[21]

Sensitivity analyses were performed by inclusion and exclusion of trials as some characteristics of the interventions or of the participants varied between trials. The effect of intervention was related to initial risk of coronary heart disease using the event rates in the control group and also the combined control and intervention group.

Relations between baseline risk factors and the size of changes in risk factors in each of the trials were examined by using the statistical package for social sciences weighted least squares method with the trial sample sizes as weights.[22]

In trials where randomisation was by paired clusters—for example, those based in factories or general practices—rather than in individual people it is appropriate to take the variation between clusters into account in estimating the effects of intervention (S G Thompson, personal communication). However, the data available in published reports or from authors were insufficient to carry out such analyses and our estimates of treatment effects of these trials will tend to be overprecise, with their contribution to the pooled effect estimates being exaggerated.

Previously unpublished data on mortality, changes in risk factors, and use of pharmacological treatments were also obtained for some of the trials (see acknowledgements) and are available from us.

Results

We found 14 trials of multiple risk factor intervention, of which nine reported both disease events and changes in risk factors as outcomes.[23-38] We excluded several trials of multiple risk factor interventions from consideration for the following reasons: changes in risk factors were not measured or reported,[39-44] allocation to intervention and control groups was not random,[45-50] randomisation was inadequate,[51 52] there was no specific multiple risk factor intervention,[53] the control group received some form of intervention,[54-56] and follow up for six months was not reported.[57-59] Some studies were set up under the auspices of the former Soviet Union,[49-63] but allocation to intervention and control groups seemed not to be random, although we have not been able to trace the investigators.

Details of the 14 trials are summarised, with those reporting both changes in risk factors and disease event outcomes in table 1 and those reporting only changes in risk factors in table 2. In general, the trials compared an intervention comprising some form of counselling and information provision with control groups that either received nothing or usual care. The type of behavioural intervention used was seldom reported, but when it was, a "negotiated behaviour change" model was most often described.

The nine trials with clinical event outcomes comprise about 903 000 patient years of observation and the five trials with risk factor end points alone 303 000. The oldest subjects included in any of the trials were under 74, with most trials studying only middle aged people.

Changes in risk factors

The changes in blood pressures, smoking, and blood cholesterol concentrations observed in the trials are summarised in tables 3-5. Not all trials reported or were able to provide data on each of these three risk factors. The Spanish arm of the World Health Organisation's factories study reported its risk factor changes separately and is considered as a separate trial. The Oslo Study Investigators[26] could not provide data on changes in blood pressure but stated that there were no changes observed (personal communication).

Table 1 Multiple risk factor intervention trials with both risk factor changes and disease event outcomes that were included in overview

Study	Sample	Sample size; mean age (range) (years)*	Intervention and follow up	Findings
WHO factory study[23 24]	Workforces in Belgium, Italy, Poland, Spain, United Kingdom; randomisation by factory; men only	63 732; 48.5 (40-59)	Diet, smoking, weight, exercise, antihypertensive drugs, mass media; 6 years	Small reductions in risk factors. Spanish trial arm not included in event ascertainment. Belgian arm showed significant reduction in mortality. Concluded that advice on risk factor reduction is effective to the extent that it is accepted and seems to be safe
Gothenburg study[25]	Population screening with targeting of those at high risk; men only	30 022; 51 (47-55)	Diet, smoking, antihypertensive drugs, cholesterol lowering drugs; 11.8 years	Large falls in risk factors in both intervention (25% were non-participants) and control groups. Concluded that strategies other than intervention in men at high risk must be used to have a major impact on incidence of disease in general population
Oslo study[26]	High risk but systolic pressure <150 mm Hg; men only	1232; 45.2 (40-49)	Diet, smoking; 5 years	Reduction in smoking rates and blood cholesterol concentrations. Significant reduction in cardiovascular disease events. Concluded that advice to stop smoking and change eating habits reduces first myocardial infarctions and sudden deaths
Multiple risk factor intervention trial[27]	Workplace, population, and volunteer screening; high risk; men only	12 866; 46 (35-47)	Diet, smoking, weight, antihypertensive drugs; 6 years	Small reductions in blood cholesterol concentration, large reductions in blood pressure and smoking rates. No significant reduction in disease events. Concluded that possibly effective in subgroups but no net benefit because of potentially harmful effects of antihypertensive drugs used. Small benefits emerging after prolonged follow up
Finnish businessmen study [28 29]	Volunteers; high risk; men only	1222; 48 (40-55)	Diet, smoking, exercise, antihypertensive drugs, cholesterol lowering drugs; 5 years	Large reductions in blood pressure and blood cholesterol concentrations achieved largely through drug treatments and reductions in smoking rates. Control group risk factors increased. Coronary heart disease event rates were slightly higher (P=0.06) but stroke rates declined significantly in intervention group. Concluded that adverse effects of drug treatment may explain lack of benefit
Hypertension detection and follow up programme[30]	Population screening; all had high blood pressure; men and women	10 940; (30-69)	Antihypertensive drugs, diet, smoking, weight, exercise; 5 years	No reductions in smoking rates or in blood cholesterol concentration (probably related to limited emphasis of intervention), but significant reduction in blood pressure. Total mortality and mortality from coronary heart disease and stroke significantly lower in intervention group. Benefits attributed to treatment of high blood pressure. Effects sustained after prolonged follow up
Johns Hopkins patient education hypertension study[31]	Clinic attenders; all had high blood pressure; men and women	400; 54.1	Weight, antihypertensive drugs, general health advice, factorial design; 5 years	Better blood pressures, weight control, appointment keeping, and treatment adherence in intervention groups. Total mortality and mortality related to hypertension lower in intervention groups. Concluded that educational programmes for hypertensive patients were valuable
Cost effectiveness of lipid lowering study[32]	Primary care screening; those with at least two risk factors for cardiovascular disease in addition to moderately high cholesterol concentration; randomisation in a 2×3 factorial design (counselling or usual care with pravastatin, placebo, no drug); men and women	681; 49 (30-59)	Nurse or doctor counselling, videos and group discussions, personal risk factor management, food purchasing, exercise; 1 year	At one year intervention group had lower blood cholesterol concentrations and lower overall Framingham risk factor scores compared with control group. No significant differences in blood pressures, smoking rates, or exercise scores
Oxcheck study[33]	Primary care practices in urban area; randomisation by household; no risk screening; men and women	11 090; 49 (35-64)	Diet, smoking, weight, alcohol, exercise, protocols for management of high blood pressure and raised blood cholesterol concentration; 3 years	Changes in diet and small changes in blood cholesterol concentration, blood pressure, and body mass index but no effect on smoking rates. Concluded that primary prevention programmes were able to achieve benefits which were real but must be weighed against the costs in relation to other priorities

*When available.

Overall, the fixed effects analyses showed highly significant falls in systolic (net difference 4.2 mm Hg (SE 0.19 mm Hg)) and diastolic (net difference 2.7 mm Hg (0.09 mm Hg)) blood pressures. The multiple risk factor intervention trial,[27] the hypertension detection and follow up programme,[30] the Finnish businessmen study,[29] and the family heart study[37] stand out as showing particularly substantial falls in blood pressure, and all but the family heart study used antihypertensive drug treatment. The family heart study reported only one year follow up data and its design did not allow for measurement habituation effects.[37] Exclusion of those trials in which a high proportion of participants were receiving pharmacological treatment (Gothenburg study,[25] multiple risk factor intervention trial,[27] Finnish businessmen study,[28 29] hypertension detection and follow up programme,[30] cost effectiveness of lipid lowering study[32]) resulted in much smaller net reductions in blood pressure: systolic pressure 2.3 mm Hg (0.3 mm Hg), diastolic 1.1 mm Hg (0.1 mm Hg).

Smoking rates, expressed as the changes in prevalence of smoking, showed an overall net reduction of 4.2% (0.3%). The rates fell particularly sharply in the multiple risk factor intervention trial[27] and in the Oslo study,[26] which both used individual smoking advice given by a doctor. Reported reductions in smoking rate in the multiple risk factor intervention trial[27] were overestimated when compared with serum thiocyanate concentrations.[64] The hypertension detec-

Table 2 Multiple risk factor intervention trials reporting changes in risk factors as outcomes that were included in overview

Study	Sample	Sample size; mean age (range) (years)*	Intervention and follow up	Findings
Primary prevention of hypertension trial[34]	Volunteers from occupational groups; randomisation of those with raised body weight <150% ideal, high pulse rate, and diastolic pressure 80-89 mm Hg; men and women	201; 37.5 (30-44)	Diet, weight, exercise, alcohol; 5 years	Small but significant reduction in blood pressure; other risk factors not reported. Volunteers who were thought unlikely to comply with intervention—for example, heavy drinkers, those weighing ⩾150% of ideal weight—were excluded from trial
Abingdon trial[35]	Primary care, patients selected at random; men and women	368; 42 (25-60)	Conducted by nurse; diet, weight, smoking, exercise, alcohol; 1 year	Main focus was on dietary change, but despite self reported behaviour change, no changes in blood cholesterol concentration found. Blood pressure and smoking rates not reported
Tromsø family trial[36]	Primary care screening; randomisation of those at high risk because of hypertension, diabetes, angina, previous myocardial infarction; men randomised and wives also included	1373 men, 809 wives; 30-54	Physician and dietitian counselling of family; diet, smoking, exercise; 6 years	Participants showed limited interest in group meetings. Small significant reduction in blood cholesterol concentration but no effects on smoking or blood pressure
Family heart study[37]	Primary care; random allocation of families on basis of male member of household; men and women	9348; 50 (40-59)	Intensity of intervention dependent on level of person's risk; nurse counselling; diet, weight, smoking, exercise, alcohol: 1 year	Two control groups used, internal to study and an external group (comparisons made with internal controls in this review). Drop outs were more likely to have high risk factors for cardiovascular disease. An overall reduction in cardiovascular risk of 12% achieved but thought to be impracticable for widespread use as too costly. However, no formal cost effectiveness study undertaken
Take Heart study[38]	Workplace screening, cholesterol, diet history, and smoking; randomisation by work site; men and women	1977; 40 (17-73)	Stage of change model used; motivational, educational, workplace environment, and community reinforcement; focus on smoking and food choices; 18 months	Despite documented implementation of interventions, no evidence that changes in smoking, cholesterol concentration or dietary intakes were greater than improvements associated with secular trends observed in control sites. Large variation in rates of stopping smoking between sites suggested variable use and uptake of interventions

*When available.

Table 3 Changes in blood pressure in multiple risk factor intervention trials

Study	Systolic pressure at baseline	Net (SE) difference between intervention and control groups	Diastolic pressure at baseline	Net (SE) difference between intervention and control groups	Sample size		Percentage taking antihypertensive drugs at end of intervention	
					Intervention	Control	Intervention	Control
WHO factories study[23 24]	135	−0.5 (0.44)	84	−0.3 (0.28)	16949	1902	NA	NA
Spanish arm[24]	138	−2.8 (1.61)	NA	NA	807	150	NA	NA
Gothenburg study[25]	149	−2.0 (0.77)	95	−1.0 (0.40)	1464	1400	26.0	19.6
Multiple risk factor intervention trial[27]	135	−5.3 (0.27)	91	−3.1 (0.16)	5740	5633	57.4	46.4
Finnish businessmen study[28 29]	148	−6.0 (1.06)	96	−5.0 (0.60)	575	580	32.0	15.0
Hypertension detection and follow up programme[30]	NA	NA	101	−4.9 (0.19)	5485	5455	77.8	58.3
Cost effectiveness of lipid lowering study[32]	132	−1.2 (0.97)	82	−0.1 (0.59)	306	320	27.4	30.7
Oxcheck study[33]:								
Men	130	−2.5 (0.92)	78	−1.2 (0.56)	987	885	0.8†	0.8†
Women	126	−2.3 (0.87)	75	−1.7 (0.51)	1218	1031	0.8†	0.8†
Primary prevention of hypertension trial[34]								
	122	−2.0 (0.90)	82	−1.9 (0.80)	99	95	5.1	16.8
Abingdon trial[35]	131	−1.7 (1.57)	80	−1.4 (1.22)	167	168	0	0
Tromsø family trial[36]:								
Men	132	−0.6 (0.89)	86	−0.4 (0.59)	525	535	NA	NA
Wives	123	0 (1.14)	79	1.9 (0.73)	422	387	NA	NA
Family heart study[37]:								
Men	139	−7.3 (0.8)	87	−3.5 (0.4)	1767	2174	5.7	5.9
Women	129	−6.2 (0.9)	82	−3.0 (0.4)	1217	1402	5.3	5.4
Pooled net differences*								
Fixed effects analyses								
All studies		NA		−2.7 mm Hg (95% CI −2.5 to −2.9), χ^2=418.3,df=13, P<0.0001‡				
Without hypertension detection and follow up programme		−4.2 mm Hg (−3.8 to −4.6), χ^2=178.1, df=13, P<0.0001‡		−2.1 mm Hg (−1.9 to −2.3), χ^2=249.6, df=12, P<0.001‡				
Random effects analyses								
All studies		NA		−2.2 mm Hg (0.7 to −5.1)				
Without hypertension detection and follow up programme		−4.6 mm Hg (0.7 to −9.9)		−2.4 mm Hg (0.9 to −5.7)				

NA=not available. *Estimated SE difference and pooled differences based on SD of systolic pressure of 20 mm Hg and of diastolic pressure of 10 mm Hg
†Values not given, but <0.8% of total population took antihypertensive drugs.
‡In test for heterogeneity.

Table 4 Changes in rates of smoking in multiple risk factor intervention trials

Study	Smoking prevalence (%) at baseline in intervention group	Net (SE) difference between intervention and control groups	Sample size	
			Intervention	Control
WHO factory study[23 24]	56.2	0.03 (1.2)	16908	1902
Spanish arm[24]	60.1	–1.7 (4.4)	807	150
Gothenburg study[25]	49.7	–2.8 (1.7)	1473	1404
Oslo study[26]	79.1	–7.0 (2.8)	604	628
Multiple risk factor intervention trial[27]	63.8	–13.5 (0.9)	5800	5690
Finnish businessmen study[28 29]	24.8	–1.5 (2.4)	575	580
Cost effectiveness of lipid lowering study[32]	50.0	–2.1 (4.1)	292	310
Oxcheck study[33]:				
Men	35.0	–0.5 (2.1)	987	885
Women	24.0	–1.9 (1.8)	1218	1031
Abingdon trial[35]	30.0	4.6 (5.1)	167	168
Tromsø family trial[36]:				
Men	54.0	0 (3.1)	525	535
Wives	43.0	2.0 (3.5)	422	387
Family heart study[37]:				
Men	24.3	–4.1 (1.3)	1767	2174
Women	22.2	–2.9 (1.5)	1217	1402
Take Heart study[38]	19.0	0 (1.6)	1057	920
Pooled net differences				
Fixed effects analysis:				
All studies (SE)	–4.2% (95% CI–3.6% to –4.8%), χ^2=558.5, df=14,P<0.0001*			
Random effects analysis:				
All studies (SE)	–2.8% (0.5% to –6.1%)			

*In test for heterogeneity.

tion and follow up programme did not detect any changes in smoking rates,[30] but published data are not available.

Blood cholesterol concentrations showed a small but highly significant fall (net fall 0.14 mmol/l (0.01mmol/l)). The hypertension detection and follow up program did not show any reduction in blood cholesterol concentrations,[30] but published data are not available. Exclusion of the Finnish businessmen study[28 29] on the grounds of use of cholesterol lowering drugs did not make a difference to the pooled fall observed (net difference –0.12 mmol/l (0.01 mmol/l)).

Blood pressure, smoking, and blood cholesterol outcomes were subject to substantial heterogeneity (see tables 3-5). Random effects analyses were also conducted which showed similar pooled net effects, but as the variation between trials was taken into account (which was large), much larger standard errors were estimated.

Net changes in risk factors were strongly correlated with the initial diastolic blood pressure, smoking, and blood cholesterol concentration but not with systolic blood pressure. The sample size weighted correlation coefficients between initial value of and size of reduction in risk factor for diastolic blood pressure, smoking, and blood cholesterol concentration were 0.73 (P=0.006), 0.63 (P=0.01), and 0.74 (P=0.004) respectively. The studies with the highest baseline diastolic blood pressure, smoking prevalence, and blood cholesterol concentrations showed larger falls in these risk factors in association with the interventions.

Changes in mortality and rates of non-fatal myocardial infarction

Details of the nine trials reporting outcome in terms of total mortality and mortality from coronary heart disease are shown in table 6. The Oxcheck study was not designed to examine effects on mortality, but an intention to treat analysis was conducted in which the people randomised to health checks in years 1 to 3 were considered to be the intervention group and those randomised to health checks in year 4 were the

Table 5 Changes in blood cholesterol concentration (mmol/l) in multiple risk factor intervention trials

Study	Blood cholesterol in intervention group at baseline	Net (SE) difference between intervention and control groups	Sample size		Percentage taking cholesterol lowering drugs at end of intervention	
			Intervention	Control	Intervention	Control
WHO factory study[23 24]	5.5	0.004 (0.02)	16481	1854	NA	NA
Spanish arm[24]	5.8	–0.21 (0.09)	807	150	NA	NA
Gothenburg study[25]	6.5	–0.01 (0.04)	1465	1399	1.0	0.8
Oslo study[26]	8.5	–0.51 (0.04)	604	628	0	0
Multiple risk factor intervention trial[27]	6.6	–0.13 (0.02)	5743	5607	0.6	1.3
Finnish businessman study[28 29]	7.1	–0.45 (0.06)	575	580	37.0	0
Cost effectiveness of lipid lowering study[32]	6.8	–0.15 (0.06)	306	320	33.3*	33.3*
Oxcheck study[33]:						
Men	6.1	–0.10 (0.05)	987	885	<0.5%†	<0.5%†
Women	6.2	–0.28 (0.05)	1218	1031	<0.5%†	<0.5%†
Abingdon trial[35]	4.9	–0.02 (0.10)	167	166	0	0
Tromsø family trial[36]:						
Men	7.5	–0.16 (0.07)	525	535	NA	NA
Wives	6.0	–0.08 (0.09)	422	387	NA	NA
Family heart study[37]:						
Men	5.7	–0.13 (0.03)	1767	2174	0.9	0.4
Women	5.5	–0.09 (0.07)	1217	1402	0.7	0
Take Heart study[38]	5.0	–0.01 (0.01)	1057	920	3.0	3.0
Pooled net differences						
Fixed effects analysis	–0.14 mmol/l (95% CI –0.12 to –0.16), χ^2= 213.8, df=18,P<0.0001‡					
Random effects analysis	–0.19 mmol/l (0.08 to –0.46)					

NA=not available.
*Fixed by factorial design.
†Concentrations not given, but <0.5% of total population took cholesterol lowering drugs.
‡In test for heterogeneity.

Table 6 Effects of multiple risk factor intervention on total mortality and mortality from coronary heart disease. Numbers of participants, total deaths, and deaths from coronary heart disease are for intervention/control groups

Study	No of participants	Total No of deaths	No of deaths from coronary heart disease	Mean age (years)	Duration of follow up (years)	Mortality (odds ratio (95% CI)	
						Total	Coronary heart disease
WHO factory study[23 24]	30 489/26 971*	1325/1186	428/398	48.5	6	0.99 (0.91 to 1.07)	0.95 (0.83 to 1.09)
Gothenburg study[25]	10 004/20 018	1293/2636	462/923	51	11.8	0.98 (0.91 to 1.05)	1.00 (0.89 to 1.12)
Oslo study[26]	604/629	16/24	5/10	45.2	5	0.69 (0.36 to 1.32)	0.44 (0.17 to 1.15)
Multiple risk factor intervention trial[27]	6428/6438	265/260	115/124	46.2	7	1.02 (0.86 to 1.22)	0.93 (0.72 to 1 .20)
Finnish businessmen study[28 29]	612/610	10/5	4/1	48.0	5	2.36 (0.90 to 6.17)	4.01 (0.45 to 35.95)
Hypertension detection and follow up programme[30]	5485/5455	349/419	131/148	50.8	5	0.82 (0.71 to 0.95)	0.88 (0.69 to 1.11)
Johns Hopkins hypertension study[31]	350/50	35/11	23/8†	54.1	5	0.39 (0.18 to 0.84)	0.37 (0.16 to 0.88)
Cost effectiveness of lipid lowering study[32]	339/320	2/1	2/1	49.0	1.5	1.89 (0.2 to 21.0)	1.89 (0.2 to 21.0)
Oxcheck study[33]	8307/2783	146/40	52/13	49.5	4	1.22 (0.86 to 1.74)	1.33 (0.73 to 2.46)
Pooled estimates							
All studies (odds ratio)						0.97 (0.92 to 1.02)	0.96 (0.89 to 1.04)
						χ^2=15.8,df=8, P<0.05‡	χ^2=10.2, df=8, P<0.05‡
Without hypertension detection and follow up programme						0.99 (0.94 to 1.04)	0.97 (0.90 to 1.06)
						χ^2=10.1,df=7	χ^2=9.6,df=7
Without hypertension detection and follow up programme and Johns Hopkins hypertension study						0.99 (0.94 to 1.04)	0.98 (0.90 to1.06)
						χ^2=5.0, df=6	χ^2=5.3, df=6

*10% Of control group not included in event ascertainment.
†Includes all deaths related to hypertension.
‡In test for heterogeneity.

control group.[33] We compared deaths up to the start of year 4 using data provided by the investigators. Only the hypertension detection and follow up programme[30] and the Johns Hopkins hypertension trial[31] reported significant effects on total mortality; the Johns Hopkins trial also reported significant effects on mortality from coronary heart disease.

Evidence of statistical heterogeneity was apparent in the pooled odds ratios for total mortality and to a lesser extent for mortality from coronary heart disease when all studies were included. Removal of the trials including hypertensive patients (hypertension detection and follow up programme[30] and Johns Hopkins hypertension trial[31]) reduced the heterogeneity for total mortality but not for mortality from coronary heart disease. Including a term for interaction between treatment effect and baseline level of coronary heart disease risk calculated using either control group coronary heart disease risk or combined control and intervention group risk reduced heterogeneity between the trials to insignificant levels for total and coronary heart disease mortality.

Modelling the effects of age using the mean age of study participants and proportion of patients taking antihypertensive and cholesterol lowering drug treatment did not show any significant interactions between age, drug treatments, and outcome. The significant interaction between intervention and degree of risk of coronary heart disease (indexed either by event rate in the control group or by combined treatment and control group rate) indicated that trials recruiting participants at higher risk were more likely to show beneficial effects. This effect is explained by the inclusion of the two trials which studied hypertensive patients rather than members of the general population or of a workforce. It is impossible to separate this effect of baseline coronary heart disease risk from the benefits of pharmacological treatment of hypertension.

Non-fatal myocardial infarctions were reported in the WHO factory study,[23] the Gothenburg study,[25] the Oslo study,[26] the multiple risk factor intervention trial,[27] and the Finnish businessmen study.[29] The pooled odds ratio for non-fatal myocardial infarction in these five trials was 1.0 (95% confidence interval 0.92 to 1.07).

The odds ratios for both fatal and non-fatal events were all close to 1. Clearly, any effect on mortality of multiple risk factor intervention in the follow up period was not large as the confidence intervals were tight; a difference as small as an 8% reduction in total deaths and an 11% reduction in deaths from coronary heart disease may be excluded by these data.

Discussion

Systematic review and meta-analysis are powerful tools to aid policy and practice decisions in multiple risk factor intervention, in which received wisdom and current practice are at odds with the emerging scientific evidence.

Findings

Multiple risk factor interventions comprising counselling, education, and drug treatments were ineffective in achieving reductions in total mortality or mortality from cardiovascular disease when used in general or workforce populations of middle aged adults. The pooled effects of intervention were insignificant, but a potentially useful benefit of treatment (about a 10% reduction in mortality from coronary heart disease) may have been missed.

The changes in risk factors associated with interventions were modest but are probably optimistic estimates as changes could be measured only in those remaining in the trials. Habituation to blood pressure measurement, regression to the mean, and self reports of smoking will also tend to exaggerate the changes observed. It is, however, not possible to separate participants' degree of risk from the use of antihypertensive drugs in this set of trials because studies with participants at high risk tended to include participants with high rates of use of antihypertensive drugs.

Furthermore, there are many problems in relating the outcome of a trial to a risk measure that is itself dependent on the outcome in meta-analysis.[65] Therefore our conclusions on these issues can only be tentative.

Heterogeneity in the effects of intervention is apparent. This is caused by two factors: the participants included in the trials and the use of pharmacological treatments. People with hypertension, at highest risk, were more likely to benefit from counselling and education and effective drug treatment. These findings suggest that targeting of current health promotion activities to people at high risk would be valuable.

Interventions used

The benefits of drug treatments for lowering blood pressure and cholesterol are clear.[66-69] However, those people at highest risk of disease either in needing control of hypertension[70] or lowering of cholesterol concentration[69] benefit most. Treatment of low risk populations may result in small treatment benefits being outweighed by small treatment risks,[71] which may have occurred in subgroups within the multiple risk factor intervention trial[27] and in the Finnish businessmen study.[29] There were strong associations between baseline levels of risk factors and net falls experienced, suggesting that intervention may be more effective in populations with particularly adverse risk factor profiles.

More intensive interventions might be expected to produce better effects, although those used in many of the trials would far exceed what is feasible in routine practice. A recent meta-analysis of dietary modifications found that increasing intensity of dietary intervention was associated with greater falls in blood cholesterol concentrations in participants at high risk.[72] In the Minnesota heart health programme, a non-randomised community trial of intensive health promotion, changes in risk factors and mortality showed virtually no difference between intervention and control communities.[73 74] The limited impact on the practice of health promotion of the essential failure of these community intervention trials is curious, especially given the huge resources that have been put into them.

Latency of effects

Benefits may not be detected in the early stages of an intervention, but they may emerge over time. Longer term follow up of participants in the multiple risk factor intervention trial has shown increased divergence in mortality between the control and intervention groups[75]; this has also been found in the Tromsø family trial (S Knutson, personal communication). However, evidence from pharmacological trials suggests that benefits from reducing blood pressure and blood cholesterol concentration are observed within two to four years.[66 76] The effects of giving up smoking vary depending on the clinical outcome considered: the risk of stroke falls rapidly after stopping,[77] but the risk of coronary heart disease may be less reversible.[78 79]

Quality of trials

The quality of the trials examined deserves comment. Few of the published reports provided sufficient detail to replicate the intervention used, and in several trials the intervention varied between sites and over time. The quality of the intervention, in terms of intensity and frequency, person carrying out activities, and the theoretical framework of behavioural change used will probably determine the impact of intervention. Losses to follow up were a particular problem as changes in risk factors cannot be assessed in an intention to treat analysis. Validation of smoking outcomes using biochemical assay of thiocyanate was only used in one trial.[27]

Key messages

- The effectiveness of health education approaches modifying lifestyle to prevent coronary heart disease is in doubt
- Health promotion interventions result in only small changes in risk factors and mortality in the general population
- In people with hypertension and in other high risk groups risk factor interventions have beneficial effects
- Health protection by fiscal and legislative means deserves a higher priority

Evidence of benefit

The quasi-experimental North Karelia study has been highly influential in supporting multiple risk factor intervention. Examination of the trends in both risk factors[80 81] and mortality from coronary heart disease[82] observed in North Karelia and comparison regions show similar patterns occurring at the same time, suggesting that the interventions in North Karelia were not instrumental in causing the improvements observed. Indeed, the North Karelia and similar projects may be viewed as effects, or epiphenomena, of the high mortality from coronary heart disease experienced in many countries in the 1960s.

In secondary prevention after myocardial infarction and angina, trials of multiple and single risk factor interventions have shown substantial benefits.[69 83-86] Intervention aimed at modifying lifestyle after myocardial infarction is probably effective because participants are much more likely to change their behaviours.

Limitations of randomised controlled trials

The interventions reviewed were essentially individual or family approaches. Randomised controlled trials impose limitations on the nature of interventions that may be tested and are of more value in examining high risk rather than population and social approaches to prevention.[87]

Policy implications

Health protection through national fiscal and legislative changes that aim at reducing smoking and dietary consumption of fats and so called hidden salt and calories and at increasing facilities and opportunities for exercise should have a higher priority than health promotion interventions applied to general and workforce populations. The current concepts and practices of multiple risk factor intervention, primarily through individual risk factor counselling, must not be exported to poorer countries as the best policy option for dealing with existing and projected burdens of

cardiovascular disease, as is currently happening.[88] Health protection should be promoted as the mainstay of preventing chronic diseases in poorer countries.

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When I use a word …
Fortysomething

Before people invented systems of arithmetic they used their fingers to count. This meant that anything more than a few was an indeterminately large number, as it was to the rabbits in *Watership Down*, who could count up to four, any number above which was Hrair—"a lot" or "a thousand."

The number 40 was used in this indeterminate way, and the Bible, in which only the number seven is mentioned more often, overflows with instances. Noah's ark was afloat for 40 days and 40 nights; it took 40 days to embalm Jacob; the Children of Israel wandered in the wilderness for 40 years and Moses spent 40 days and nights on Mount Sinai; King Solomon, King David, and King Joash each ruled for 40 years, and Eli and Deborah were judges for as long; the Philistines oppressed Israel for 40 years and Goliath challenged their army for 40 days; Jonah gave Nineveh 40 days to repent; Jesus fasted for 40 days and nights in the desert, being tempted by Satan, and 40 hours in his tomb before the resurrection.

In Shakespeare too: "I'll put a girdle round about the earth," claims Puck, "in forty minutes" (at 37 500 mph). "I loved Ophelia," says Hamlet; "forty thousand brothers could not with all their love make up my sum." Othello wishes that Cassio had 40 000 lives, for "one is too poor, too weak for my revenge." And Petruccio's lackey, as mad as his master, is said to have "the humour of forty fancies."

Other examples include Ali Baba's 40 thieves and the 40 days of rain that you get after a wet St Swithin's day. The latter, reminiscent of Noah's flood, perhaps arose from the fact that the rainy season in Babylon occurred during the time when the Pleiades were below the horizon for 40 days.

But the use of 40 goes beyond mere indeterminacy; it often symbolised a period of waiting and preparation. Many of the Biblical examples illustrate that, as do the 40 days of Lent, in preparation for Easter. Quarantine (Latin quadraginta) was originally the period of 40 days during which an English widow, entitled to a portion of her dead husband's estate, could stay in his house; if she married during that time she lost her right. At one time if a church offered sanctuary to a fugitive it did so for 40 days, and an MP was immune from arrest for 40 days before and after a session of parliament. Purification rituals often lasted 40 days—for example, after the birth of a Jewish boy (twice as long for a girl). And when the period of waiting is over, then, as the American psychologist Walter B Pitkin put it, "Life begins at 40," a sentiment later espoused by Sophie Tucker.

My most recent experience with 40 occurred during a half day short stay medical take, when we admitted 40 patients, only two of whom probably did not need admission. The number was in no way indeterminate, the experience in no way purifying, and I hope that it was not a preparation for things to come.

Jeff Aronson *is a clinical pharmacologist in Oxford*

We welcome filler articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.