Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies

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Abstract

Objective and design To relate UK national trends since 1950 in smoking, in smoking cessation, and in lung cancer to the contrasting results from two large case-control studies centred around 1950 and 1990.
Setting United Kingdom.
Participants Hospital patients under 75 years of age with and without lung cancer in 1950 and 1990, plus, in 1990, a matched sample of the local population: 1465 case-control pairs in the 1950 study, and 982 cases plus 3185 controls in the 1990 study.
Main outcome measures Smoking prevalence and lung cancer.
Results For men in early middle age in the United Kingdom the prevalence of smoking halved between 1950 and 1990 but the death rate from lung cancer at ages 35-54 fell even more rapidly, indicating some reduction in the risk among continuing smokers. In contrast, women and older men who were still current smokers in 1990 were more likely than those in 1950 to have been persistent cigarette smokers throughout adult life and so had higher lung cancer rates than current smokers in 1950. The cumulative risk of death from lung cancer by age 75 (in the absence of other causes of death) rose from 6% at 1950 rates to 16% at 1990 rates in male cigarette smokers, and from 1% to 10% in female cigarette smokers. Among both men and women in 1990, however, the former smokers had only a fraction of the lung cancer rate of continuing smokers, and this fraction fell steeply with time since stopping. By 1990 cessation had almost halved the number of lung cancers that would have been expected if the former smokers had continued. For men who stopped at ages 60, 50, 40, and 30 the cumulative risks of lung cancer by age 75 were 10%, 6%, 3%, and 2%.
Conclusions People who stop smoking, even well into middle age, avoid most of their subsequent risk of lung cancer, and stopping before middle age avoids more than 90% of the risk attributable to tobacco. Mortality in the near future and throughout the first half of the 21st century could be substantially reduced by current smokers giving up the habit. In contrast, the extent to which young people henceforth become persistent smokers will affect mortality rates chiefly in the middle or second half of the 21st century.

Introduction

Medical evidence of the harm done by smoking has been accumulating for 200 years, at first in relation to cancers of the lip and mouth, and then in relation to vascular disease and lung cancer.[1] The evidence was generally ignored until five case-control studies relating smoking, particularly of cigarettes, to the development of lung cancer were published in 1950, one in the United Kingdom[2] and four in the United States.[3–6] Cigarette smoking had become common in the United Kingdom, firstly among men and then among women, during the first half of the 20th century. By 1950 lung cancer rates among men in the United Kingdom had already been rising steeply for many years, but the relevance of smoking was largely unsuspected.[2 7] At that time about 80% of men and 40% of women smoked (fig 1 and *BMJ*'s website, table A). But few of the older smokers had smoked substantial numbers of cigarettes throughout their adult life, so even male lung cancer rates were still far from their maximum (except in younger men), and rates in women were much lower. Over the next few decades, a substantial decrease occurred in the United Kingdom in the prevalence of smoking (fig 1), in cigarette tar yields, and, eventually, in lung cancer rates (fig 2), and by 1990 male lung cancer mortality, although still high, was decreasing rapidly.[8–12]

In this paper we relate the UK national trends in smoking, in smoking cessation, and in lung cancer to the contrasting results from two large case-control studies of smoking and lung cancer in the United Kingdom that were conducted 40 years apart, centred on the years 1950[2 7] and 1990.[8] The 1950 study was concerned with identifying the main causes of the rise in lung cancer and showed the predominant role of tobacco. The 1990 study was concerned not just with reconfirming the importance of tobacco but also with assessing the lesser effects of indoor air pollution of some houses by radon.[8] Because there has been widespread cessation of smoking (indeed, above age 50 there are now twice as many former cigarette as current cigarette smokers in the United Kingdom[10]), the second study was able to assess the long term effects of giving up the habit at various ages.

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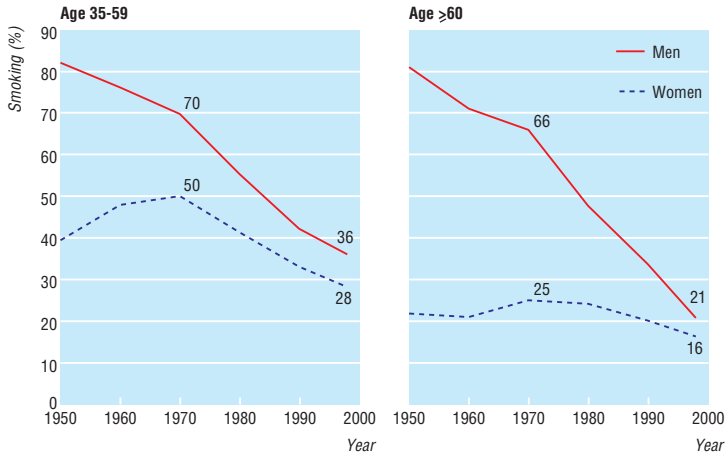

Fig 1 Trends in prevalence of smoking at ages 35-59 (left) and ≥60 (right) in men and women in the United Kingdom, 1950-98. Prevalences at ages 25-34 were 80% for men and 53% for women in 1948-52 and 39% for men and 33% for women in 1998. Further details are given on the *BMJ*'s website (table A)

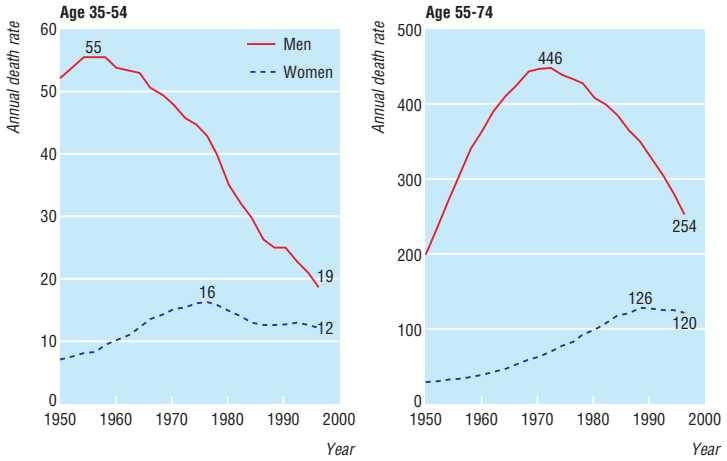

Fig 2 Trends in mortality from lung cancer in men and women in the United Kingdom, 1950-97: annual mortality per 10^5 at ages 35-54 (left) and 55-74 (right) years. Rate in each 20 year age range is mean of rates in the four component five year age groups. Age specific rates from 1950-2 to 1993-7 are given on *BMJ*'s website (tables B and C); at ages 35-54 and 55-74 in 1998 the rates were 17 and 243 (men) and 12 and 20 (women)

Participants and methods

The 1950 study was conducted in London and four other large towns during 1948-52, and its methods have been described elsewhere.[2 7] It involved interviewing, as potential "cases," patients younger than 75 years of age in hospital for suspected lung cancer and, as "controls," age matched patients in hospital with various other diseases (some of which would, in retrospect, have been conditions associated with smoking). After patients in whom the initial diagnosis of lung cancer was eventually refuted were excluded from the cases, 1465 cases and 1465 controls remained. A preliminary report on 709 case-control pairs was published in 1950, and the full results were published two years later.[2 7]

The 1990 study was conducted during 1988-93 in a part of southwest England that had not been included in the 1950 study. Potential cases were patients younger than 75 who were referred with suspected lung cancer to the five hospitals in Devon and Cornwall that investigated lung cancer. For each case a population control was obtained, selected randomly either from lists of the local family health services authority or from electoral rolls, and a hospital control was selected from patients whose current admission was for a disease not thought to be related to smoking. Controls were matched for age, sex, and broad area of residence to the patients with suspected lung cancer. Cases and controls were eligible for the 1990 study only if they were current residents of Devon or Cornwall, had lived in one of these two counties for at least 20 years, and could be interviewed in person by research assistants about smoking habits and other relevant characteristics. The final diagnosis of cases was sought; those who had a smoking related disease other than lung cancer were excluded; and the few who had a disease not known to be associated with smoking were transferred to the hospital control group. Similarly, in 1990 (although not in 1950) the final diagnosis of all the hospital controls was sought, and those whose main reason for being in hospital was a disease known to be related to smoking were excluded from the study.

The distributions of the smoking habits of the population controls and hospital controls in 1990 were closely similar, and the results are presented here with these two control groups combined. Further details of the study design and methods of data collection and analysis have been given elsewhere.[8] Information was obtained in the 1990 study about the smoking habits of 667 men and 315 women with a confirmed diagnosis of lung cancer and of 2108 male and 1077 female controls.

Statistical methods

Relative and cumulative risks

Relative risks for men and women comparing particular categories of smoker with lifelong non-smokers in the 1990 study (and the ratios of the risks in former smokers to those in continuing smokers) were calculated by logistic regression with adjustment for age.[13] Further adjustment for social class, radon exposure, and county of residence made no material difference. Relative risks for men and women in the 1950 study were taken as the odds ratios indicated by the published frequency distributions of the age matched cases and controls.[7] Relative risks from the studies were then combined with national lung cancer mortality rates from 1950 and 1990 respectively to estimate the absolute hazards in various categories of smoker, former smoker, and non-smoker. Because they are linked to known national rates, these absolute risks are statistically stable among smokers (and among former smokers), even though the risks relative to lifelong non-smokers would not be stable as so few non-smokers develop the disease. Such calculations of absolute risk allow comparisons between different categories of smoker not only within this study but also between this and other studies that report absolute risks.

For the 1990 study, within one particular age group, the absolute lung cancer rates for the different smoking categories were obtained by multiplying the all ages relative risks for each of the smoking categories

Table 1 Comparisons of risk of lung cancer between all current smokers, all former smokers, and lifelong non-smokers in 1990 study

	Men			Women		
Smoking status	Cases/ controls	Ratio of risks*	No of cases expected without cessation†	Cases/ controls	Ratio of risks*	No of cases expected without cessation†
Current smoker	379/602	1.00	379	197/218	1.00	197
Former smoker, by years stopped						
<10	146/339	0.66	222	68/93	0.69	99
10-19	92/306	0.44	208	18/80	0.21	86
20-29	31/221	0.20	152	8/144‡	0.05‡	166‡
⩾30	16/240	0.10	168			
Lifelong non-smoker	3/400	0.03§	3	24/542	0.05§	24
Total	667/2108	—	1132	315/1077	—	572

*Risk ratio versus current smoker, adjusted for age.
†In former smokers, number of cases observed divided by risk ratio.
‡Women who stopped ⩾20 years ago.
§Lifelong risks for non-smokers taken from US prospective study.

by a common factor. This factor was chosen so that combination of these risks with the prevalences of such smoking habits among study controls in that age group yielded the 1990 age specific lung cancer death rate in that age group. If, for one particular category of smoker, the lung cancer rates per 10^5 in all the five year age groups before age 75 add up to c, then the cumulative risk by age 75 is $1 - \exp(-5c/10^5)$. For the 1950 study the relative risks were multiplied by 0.6 (men) and 0.5 (women) to yield the cumulative risk (%) by age 75. These factors were chosen to ensure that the population weighted means of the cumulative risks for lifelong non-smokers, former smokers, cigarette smokers, and other smokers were 4.7% (men) and 0.7% (women) as in the 1950 population. (The cumulative risk, which depends only on the age specific lung cancer rates up to age 75 and not on competing causes of death, is somewhat less than the lifetime risk.)

Use of statistically stable non-smoker rates from a large US study

The most reliable recent evidence on lung cancer rates among lifelong non-smokers in developed countries is that from a prospective study of mortality in one million Americans during the 1980s (see table D on *BMJ*'s website).[14 15] These American rates seem to correspond not only to what normally happens in the United States but also to what normally occurs in the United Kingdom, at least among professional men. For, when these figures were used to predict the total number of deaths from lung cancer among the non-smokers in a cohort of male British doctors that has been followed prospectively for 40 years from 1951 to 1991,[16 17] the number expected was 19.03; the number actually observed was 19 (R Doll, personal communication). The American lung cancer rates for non-smokers suggest cumulative risks by 75 years of age of 0.44% for men and 0.42% for women.

Cumulative risks for the different categories of smoker in the 1990 study are shown on the *BMJ*'s website (table E), representing the probabilities of death from lung cancer before age 75: that calculated for lifelong non-smokers is 0.2% for men and 0.4% for women. The male rate is about half that in the American study but is based on only three cases, which is too few to be reliable. Conversely, the American results suggest that the cumulative risks calculated from the 1950 study—0.6% (men) and 0.5% (women) in lifelong non-smokers—may be slightly too high, although the rate in men is based on only seven cases and was inflated by problems with the 1950 male controls (see Results). We have therefore used the American results for non-smokers in most of our analyses. This does not affect the risk ratios comparing smokers and former smokers or the estimated absolute risks among smokers and former smokers.

Results

Effects of current smoking in 1990 study

Most of the participants who were still current cigarette smokers in 1990 would have been cigarette smokers throughout adult life, and the cumulative risk of lung cancer by age 75 in this group was 15.9% for men and 9.5% for women (see *BMJ*'s website, table E). These cumulative risks reflect the death rates from lung cancer of cigarette smokers in 1990 and were obtained by combining the relative risks from the 1990 case-control study with national death rates. Had these men and women smoked as intensively when they were young as adolescent smokers do nowadays, the cumulative risks might have been greater. Only 34% of the male and 11% of the female controls who were current smokers had started before the age of 15 years, and the case-control comparisons indicate that smokers who had done so had double the risk of lung cancer of those who had started aged 20 or older (risk ratios adjusted for age and amount smoked were 2.3 (95% confidence interval 1.4 to 3.8) for men and 1.8 (0.9 to 3.4) for women).

Effects of cessation in 1990 study

A large number of men and, to a lesser extent, of women had stopped smoking well before 1990. Hence, particularly for men, robust estimates can be obtained from the 1990 data of the effects of prolonged cessation on the avoidance of risk (table 1).

The ratio of the risk of lung cancer in those who have stopped smoking to that in continuing smokers gets progressively lower as the time since cessation gets longer, although it never gets quite as low as in lifelong non-smokers. Once people have started to smoke, however, the comparison that is relevant for them is of former smokers with continuing smokers, and table 1 contrasts the numbers of cases among former smokers with the numbers that would have been expected if smoking had continued. In the 1990 study there were

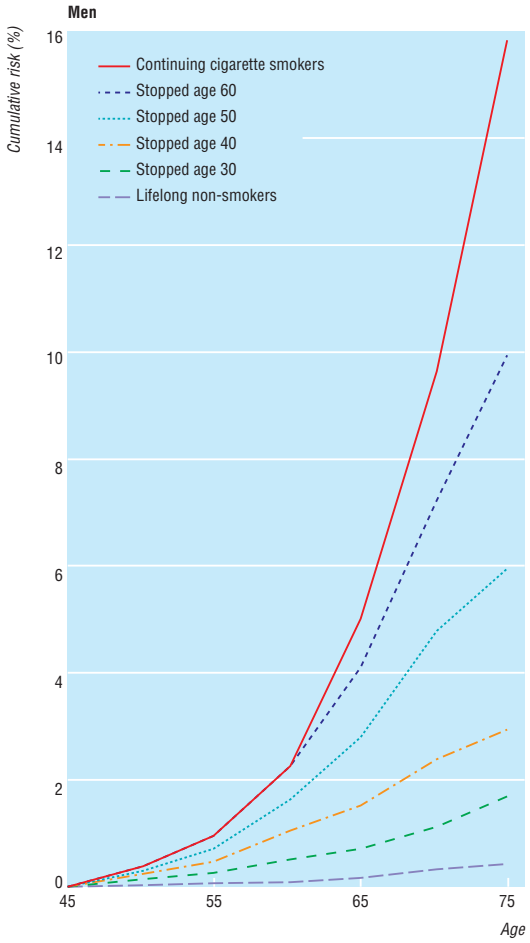

Fig 3 Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in United Kingdom in 1990. (Non-smoker risks are taken from a US prospective study of mortality[14])

substantially more former smokers than continuing smokers among the controls, and this widespread cessation had almost halved the number of cases that would have been expected if the former smokers had continued smoking. The risk ratios comparing former cigarette smokers with continuing cigarette smokers (see *BMJ*'s website, table F) are essentially the same as those in table 1 for all smokers and can be used to calculate the cumulative risks of lung cancer for men who stop smoking cigarettes at different ages (fig 3). The cumulative risks by 75 years of age are 15.9% for men who continue to smoke cigarettes and 9.9%, 6.0%, 3.0%, and 1.7% for those who stopped around 60, 50, 40, and 30 years of age. The pattern among women was similar: the cumulative risk of lung cancer by age 75 among continuing smokers was 9.5% compared with 5.3% and 2.2% among women who stopped around 60 and 50 years of age, respectively. The risk seemed even smaller for women who had stopped earlier in life, but the number of such women was too small for statistical stability. The results for smokers and for former smokers in table 1 and figure 3 are not affected by any assumptions that may be made about non-smoker risks.

Comparison of findings for smoking in 1950 and 1990 studies

The hazards at the death rates among current smokers in the 1990 study, when the male lung cancer epidemic was well past its peak, can be compared with the hazards at the death rates among current smokers in the 1950 study,[2 7] when the epidemic was still increasing rapidly, except among men in early middle age (table 2).

Absolute risks in smokers unaffected by biases in 1950 male controls

The findings in the earlier study were reported for categories of smoking that differ slightly from those now considered appropriate, but this probably makes little difference. In addition, the hospital controls in the earlier study included an unknown, but appreciable, proportion of patients who were in hospital for conditions that were subsequently shown to be related to smoking but were not known to be so in 1950. This means that the proportion of smokers was higher than in the general population and also that the relative risks estimated from the 1950 study for different levels of smoking were too low. Both effects will have been relatively unimportant for women, as few women at that time had been smoking long enough to have been admitted to hospital because of a smoking related disease. Even for men, they will have had little effect on the calculated absolute risk among smokers. If, for example, the male rate of hospital admission for the control diseases was about 1.5 times as great among smokers as among non-smokers, then correction for this would multiply the relative risk of lung cancer in male smokers by about 1.5 and would indicate that the percentage of current smokers in the study areas was not 86%, but about 80% (which was about the percentage in the country as a whole). But this correction would have no material effect on the cumulative risk calculated for cigarette smokers (and little effect on that calculated for other smokers or former smokers), as the weighted average has to remain 4.7% to match the 1950 male death rates. It would merely reduce the cumulative risk calculated for male non-smokers from 0.6% to about 0.4%, thereby bringing it closer to that in US non-smokers.

Changes in prevalence of smoking

One clear difference between the 1950 and 1990 study results in table 2 is that many of the controls in the 1990 study had given up smoking, so there was a large decrease in the prevalence of smoking between the two studies. (In both 1950 (after correction) and 1990, the prevalence of smoking among controls resembled that in national surveys.) The reduction in the proportion currently smoking cigarettes was smaller in women than in men. Among women who still smoked in 1990, a higher proportion smoked heavily than was the case in 1950, and a substantially larger proportion had started before the age of 20 (68% in 1990 and 24% in 1950 among women, compared with 83% and 76% respectively among men). Moreover, the way that women smoke a cigarette has become more like the way men do.[22] Nevertheless, among women old enough to be in the 1990 study more than half of those who had been cigarette smokers had given up the habit, and an even greater proportion of the men had

Table 2 Smoking status versus cumulative risk of death from lung cancer by age 75, from 1950 and 1990 studies

	Men				Women			
	% of cases/controls		Cumulative risk (%)		% of cases/controls		Cumulative risk (%)	
Smoking status	**1950**	**1990**	**1950***	**1990**	**1950**	**1990**	**1950***	**1990**
Lifelong non-smoker	0.5/4.5	0.5/19.0	~0.4	~0.4	37.0/54.6	7.6/50.3	~0.4	~0.4
Former smokers	5.2/9.1	42.7/52.5	2.9	5.5	9.3/7.4	29.8/29.4	0.9	2.6
Current pipe or cigar only	3.9/7.2	8.5†/7.1	2.8	8.1†	0/0	0.6/0.1	—	—
Current cigarette smokers	90.4/79.2	48.3/21.5	5.9	15.9	53.7/38.0	61.9/20.1	1.0	9.5
Amount smoked (% of smokers)‡								
<5/day	3.6/7.0	6.2§/9.5	2.8	10.4§	20.6/36.7	4.1§/10.1	0.6	3.4§
5-14/day	38.2/47.5	33.5/39.7	4.4	12.8	44.1/44.9	32.3/37.8	1.0	7.7
15-24/day	33.0/31.5	39.1/37.3	5.7	16.7	35.3/18.4**	44.1/42.4	2.0**	10.4
⩾25/day	25.2/14.0	21.1/13.5	9.8	24.4		19.5/9.7		18.5
Total	100/100	100/100			100/100	100/100		
No of cases	1357/1357	667/2108	—	—	108/108	315/1077	—	—

*The cumulative risk by age 75 in 1950 was estimated for smokers and former smokers by multiplying the published relative risks[7] by 0.6 for men and 0.5 for women. This, together with the population prevalences, yields the cumulative risks of 4.7% for men and 0.7% for women seen in 1950 UK national statistics (see *BMJ's* website). That for lifelong smokers in 1950 and 1990 was estimated from a US prospective study.
†The effects of smoking only pipes or cigars cannot be assessed here, as 88% of these cases had previously smoked cigarettes.
‡By tobacco most recently smoked (1950 study, taking 1 g of other tobacco as one cigarette) or by current cigarettes (1990 study).
§The effects of <5 cigarettes a day cannot be assessed here, as 93% of these cases had previously smoked over 15 a day and several had smoked over 30.
**Women in 1950 study who smoked ⩾15 cigarettes a day.

done so. A recent national survey confirms that among men and women aged over 50 in the United Kingdom, the number of former cigarette smokers is double the number of continuing cigarette smokers.[10] But those who are continuing smokers nowadays may well have smoked substantial numbers of cigarettes throughout adult life, whereas national cigarette sales during the first few decades of the last century[9 18] show that few of the older smokers in 1950 can have done so.

Changes in lung cancer rates among continuing smokers

Another clear difference between the two studies is that the cumulative risk of lung cancer among smokers increased substantially. The increase occurred not only among women (among whom the cumulative risk for cigarette smokers was 1.0% in 1950 and 9.5% in 1990) but also among men (among whom it increased from 5.9% at 1950 cigarette smoker lung cancer rates to 15.9% at 1990 rates). As lung cancer mainly occurs above the age of 55, the increase in the cumulative risk is mainly because current smokers aged 55-74 in 1950 were less likely to have smoked a substantial number of cigarettes throughout adult life than current smokers in 1990.[18 19] Among younger men, however, the death rate from lung cancer decreased more rapidly than the prevalence of smoking (figs 1 and 2), indicating lower death rates from lung cancer in 1990 than 1950 among male cigarette smokers in early middle age.

Discussion

Prolonged cigarette smoking

The 1990 study provides reliable evidence, particularly among men, about the absolute effects of prolonged cigarette smoking and about the effects of prolonged cessation (table 1, fig 3). Information about the effects of prolonged cigarette smoking could not have been obtained in 1950 because the habit became widespread in the United Kingdom (firstly among men and then among women) only during the first half of the 20th century. By 1950 the increase in smoking was too recent to have had its full effects on disease rates, except perhaps among men in early middle age. The fact that by 1990 many of the current smokers would have smoked substantial numbers of cigarettes throughout adult life is the chief reason for the large increase in the cumulative risk of lung cancer among continuing smokers.[19] For the same reason, increases in the risks associated with smoking were also seen between the first 20 years (1951-71) and the next 20 years (1971-91) of follow up in the prospective study of smoking and death among British doctors,[17] and between the two large prospective studies carried out by the American Cancer Society in the 1960s and 1980s.[15 20]

At the lung cancer rates for female cigarette smokers in 1950 the cumulative risk of death from lung cancer before age 75 (in the absence of other causes of death) would have been only 1% compared with 10% at 1990 rates. The effect of longer exposure (together with the effect of changes in the way women smoke cigarettes[22]) overwhelms the lesser effect of the reduction in cigarette tar yields (and of other changes in cigarette composition) over this period.[19]

Among male cigarette smokers the cumulative risk of death from lung cancer by age 75 increased from 6% in 1950 to about 16% in 1990. Again the most plausible explanation for this increase is that the effect among continuing smokers aged 55-74 of a greater duration of smoking substantial numbers of cigarettes outweighed the effect of changes in cigarette composition. At ages 35-54, there was a twofold decrease between 1950 and 1990 in the prevalence of smoking among men, but, particularly at ages 35-44, male mortality from lung cancer in the United Kingdom decreased more rapidly than the prevalence of smoking (figs 1 and 2), suggesting a decrease in hazard among smokers. These increases and decreases in the hazards among smokers, together with large changes in smoking uptake rates and cessation rates, underlie the large fluctuations in UK lung cancer death rates shown in fig 2 and reviewed in more detail elsewhere.[19 21 23]

Prolonged cessation

In the 1990 study we were able to assess the effects of prolonged cessation among those who had smoked cigarettes for many years. Although efforts to change

from cigarettes to other types of tobacco, or from smoking substantial numbers of cigarettes to smoking smaller numbers, seemed to confer only limited benefit (table 2), stopping smoking confers substantial benefit. Figure 3 indicated that even people who stop smoking at 50 or 60 years of age avoid most of their subsequent risk of developing lung cancer, and that those who stop at 30 years of age avoid more than 90% of the risk attributable to tobacco of those who continue to smoke (see fig 3 and *BMJ*'s website, table G). In the United Kingdom widespread cessation has roughly halved the number of cases of lung cancer that would now be occurring, as by 1990 it had already almost halved the number that would have occurred in the study (table 1).

Past and future trends in total mortality attributable to tobacco

Despite cessation of smoking and improvements in cigarette composition, lung cancer is still the chief neoplastic cause of death in the United Kingdom, and tobacco causes even more deaths from other diseases than from lung cancer.[14 15] The changes since 1950 in tobacco-attributable mortality from diseases other than lung cancer can be estimated indirectly from national mortality statistics.[14 15] Such estimates indicate that in 1965 the United Kingdom probably had the highest death rate from tobacco related diseases in the world, but that since then the number of deaths in middle age (35-69) from tobacco has decreased by about half, from 80 000 in 1965 to 43 000 in 1995. Nevertheless, cigarette smoking remains the largest single cause of premature death in the United Kingdom and eventually kills about half of those who persist in the habit.[17] The 1990 study assessed the effects of stopping smoking only on lung cancer, but a comparably large benefit of stopping was found for all cause mortality in the prospective study of smoking and death among British doctors.[17] This reinforces similar evidence from many other countries that even in middle age those who stop smoking avoid most of their subsequent risk of being killed by tobacco.

Two thirds of those in the United Kingdom who are still current smokers say they want to give up the habit,[10] and the extent to which they succeed in doing so will be the chief determinant of the number of deaths caused by tobacco over the next few decades. Both in the United Kingdom and elsewhere,[24 25] the extent to which young people become cigarette smokers over the next few decades will strongly affect mortality only in the middle and second half of the 21st century, but mortality in the first half of the century will be affected much less by the numbers of new smokers who start than by the numbers of current smokers who stop.

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Contributors: RD planned the 1950 study with A Bradford-Hill and planned the 1990 study with SD. SD, RD, HD, PS, and EW conducted and analysed the 1990 study in the Imperial Cancer Research Fund Cancer Epidemiology Unit. RP, SD, and RD planned and wrote the paper. SD is the guarantor.

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What is already known on this topic

Smoking is a cause of most deaths from lung cancer in the United Kingdom

Early studies could not reliably assess the effects of prolonged cigarette smoking or of prolonged cessation

What this study adds

If people who have been smoking for many years stop, even well into middle age, they avoid most of their subsequent risk of lung cancer

Stopping smoking before middle age avoids more than 90% of the risk attributable to tobacco

Widespread cessation of smoking in the United Kingdom has already approximately halved the lung cancer mortality that would have been expected if former smokers had continued to smoke

As most current smokers in the United Kingdom have consumed substantial numbers of cigarettes throughout adult life, their risks of death from lung cancer are greater than earlier studies had suggested

Mortality from tobacco in the first half of the 21st century will be affected much more by the number of adult smokers who stop than by the number of adolescents who start

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Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety

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Abstract

Objectives To determine whether use of an oral nicotine inhaler can result in long term reduction in smoking and whether concomitant use of nicotine replacement and smoking is safe.
Design Double blind, randomised, placebo controlled trial. Four month trial with a two year follow up.
Setting Two university hospital pulmonary clinics in Switzerland.
Participants 400 healthy volunteers, recruited through newspaper advertisements, willing to reduce their smoking but unable or unwilling to stop smoking immediately.
Intervention Active or placebo inhaler as needed for up to 18 months, with participants encouraged to limit their smoking as much as possible.
Main outcome measures Number of cigarettes smoked per day from week six to end point. Decrease verified by a measurement of exhaled carbon monoxide at each time point compared with measurement at baseline.
Results At four months sustained reduction of smoking was achieved in 52 (26%) participants in the active group and 18 (9%) in the placebo group ($P < 0.001$; Fisher's test). Corresponding figures after two years were 19 (9.5%) and 6 (3.0%) ($P = 0.012$).
Conclusion Nicotine inhalers effectively and safely achieved sustained reduction in smoking over 24 months. Reduction with or without nicotine substitution may be a feasible first step towards smoking cessation in people not able or not willing to stop abruptly.

Introduction

The best way to prevent the detrimental health consequences of cigarette smoking is to quit, and efforts to date have focused on this strategy.[1 2] Many smokers, however, find it impossible to quit, even with help, because of their dependence on nicotine, which is a highly addictive psychoactive drug.[3] Nicotine replacement therapy is an established pharmacological aid to help smokers quit and has consistently been shown almost to double the abstinence rate, irrespective of the level of additional interventions.[4] Increasing experience with trials on smoking cessation, however, has shown that successful abstinence is usually obtained in smokers with low to moderate nicotine dependence, whereas heavily dependent smokers have the highest relapse rates.[5] Unfortunately this latter group has the highest cigarette consumption and is therefore at the highest risk of developing disease related to tobacco consumption.

Given that few smokers are ready to quit at any time, plus the fact that many smokers try to quit several times before succeeding, new treatment approaches are clearly needed. One such strategy could be to reduce tobacco consumption substantially in smokers who are unwilling or unable to quit right away. For such smokers, sustained reduction might reduce the known health risks by reducing tobacco exposure and may also move them towards the ultimate goal of quitting.[6 7] In a preliminary study Fagerström et al showed that short term smoking reduction with nicotine replacement therapy over a period of five weeks was possible and that the combination of reduced smoking with nicotine replacement therapy was well tolerated.[8] The efficacy and safety of nicotine replacement therapy in achieving sustained smoking reduction, however, has not yet been assessed. Another important issue is whether smoking reduction can increase motivation to quit in recalcitrant smokers.

Smoking cessation is no longer regarded as a dichotomous process (cessation or not) but rather as a continuum that entails several stages, as described by DiClemente and Prochaska.[9] There is empirical evidence to suggest that reduced smoking, also referred to as controlled smoking or harm reduction, is a therapeutic option for those smokers unable or unwilling to quit. Glasgow et al[10] and Hughes et al[11] found that smokers randomised to such an intervention were no less likely, and possibly even more likely, to quit smoking in the long term compared with smokers randomised to more conventional interventions. While not the first treatment of choice, reduced smoking might be considered for recalcitrant smokers unwilling to repeat traditional cessation attempts.

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Fulfilling the potential for cancer prevention: policy approaches

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Introduction

We currently have sufficient knowledge of cancer causes and prevention to reduce cancer burden in the United States by over 50% in the coming decades [1, 2]. To achieve such a significant reduction, it will be necessary to develop public policies that rely on our current scientific knowledge of cancer and on the vast social and political movement currently aligned behind cancer research [3, 4]. As public awareness of cancer and the potential for risk reduction continues to rise, we must structure policies that effectively utilize our current knowledge of cancer prevention and that reinforce healthy behavior changes. The purpose of this report is to summarize that knowledge in a manner that will inform and activate future cancer prevention policy.

In this report, we discuss five major behavioral risk factors and their impact on cancer incidence: tobacco use, physical activity, weight maintenance, diet, and alcohol use. While other lifestyle factors, such as sun exposure, sexual practices, and exposure to infected blood, also contribute substantially to cancer incidence, we have chosen to focus only on the factors that also have a large impact on the incidence of other major chronic diseases, such as cardiovascular disease, diabetes, and osteoporosis. The benefits of intervention are far greater when the potential reduction in other chronic diseases is added to the reduction in cancer [5].

For each of the five selected risk factors, we briefly summarize the epidemiologic evidence with respect to cancer incidence. We then identify a select number of key policies that draw on current knowledge. Obviously, by focusing on only a limited selection of policy priorities, our recommendations are not meant to be exhaustive. Rather, they are meant to bring into focus the top priorities based on the current state of scientific research.

To make effective population-wide improvements in the major behavioral risk factors, changes must occur on many different social levels, and the policy recommendations in this report reflect this. They aim to create a prevention-oriented environment that makes risk-reduction behaviors easier for individuals to choose and maintain. It is not enough to assume that individuals who are educated about their cancer risk will modify their behavior to lower their risk [6]. Barriers to behavioral change exist beyond the individual at the community level and within the broader social milieu. As social epidemiologists have pointed out, broad social movements are needed if we are to eliminate these barriers at the population level and truly stimulate and sustain health behavior change.

The wealth of existing scientific knowledge on cancer prevention shows that meaningful reductions in the burden of poor health are within our reach. While further research is needed to better quantify issues such as strengths of association and biological latency, calls for such research should not be used as excuses to delay acting on what is already scientifically established [7]. The recommendations outlined here are meant to advance public policy and its utilization of the best and most relevant scientific knowledge as it pertains to public health and the burden of cancer. Because public health is a field of practice as well as an academic area of study, the overarching goal of this report is to bridge these two aspects of public health so that as many people as possible can reap the benefits of decades of scientific study on cancer.

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Tobacco

Tobacco is the scourge of public health. In the United States alone, the active use of tobacco, primarily in the form of cigarette smoking, causes over 400,000 deaths each year and is responsible for approximately 30% of all cancer-related deaths [8]. Worldwide, the numbers are even more staggering. The World Health Organization estimated that in 1998 there were approximately 4 million deaths worldwide linked to tobacco use [9]. By 2020 this number is expected to at least double.

The causal link between smoking and cancer was established as early as 1964, when the first Surgeon General's report on smoking and health was released [10]. At that time data were able to support a causal link with only two cancers: lung cancer and laryngeal cancer. Since then, however, enough evidence has accrued that smoking is now known to cause at least 11 cancers: lung, laryngeal, oral, pharyngeal, esophageal, bladder, kidney, pancreatic, cervical, colon, stomach, and leukemia. Clearly, tobacco's huge impact on cancer risk alone necessitates action, but when its ill effects on other important chronic diseases – such as coronary heart disease and stroke – are also added to the equation, the need for action becomes even more pronounced.

Policy recommendations to decrease tobacco use

Although great strides have been made in curbing tobacco use over the past 35 years, much work remains. A quarter of the population still smokes, and after declining significantly for the past 30 years, rates of tobacco use have begun to plateau among adults and even increase among high school students [11]. Given the pervasiveness of smoking in our society, a multifaceted approach will be required to successfully combat tobacco use. Such an approach will need to address both prevention and cessation.

Achieve optimal levels of excise taxation on tobacco products, and ensure that sufficient funds from these taxes and from tobacco settlement monies are allocated to support state-based tobacco control efforts

According to the World Health Organization, taxation is the single most effective method of reducing the demand for tobacco [12]. Presumably, as the price of tobacco increases, smokers will be more likely to quit, and those who are contemplating smoking will be dissuaded from starting. Since adolescents and lower-income individuals are the most price-sensitive populations, taxation is likely to affect them most [13, 14].

In California, cigarette taxes are an integral part of a comprehensive tobacco control program and have contributed to large reductions in the prevalence of smoking [15]. These reductions have translated into numerous health benefits for Californians, including lower rates of both lung cancer and heart disease [15–17].

In addition to the health benefits, tobacco taxation can also be an excellent source of revenue to fund prevention and cessation programs. However, these monies often end up being used for non-tobacco-related state projects instead. This is not unlike the fate of the Master Settlement Agreement (MSA) payments. Under the MSA, the tobacco industry agreed to pay the states approximately $206 billion over 25 years. Although states suddenly have millions of dollars from this agreement, most have allocated only a small percentage of the funds for tobacco control. In fact, only six states (Maine, Mississippi, Massachusetts, Minnesota, Arizona, and Indiana) have allocated funding that falls within the CDC's annual recommended spending levels [18].

Because the allocation of state funding is given little attention by the media, citizens are frequently unaware that tobacco taxes and MSA funds are no longer being used as intended. To ensure that their legislatures allocate sufficient funds to tobacco control, citizens need to stay informed about their state budgets and contact their representatives about the importance of tobacco control programming.

Increase regulatory efforts to reduce environmental tobacco smoke at the municipal, state, and federal levels

Concern over the harmful effects of environmental tobacco smoke (ETS) has grown rapidly since the release of the 1986 US Surgeon General Report, which concluded that ETS caused numerous diseases, including lung cancer, in healthy non-smokers [19]. More recent data suggest that it may also raise the risk of heart disease [20]. Limiting areas where smoking is permitted will clearly benefit the health of non-smokers by reducing their exposure to ETS and may also encourage smokers to quit [21, 22]. Additional benefits are derived when children are not exposed to smokers in public areas, and nonsmoking is reinforced as the normative behavior in society [23].

Regulatory efforts aimed at creating smoke-free environments are controlled at various levels of government. For example, federal legislation prohibits smoking on all airline flights in and out of the US, in all federal office buildings, and in child-care facilities that receive federal

funding. However, regulations at the state level and within states vary greatly. Eight states still have no restrictions on state government worksites, and 30 states have no restrictions on smoking in non-governmental workplaces [24]. Thus, although many local communities and individual workplaces have designated smoking areas or implemented smoking bans in public areas, the lack of coordination between communities and states means that people are still exposed to ETS on a daily basis.

One of the biggest obstacles that local governments must overcome to pass clean air legislation is preemption [25]. Preemption is a rule that many states invoke to make it unlawful for local governments to enact clean air restrictions that are more stringent than those imposed at the state level. Therefore, if a state has no restrictions on worksite smoking, it may be impossible for a local community to ban smoking in restaurants or other workplaces. Preemption laws must be overturned in order to give local governments the right to protect their communities from ETS.

Enforce regulations to reduce the marketing and promotion of tobacco products, particularly to youth

When the Master Settlement Agreement was established in 1998 between the tobacco industry and 46 State Attorneys General, many hoped that it would signal the end of an era for the industry's marketing tactics. The intent of the MSA was to reduce youth smoking by prohibiting the tobacco industry from targeting youths with their marketing and promotion efforts. To achieve this goal, the MSA imposed a number of restrictions, including bans on the use of cartoons in all advertising, promotion, and packaging; bans on any industry action that attempted to initiate, maintain, or increase youth smoking; bans on both outdoor and transit advertising; and bans on the distribution and sale of brand-name promotional items, such as t-shirts and caps.

Unfortunately, despite the comprehensiveness of the MSA, there are many loopholes in its provisions, and these have hindered its potential to truly reduce youth exposure to tobacco. For example, one of the provisions in the MSA limits tobacco companies to only one brand name sponsorship per year. However, a closer look at the wording in this provision shows that tobacco companies are actually able to host as many events as they like if the events are under the guise of one tour or series. For example, the Winston Cup NASCAR series may have eight racing events throughout the year, but this is considered only one sponsorship. While this may seem innocuous, studies have shown that children who watch tobacco-sponsored sporting events are more likely to smoke than children who do not watch these events [26–28]. With loopholes such as these, the MSA is limited in its ability to reach its ultimate goal of reducing the prevalence of youth smoking.

To complement the MSA, federal laws that are currently in place to limit the industry need to be enforced and, in some instances, enhanced. For example, in 1965 the US Congress passed the Federal Cigarette Labeling and Advertising Act, which mandated health warnings on cigarette packaging and banned cigarette advertisements from television (Public Law 89-92). In an exemplary effort, the Department of Justice recently used this Act to force tobacco companies to remove their brand name billboards from baseball, basketball, football, and hockey stadiums, since the billboards appeared in televised broadcasts and were therefore found to be televised advertising. There is nothing to prohibit the Department of Justice from further enforcing this Act to also include other types of sponsorships that appear on television.

Enforce laws that restrict youth access to tobacco

Despite local ordinances and state legislation that limit youth access to tobacco, adolescents are still able to obtain cigarettes from a number of sources, including retail stores, vending machines, and online retailers. This suggests that legislation in each of these areas needs to be enforced and in some cases expanded.

1. *Retail stores.* Currently, states are required under the 1992 Synar Amendment to have laws in place that ban the sale and distribution of tobacco products to those under age 18. The Amendment was intended to deter merchants from selling tobacco to underage youth, rather than to punish youth for smoking or possessing tobacco. Unfortunately, implementation and enforcement of state laws under the Amendment have proven difficult. In 1998, 15 states and territories failed to meet the Amendment's standards by, for example, failing to prosecute merchant vendors or conduct compliance checks [29]. In order for the Amendment to be effective in reducing youth access, states need to provide adequate resources to local law enforcement agencies, since these agencies ultimately bear the burden of upholding the youth access laws. One way for states to do this is to require mandatory tobacco licenses for merchants, as was recommended in the 2000 Report of the Surgeon General [30]. In other instances, such as liquor sales, licensing has provided a strong incentive for merchants to comply with existing laws.

2. *Vending machines*. Many state and local governments have been successful in restricting youth access to vending machines. For example, California and Colorado have restricted vending machines to adult-only venues, while Illinois is looking to eliminate them altogether [30]. Other states and municipalities should consider making similar efforts.
3. *Online retailers*. The most recent venue through which both minors and adults obtain tobacco products is the Internet. Currently, more than 40 Web sites sell cigarettes in the United States, and this number is expected to grow [31]. This is of special concern because there are currently no laws in place to regulate or restrict the online sale of tobacco products to minors, and Internet tobacco products are often not subject to state sales taxes, making them much less expensive than their retail store counterparts. Some states are taking action to address this problem, including Maryland, Michigan, and Oregon, but others need to follow suit.

Provide universal insurance coverage for evidence-based treatment of nicotine dependency

Despite the demonstrated effectiveness of various tobacco cessation tools, including nicotine replacement therapy and counseling, access to these products and services remains limited [32–35]. Smoking levels among low-income populations are high [14], yet nicotine replacement therapy is expensive and is often not covered by insurance. For example, very few health-management organizations cover the cost of pharmaceutical treatment for cessation [36]. Fewer than half of state Medicaid programs cover cessation treatment, and only 10 allow reimbursement for over-the-counter cessation products [37].

Studies have concluded that increased access to proven cessation therapies would enhance the impact of cessation interventions by encouraging more smokers to attempt to quit [32, 33, 38]. By providing universal coverage of evidence-based cessation treatments, these therapies would be accessible to more smokers and could thus have a significant impact on the burden of disease in the population. In addition, Curry *et al*. have shown that such coverage could be cost-effective and even cost-saving [39].

Develop creative strategies for smoking cessation using under-utilized channels

Currently, best practice guidelines for cessation are disseminated passively to physicians, public health practitioners, and the public. This information is available in journals, on Web sites, and through various training programs and directed mailings throughout the country. However, access to cessation information and programs continues to be limited. More creative dissemination strategies need to be developed and utilized, and programs need to be crafted that appeal to diverse target audiences. One example would be to develop a program that promotes cessation among blue-collar and service industry workers.

The prevalence of tobacco use among blue-collar and service-industry workers is higher than that among the general public [40–44]. In addition, these workers are more likely than white-collar workers to be exposed to ETS, since their worksites are less likely to have smoke-free policies [45, 46]. In order to promote smoking cessation among blue-collar and service-industry workers, public health experts need to develop effective programs in collaboration with the labor unions that represent these workers. When tobacco use and exposure to ETS are defined in terms of occupational safety and potential reductions in sick leave and health-care costs, there is an inherent appeal not only to unions and management but also employees. Evidence from worksite programs has shown that when workers are aware that employers are taking action to reduce occupational hazards, they are more likely to participate in employer-sponsored smoking cessation programs [47].

Physical activity

Physical activity has numerous mental and physical health benefits, including reductions in the risk of premature mortality, cardiovascular disease, hypertension, diabetes, and osteoporosis [48]. Among these many benefits are a reduced risk of colon and breast cancer, and possibly a reduced risk of lung and prostate cancer. In addition, physical activity is an important component of weight control and weight reduction, which is critical because overweight is itself an important risk factor for cancer and is increasing rapidly in the United States [49].

Fortunately, the negative effects of a sedentary lifestyle are reversible: evidence shows that increasing one's level of physical activity, even after years of inactivity, can reduce mortality risk [50] – and the level of activity necessary to do so is not as vigorous as was once believed. Walking briskly for at least 30 minutes a day will lower individuals' risk of premature death, heart disease, stroke, diabetes, and colon cancer [48, 51–53].

Despite these vast benefits, both adult and adolescent populations in the United States are remarkably seden-

tary. About 28% of adults are not physically active at all, and another 27% are not regularly active, according to the Surgeon General's guidelines (which recommend a minimum of 30 minutes of moderate activity a day) [54]. Statistics are equally alarming for adolescents: about 14% of young people report no recent physical activity, including that of light to moderate intensity [55]. Obviously, this is of great public health concern and warrants immediate attention.

Policy recommendations to promote physical activity

Policy approaches to increasing physical activity have the potential to influence large segments of the population simultaneously and, therefore, can often be less costly (on a *per-capita* basis) and more enduring than approaches that focus on convincing people to be more active [56]. Rather than persuade individuals to change, policies and other environmental approaches aim to make it easier for people to choose and maintain physically active lifestyles. They do so by changing social norms (for example, making it more acceptable to commute to work by bicycle or foot or to exercise during the lunch hour) or by changing the environment (for example, improving road and sidewalk conditions for pedestrians and cyclists or making workplace stairways as safe, well-lit, and accessible as elevators).

To date, few studies have assessed the effects of environmental and policy approaches to increasing physical activity [56, 57]. However, the history of tobacco control in the United States is informative, and several conclusions can be applied to the development of physical activity strategies. First, to bring about notable change in ingrained behaviors, and to have the change diffuse through the population, time is needed to ignite and build a social movement at non-governmental levels [58]. Such a social movement can only result from local-based programs and initiatives being taken up at multiple venues, including schools, workplaces, and the outdoor environment. A second lesson from the tobacco control effort is that, once a social movement is strong enough to induce government leaders and policymakers to bring about formal legal and policy changes, the pace of behavior change in the population accelerates [58]. In the case of smoking, entrenched norms and values have yielded, and will hopefully continue to yield, to the sustained efforts of the public health movement to counter them.

Can public health evidence of the detrimental effects of sedentariness induce a social movement that will lead to the changing of values, behavior, and ultimately laws and regulations? Because our modern society is currently structured to promote widespread sedentariness, and because sedentariness is not associated with the same extremely high health risk of smoking, it may be more difficult than it was with smoking to spur a social movement. However, as individuals in our population continue to enjoy longer lifespans – and as evidence continues to mount demonstrating that physical activity can help individuals maintain the strength and coordination necessary to function in their daily lives – physical activity should come to be seen as one of the best guarantors of a high quality of life in older adulthood.

Provide adequate funding to strengthen physical activity initiatives in local and state health departments

By incorporating the promotion of physical activity into the mission and objectives of local and state health departments, and having these departments maintain a trained staff that focuses on physical activity, a strong foundation for environmental and policy action can be built [56]. Such action should ideally involve many groups, both public and private, who have the promotion of physical activity as part of their mission. For example, state and local health departments can actively collaborate with other public agencies, such as the departments of parks and recreation, education, and transportation, to develop consistent and unified plans that encourage increased physical activity [56]. Parks might charge lower fees (or none at all) to visitors who are on foot or bicycle, the education department might develop a curriculum regarding the health benefits of physical activity and the environmental and esthetic benefits of a decrease in automobile usage, and the transportation department might work in conjunction with community employers to develop and enforce incentives for non-automotive commuting. With adequate funding and active collaboration, health departments can help to institutionalize new social norms around physical activity.

Increase availability of and access to school-based physical activity programs

The importance of instilling good health habits in youth cannot be overemphasized. The early development of healthy habits not only helps to maintain and improve the immediate health of youth, but there is also compelling evidence that such habits track into adulthood. This is certainly true for tobacco [6], and data show that it is also so for physical activity [59, 60]. A study from the Minnesota Heart Health Program found that individuals who displayed high

levels of physical activity in youth also displayed high levels of physical activity as they crested into adulthood [60].

Schools are one effective intervention point for increasing youth and adolescent physical activity and fitness levels. School-based programs provide an opportunity to reach a large percentage of the nation's youth, and numerous intervention studies have demonstrated that improving school-based physical education classes can increase youth fitness and physical activity levels [61, 62]. These data are so strong that the CDC's Community Prevention Task Force strongly recommends policies and interventions focused on school-based education as one means to increasing levels of physical activity nationwide [61].

Despite demonstrated benefits, however, such recommendations come at a time when participation in physical education is dropping rapidly. Between 1991 and 1997, the proportion of high-school students who were physically active for more than 20 minutes a day in physical education classes decreased from 34% to 22% [63]. Such trends highlight the need for effective local, state, and federal policies that will increase and/or improve the physical education instruction that youth and adolescents receive in the United States.

Though the benefits are less well established, other school-based opportunities also exist for increasing physical activity among youth. Examples include expanding or creating extramural sports at school; providing later bus transportation for youths involved in after-school sports; and providing affordable physical activities during the weekends on school grounds. Developing programs such as these will likely require collaborative partnerships between local boards of education, state departments of education, and other community- and state-level organizations.

Encourage employers to develop wellness programs that promote physical activity

In the past, many individuals engaged in regular physical activity as part of their jobs. For example, at the turn of the twentieth century more than 50% of the US population was employed in agriculture, one of the most physically demanding occupations [64]. Today that figure is less than 20%, with most Americans now working in jobs that have few if any physical demands [64]. Although it is very unlikely that current trends in workplace mechanization and job sedentariness will be reversed, employers can still promote physical activity by providing financial incentives to physically active employees and creating a work environment that is supportive of active lifestyles.

While there is little published evidence on the effectiveness of such employer initiatives [57], there are several case studies highlighting their potential. For example, as part of its employee benefit package the Harvard School of Public Health reimburses faculty and staff for the money they spend on health club memberships and fitness equipment. Similarly, in Palo Alto, California, the city government reimburses employees 7 cents per mile for any local business travel that is done by bicycle. Other employers promote physical activity by incorporating flexible-time policies that allow individuals who commute by bicycle or foot to arrive and leave during non-rush-hour times, providing secure bicycle racks and shower facilities for employees, and ensuring that workplace stairways are safe and well lit.

Programs and policies that promote physical activity benefit not only the employees but also the employers. Workplace fitness programs have been shown to contain health-care costs, reduce absenteeism, increase productivity, and improve employee satisfaction [65]. While these benefits alone might spur employers to offer fitness programs, state and federal governments could provide additional financial incentives, such as tax credits or discounted health premiums.

Allocate federal transportation funds toward the creation of bicycle and pedestrian pathways

Here, the United States might take a lesson from its European counterparts. European countries generally locate bicycle and pedestrian pathways at a safe distance from streets, or they have well-marked bicycle lanes right on the streets. In the United States, however, bicycle lanes (if they exist) are often located on the street with few or no demarcating lines. Such poorly marked lanes greatly reduce the safety and comfort of cyclists and are a strong disincentive for people who contemplate using their bikes for recreation or commuting [56]. In a survey of adults who had ridden a bicycle in the preceding year, 53% said they would commute to work by bicycle if safe designated bike paths or lanes existed. In addition, more than half of the respondents indicated they would walk, or walk more to work, if there were safe pathways protected from automobiles and if crime were not a consideration [66]. These results suggest that the provision of safe and convenient paths would be a strong incentive for individuals to travel by bike or foot.

In 1991, the US Congress enacted the Intermodal Surface Transportation Efficiency Act (ISTEA), which required states to consider cycling and walking in their transportation plans. Although the Act did not require

states to spend federal transportation funds on bicycle and pedestrian projects, it gave them the authority to do so for the first time. Such projects could include the building of new bicycle and pedestrian paths, modification of existing roadways for uses by pedestrians and cyclists, and development or modification of commuting policies that reward walking and cycling. Although ISTEA expired in 1998, Congress chose to re-authorize it with the Transportation Equity Act for the 21st Century (TEA-21). This Act increases the amount of federal funding that is available for bicycle and pedestrian projects but still does not require that states allocate federal funds for this purpose.

Evidence suggests that states have taken advantage of available federal funds but not to the extent that they could [67]. Between 1990 and 1999, the amount of federal transportation money spent on bicycle and pedestrian projects rose from $7 million to $222 million. While this is a significant increase, the proportion of money spent on bicycle and pedestrian projects is still less than 1% of all federal transportation dollars. In addition, there is substantial variability in the amount of money that states choose to spend on these projects. Some states spend only $0.05 per capita, while others spend as much as $6.27.

With federal monies readily available to them, states need to enhance their commitment to the creation and improvement of bicycle and pedestrian pathways. Although some state agencies will clearly do this on their own initiative, others will need to be lobbied. Like tobacco control programming, the success of TEA-21 will depend largely on advocacy, as well as public support from health departments, transportation departments, and local coalitions [56].

Weight maintenance

Excess body fat has long been a problem in the United States, but it is now reaching epidemic proportions. In 2000, 56% of all US adults were overweight (BMI $\geq$ 25 kg/m^2), 38.8 million of whom were obese (BMI $\geq$ 30 kg/m^2) [54]. This is a major public health concern, given that obesity is an important risk factor for many chronic diseases and is responsible for nearly 300,000 deaths each year [68], including a substantial portion from cancer. Data from the American Cancer Society's Cancer Prevention Study II indicate that overweight and obesity account for some 10% of all cancer mortality among men and 15–20% among women (personal communication, J Calle, December 2000).

In terms of site-specific cancers, there is evidence that obesity increases the risk of colorectal, endometrial, breast, uterine, kidney, and esophageal cancer [69–73]. Independent of overweight and obesity, weight gain has also been linked to cancer risk. There is a well-documented association between weight gain in adulthood and the risk of endometrial and postmenopausal breast cancer [74–76].

Policy recommendations to promote weight maintenance

Given its high prevalence and direct relationship with numerous serious chronic conditions, obesity should clearly be a public policy priority. Consistent with the US Dietary Guidelines developed since 1995 [77, 78], the primary goal of such policy should be on weight maintenance rather than weight loss. While there would certainly be health benefits gained if the overweight lost weight and maintained it, from a practical standpoint it is a much more difficult goal for individuals to achieve than to simply avoid new weight gain [79]. Substantial evidence suggests that a policy focused on stemming the tide of weight gain could have a substantial public health impact [79].

Reaching this goal population-wide, however, will require a concerted effort across many different social levels. Unfortunately, for such a widespread and grave public health problem, we currently lack a unified national strategy for preventing overweight and obesity. The development of such a strategy, therefore, should be the highest priority for the coming years [80]. Adequate funding on the federal level should be provided to develop a coordinated, multifaceted, and evidence-based approach to weight control. Tobacco control efforts offer an excellent model of a unified strategy that cuts across the social fabric, addressing the motivations of the individual consumer while also facilitating behavior change through broad environmental interventions.

On the federal level, some obesity and weight control programs currently exist, including the National Heart, Lung, and Blood Institute's (NHLBI) Obesity Education Initiative. However, the activities of such programs need to be better coordinated, expanded, and elevated at least to the level currently afforded to such programs as the NHLBI's National Cholesterol Education Program and National High Blood Pressure Education Program. One positive move in this direction is the recent release of the *US Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity* [81]. Yet this report is only the first solid step in the direction of creating a fully developed, well-funded obesity prevention strategy in the United States.

Until such a time, there are still a number of policies that can help facilitate weight maintenance on the

population level. In particular, increasing physical activity levels is one of the most effective and practical approaches to weight control. Four policies for increasing population-wide activity levels that we have detailed previously include:

1. Providing adequate funding to strengthen physical activity initiatives in local and state health departments.
2. Increasing availability of and access to school-based physical activity programs.
3. Encouraging employers to develop wellness programs that promote physical activity.
4. Allocating federal transportation funds toward the creation of bicycle and pedestrian pathways.

Diet

On a global scale, inadequate diet causes approximately the same proportion of cancers each year as tobacco use. That is, nearly one-third of all cancers (or 3–4 million cases worldwide) are caused by inadequate diet – and thus could be prevented by dietary improvements [69].

In recent years, there has been an explosion of prospective studies on diet and chronic disease, and this has greatly furthered our understanding of cancer etiology [82]. By building on international correlation studies and retrospective case–control studies, prospective cohort studies offer the potential to evaluate diet–disease relationships free from recall bias and to correct for measurement error. Here we summarize major areas of advance according to components of the American diet.

Fruits and vegetables

Apart from the effects of overweight and obesity, the most abundant evidence for an effect of diet on cancer incidence has been related to a lower risk with greater intake of fruits and vegetables. However, the large majority of this evidence has arisen from case–control studies, and prospective data have been far less consistent. In fact, prospective cohort studies are supporting fewer and fewer associations between overall fruit and vegetable intake and the risk of cancer.

Despite the diminishing evidence with respect to cancer, fruits and vegetables are still recommended as part of an overall healthy diet. These foods lower the risk of hypertension, coronary heart disease, and ischemic stroke, in addition to containing vitamins and minerals that protect against a host of other conditions [69].

Red meat

Consumption of beef, pork, and lamb has declined dramatically in the United States over the past 40 years [83], probably because of increasing concern about the effects of meat on health. While red meat is an excellent source of protein and iron, it also contains large amounts of saturated fat, which can raise the level of cholesterol in the blood. In terms of cancer risk, high intake of red meat has been linked to an increased risk of colon cancer and possibly kidney, prostate, and pancreatic cancer [69, 84].

Milk and dairy products

The impact of dairy products on cancer risk has not been well studied, and most links between the two have been made only indirectly [69]. Although available evidence suggests that milk and other dairy products may raise the risk of prostate cancer, and that higher lactose intake may raise ovarian cancer risk, this topic will require further research before serving as a basis for policy [69, 85, 86].

Nutrients

There is a growing body of evidence that both macronutrients and micronutrients affect cancer risk. For macronutrients (the major nutrients such as fat, carbohydrates, and protein that the body needs in large quantities to function properly), only one association currently reaches beyond the possible category. There is evidence of a probable relationship between animal fat and prostate cancer. For micronutrients, however, some stronger links exist, particularly that between folate and colorectal cancer. A number of studies have found that, as folate intake increases, the risk of colorectal cancer (as well as polyps) decreases [87–90]. In addition, there is evidence that the risk of colorectal cancer may also be lowered with calcium supplementation [91, 92].

Policy recommendations to promote healthy eating

There is clear and convincing evidence that a diet rich in plant foods and moderate in animal products lowers the risk of cardiovascular disease, diabetes, and other important health outcomes. While the evidence linking diet and cancer is not as strong, a large number of studies do suggest that the diet described above might also lower cancer risk modestly. Based on the collective evidence, policies should be implemented that provide access to healthy foods and nutrients.

Support efforts to provide healthy meals and snacks in schools and workplaces

Schools and workplaces are excellent channels for dietary interventions. Not only do most youth and

adults in the United States spend a great deal of their waking hours at school and work (respectively), but many schools and worksites have institutionalized food services that can facilitate generalized changes to menu and food preparation.

Over 97,000 schools in the United States offer lunch to students as part of the National School Lunch Program [93], and over 72,000 offer breakfast as part of the School Breakfast Program [94]. While the quality of food provided to students in these programs has improved since the institution of the federal School Meals Initiative for Healthy Children in 1995, there is still room for substantial improvement [95]. For example, a recent report found that only 12% of elementary schools met federal recommendations for the saturated fat content of school lunches [95].

Numerous school-based intervention studies have demonstrated not only that food service menu choices can be made healthier but also that, when combined with supporting activities, the diets of students can be improved [96–99]. One such program, Eat Well & Keep Moving, significantly increased students' intake of fruits, vegetables, and fiber and decreased their intake of saturated fat [99].

Worksite interventions have had similar success, with several studies showing increased fruit and vegetable consumption among intervention groups compared to controls [100–103]. The interventions utilized in these studies ranged in intensity from peer education [103] to worksite environmental changes [100].

All of this points to the need for public and institutional policies that will encourage and allow schools and worksites to offer healthier food choices. Even in schools and worksites that do not have cafeterias, healthy changes can still be made by improving the food offerings in vending machines [104, 105]. Vending machines are a significant source of meals and snacks for some people, even if their institutions do have cafeterias. Snacks that are high in *trans*-fatty acids, such as most cookies, can be replaced with fresh fruits and other healthy snacks, and the soda in vending machines can be replaced at least partially with bottled water and 100% fruit juice.

Increase access to multivitamins containing folic acid

Given that vitamins and minerals are plentiful in fruits, vegetables, whole grains, and many dairy products, a varied and well-balanced diet is all most people need to meet the Recommended Dietary Allowances and Dietary Reference Intakes. However, to provide extra assurance against deficiencies, a safeguard measure would be for individuals to also take a multivitamin each day. This artificial supplementation does not supplant the need for a healthy diet, but instead provides assurance that daily intakes of specific nutrients are guaranteed. For instance, the folic acid contained in multivitamins has long been known to protect against neural tube defects [106] and has more recently been shown to be associated with lower risk of colon cancer [107] and heart disease [108].

Despite the preventive potential of multivitamins, they are currently used by less than 50% of the US population [109]. One potential barrier to more widespread use might be cost, since multivitamins are an out-of-pocket expense for individuals choosing to use them. For example, the Food Stamp Program does not currently allow recipients to spend their grocery coupons on dietary supplements. However, this has the potential to change under the 2001 Farm Bill currently being considered by the US Senate. The bill includes a provision that would make it permissible to purchase vitamin supplements with food, and also requires a report on the technical issues, economic impacts, and health effects associated with making this change in the Food Stamp Program.

Another avenue of increasing access to multivitamins is through health plans. To our knowledge, most health plans do not currently provide coverage for vitamin and mineral supplements. However, coverage for multivitamins containing folate has the potential to be cost-effective and possibly even cost-saving.

Alcohol

Because alcohol use tends to be associated with cigarette use and other high-risk behaviors, its independent effects on cancer have long been questioned. However, in 1988, on the basis of abundant epidemiologic evidence, the International Agency for Research on Cancer concluded that alcohol is in fact a Group 1 carcinogen and an independent risk factor for cancers of the upper aerodigestive tract and liver [69]. Since that report, a large body of evidence has confirmed that alcohol use also increases the risk of breast cancer [110] and probably colon cancer [107].

Although numerous studies have compared the effects of beer, wine, and liquor, the type of alcohol consumed does not appear to influence cancer risk as much as the amount [69]. For cancers of the upper aerodigestive tract, breast, colon, and rectum, there is a dose–response relationship, such that even low or moderate intake increases risk slightly. For liver cancer, the most important factor is heavy and persistent use, such as that defined by alcoholism.

In contrast to its harmful effects on cancer and other conditions, alcohol has proven benefits in terms of cardiovascular health. Moderate alcohol consumption reduces the risk of death from coronary heart disease by 20–40% [111, 112]. Because cardiovascular disease is the leading cause of death in middle age and beyond, a reduction in cardiovascular disease mortality risk will translate, for many populations, into a reduction in total mortality risk. Clearly, there is a need to balance this benefit of alcohol with its many risks.

Policy recommendations on alcohol consumption

Given the epidemiologic evidence, it is clear that reducing alcohol consumption would lower the incidence of liver, breast, mouth, laryngeal, esophageal, and probably colorectal cancer. However, the evidence from cancer epidemiology alone is not sufficient to warrant broad policy action in this case. The risk–benefit equation for alcohol intake is much more complex than for physical activity or tobacco cessation, where shifts in the population distribution would clearly benefit the population as a whole, as well as the individuals that compose that population. Although shifting the population distribution of alcohol intake downward would most likely lead to decreases in the incidence of cancer, as well as accidents and injury, it would also lead to a higher rate of cardiovascular disease. Below we discuss the implications of this risk–benefit equation on public health policies and recommendations.

The optimal public health guidelines on alcohol consumption will not be the same across or even within populations, since the importance of cardiovascular disease, injuries, and trauma varies enormously with age and sex. For younger populations, the risk of alcohol-related injury and death is much higher than the age-specific risk of death from chronic disease. For example, among US men aged 15–29, deaths from injuries and other external causes account for 75% of all deaths, compared with 4% from cardiovascular diseases [113]. In addition, alcohol consumption in this age group is not likely to protect against cardiovascular mortality later in life, since many of the important effects of alcohol on high-density lipoproteins and clotting components are acute [114]. Therefore, the negative effects of alcohol greatly outweigh the potential benefits in younger populations.

Guidelines for alcohol consumption also differ by sex. Women are advised to drink less alcohol than men because women are smaller in size, have lower age-specific risks of cardiovascular disease, and have greater susceptibility to liver damage. In addition, women face the relatively high risk of breast cancer, which appears to be increased by even one drink per day of an alcoholic beverage [115].

The bottom line of all of the observational studies in the US that have examined the relationship between alcohol consumption and total mortality is that drinking one drink a day is healthier than not drinking. It must be recognized, though, that there are social risks in promoting a population-wide alcohol policy that discourages abstention, even if the policy encourages only light to moderate consumption. There is no evidence that moderate drinking is harmless. For instance, there are few data on the shape of the dose–response curve for alcohol and the risk of a motor vehicle accident. Although it is assumed that there is a threshold effect (*i.e.* that motor vehicle accidents occur only above a certain blood alcohol level), there are no conclusive data supporting this assumption [116]. It is likely that this threshold notion is too simplistic.

From a population perspective, the shape of such dose–response curves is important. Further, any public health recommendation that encourages light to moderate drinking over abstinence will likely increase the number of heavy drinkers in the population, since population distributions of risk factors tend to shift, either downward or upward, as an entity [116]. The problem of alcohol consumption in many populations is one of maldistribution, with substantial proportions abstaining and substantial proportions consuming at a hazardous level [117]. There is no precedent for a public health campaign that simultaneously seeks to "pull in" both tails of a risk factor distribution, in this case reduction in the prevalence of both abstention and heavy drinking [117].

Some researchers have noted that it is unethical for governments and other public institutions to promote low alcohol intake as a disease-preventive measure, because of the potential adverse risks at the population level. However, they also note that it is similarly unethical to promote abstinence [117]. The ethical course then may be limited to public education campaigns that focus on reductions in hazardous drinking and that encourage those who choose to drink to do so moderately, as suggested by the current Dietary Guidelines for Americans [78, 117].

Conclusion

As summarized in this report and elsewhere, there is a well-established link between lifestyle factors and cancer risk, and there is also evidence that population-wide changes in these factors can significantly reduce the

burden of cancer. Perhaps the most widely recognized example of this in the United States is the reduction in lung cancer that has occurred as a result of declining smoking rates [118]. Another well-known example is the national skin protection program in Australia, which has led to reductions in sun exposure and subsequent declines in melanoma [119]. These examples and others attest to the success of population-wide prevention strategies, and support the contention that it is time to allocate greater resources toward the implementation of existing epidemiologic knowledge.

Numerous researchers have attempted to estimate the extent to which the US cancer burden could be reduced if positive changes were to occur in terms of lifestyle factors. While the specific methods and results of analyses on this vary, they are all remarkably consistent in pointing to the benefits of reducing tobacco use, increasing physical activity, decreasing the prevalence of obesity, improving diet, keeping alcohol consumption at low to moderate levels, and being screened regularly for cancer. Using relatively conservative goals for future reductions in the prevalence of behaviors such as tobacco use, poor diet, and lack of colon cancer screening, Byers *et al*. predicted that, by 2015, overall cancer incidence and mortality could be reduced by 13% and 21%, respectively, compared to 1990 baseline rates [120].

To achieve such a significant reduction, we must reframe our approach to cancer epidemiology and prevention. The current weight of evidence on cancer and lifestyle factors is so great that it behooves a move toward action rather than a continued focus on pure epidemiologic study and clarification of biologic mechanisms. It is no longer enough to simply identify behavioral risk factors or set goals for reductions in these risk factors. Research and policy must now turn toward ways to actually bring about population-wide changes in lifestyle. This will likely require a multifaceted approach, as suggested by McKinlay's population model of prevention [121].

Strategies must be implemented not only at the individual level but also at the macro or state level, so as to strengthen social norms and support behavior change. The policy recommendations outlined in this report are meant to address this by highlighting the changes that need to occur on many different social levels (individual, interpersonal, and environmental) if prevention is to move forward.

We are currently at a crossroads of cancer prevention research. We have amassed volumes of epidemiologic research, and now it is time to put a greater emphasis on applying this knowledge. With this in mind, the current challenge before the public health community is to develop prevention strategies so that individual behavior changes are reinforced by structural changes, and all components of the prevention agenda are moved forward in a coordinated and cohesive manner.

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Explaining the Decline in Coronary Heart Disease Mortality in England and Wales Between 1981 and 2000

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Background—Coronary heart disease mortality rates have been decreasing in the United Kingdom since the 1970s. Our study aimed to examine how much of the decrease in England and Wales between 1981 and 2000 could be attributed to medical and surgical treatments and how much to changes in cardiovascular risk factors.

Methods and Results—The IMPACT mortality model was used to combine and analyze data on uptake and effectiveness of cardiological treatments and risk factor trends in England and Wales. The main data sources were published trials and meta-analyses, official statistics, clinical audits, and national surveys. Between 1981 and 2000, coronary heart disease mortality rates in England and Wales decreased by 62% in men and 45% in women 25 to 84 years old. This resulted in 68 230 fewer deaths in 2000. Some 42% of this decrease was attributed to treatments in individuals (including 11% to secondary prevention, 13% to heart failure treatments, 8% to initial treatments of acute myocardial infarction, and 3% to hypertension treatments) and 58% to population risk factor reductions (principally smoking, 48%; blood pressure, 9.5%; and cholesterol, 9.5%). Adverse trends were seen for physical activity, obesity and diabetes.

Conclusions—More than half the coronary heart disease mortality decrease in Britain between 1981 and 2000 was attributable to reductions in major risk factors, principally smoking. This emphasizes the importance of a comprehensive strategy that promotes primary prevention, particularly for tobacco and diet, and that maximizes population coverage of effective treatments, especially for secondary prevention and heart failure. These findings may be cautiously generalizable to the United States and other developed countries. **(*Circulation*. 2004;109:1101-1107.)**

Key Words: coronary disease ■ mortality ■ modeling ■ risk factors ■ treatment

Coronary heart disease (CHD) remains the most common cause of death in the United States and the United Kingdom.[1–4] However, CHD mortality rates have decreased by 50% in most industrialized countries since the 1970s. In the United States, the decline was steeper in the 1980s and then flattened slightly in the last decade. However, in the United Kingdom, the decline has been slower, and CHD mortality rates are still higher than in the United States[2] (Figure 1).

Explanations for the mortality decreases remain controversial.[3] Many authors credit the increasingly widespread use of effective therapies such as thrombolysis, aspirin, ACE inhibitors, statins, and coronary artery bypass surgery.[5,6] Others highlight reductions in major cardiovascular risk factors such as cholesterol, smoking, and blood pressure.[3,7] Although both components are probably important, answering this complex question seems difficult.

Some researchers have therefore used models of various degrees of sophistication to try to explain the observed declines in CHD mortality.[8] The majority consistently suggest that risk factor improvements explain more of the mortality decline than do treatments. For example, it has been estimated that the proportion of mortality decline attributable to risk factor reductions was 57% in the United States between 1980 and 1990[9]; 60% in Auckland, New Zealand, between 1974 and 1981[10] and 52% between 1982 and 1993[11]; and 60% in Scotland between 1975 and 1994.[12] Since then, however, many effective therapies have been introduced.[13]

A better understanding of the CHD mortality decrease in Britain, the United States, and other countries is clearly essential both to predict future trends and to clarify policy options for CHD prevention.[13,14] We have therefore examined how much of the CHD mortality decrease in England and Wales between 1981 and 2000 can be attributed to "evidence-based" medical and surgical treatments and how much to changes in major cardiovascular risk factors.

Methods

The cell-based IMPACT mortality model, previously validated in Scotland[12] and New Zealand,[11] was further developed and refined. We identified and incorporated data for men and women 25 to 84 years old in England and Wales, detailing (1) CHD patient numbers, (2) uptake of specific medical and surgical treatments, (3) population trends in major cardiovascular risk factors (smoking, total cholesterol, hypertension, obesity, diabetes, physical activity, and socioeco-

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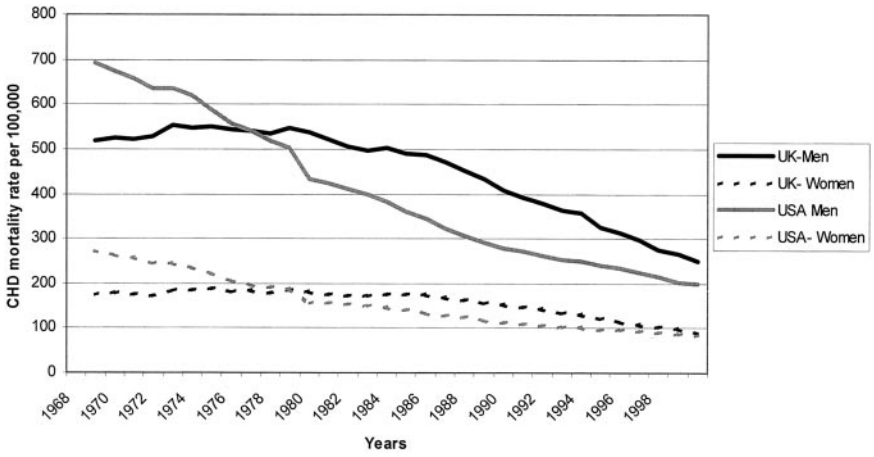

Figure 1. Age-standardized death rates from CHD for men and women in United Kingdom and United States between 1968 and 2000.

nomic deprivation), (4) effectiveness of specific cardiological treatments, and (5) effectiveness of specific risk factor reductions.

Identification and Assessment of Relevant Data

Information on population, demographic changes, mortality, and myocardial infarction incidence was obtained principally from routine health statistics from the Office for National Statistics and the British Heart Foundation's Annual CHD Statistics.[2] The number of patients admitted to hospital with myocardial infarction, angina, and heart failure was obtained from Hospital Episode Statistics. Patients undergoing cardiopulmonary resuscitation in the community or in hospital were enumerated from various surveys. Information on patients undergoing CABG surgery and angioplasty came from the United Kingdom Cardiac Surgical Register and the British Cardiovascular Intervention Society's audit returns, respectively.[15,16] Surviving patients eligible for secondary prevention therapies after myocardial infarction, CABG surgery, or angioplasty were calculated by use of routine statistics and revascularization registers.

The number of patients in the community with treated or untreated hypertension or angina was calculated using the 1998 Health Survey for England and the British Regional Heart Study. The number of treated and untreated heart failure patients in the community was obtained from General Practice returns and survey data.

Information on treatment prescription and uptake was obtained from various national and local clinical audits and surveys. Population risk factor trend data were obtained primarily from the British Regional Heart Study, the General Household Survey, and the Health Survey for England.

Data on the efficacy of therapeutic interventions and the mortality reduction from specific population cardiovascular risk factor changes were obtained from published randomized controlled trials, meta-analyses, and cohort studies. Full details of data sources are provided in Appendices 1 through 4 (see the online-only Data Supplement).

Decrease in CHD Deaths

The number of CHD deaths expected in 2000 if the mortality rates in 1981 had persisted was calculated by indirect age standardization, using 1981 as a base year. The CHD deaths actually observed in 2000 were then subtracted to provide the decrease in CHD deaths between 1981 and 2000.

IMPACT Model

This Microsoft Excel cell-based mortality model has been described in detail elsewhere.[8,11] The numbers of CHD deaths prevented or postponed by each specific cardiac intervention and by each risk factor change were calculated for England and Wales for the year 1981 and again for the year 2000.

The model aimed to include all medical and surgical treatments provided in 1981 and 2000. These interventions are listed in Table 1 and included all the interventions considered in earlier versions of the IMPACT model[11,12] plus primary angioplasty and stenting for myocardial infarction, statins for primary prevention, platelet glycoprotein IIb/IIIa inhibitors for unstable angina, and spironolactone and β-blockers for heart failure (Table 1; see also Appendices 2 and 3 in the online-only Data Supplement).

The mortality reduction for each treatment was calculated by use of the relative mortality reduction reported in published meta-analyses and trials applied to the case-fatality observed in unselected patient cohorts. Survival benefit over a 1-year time interval was used for all treatments.

Polypharmacy Issues

The potential effect of multiple treatments in an individual patient was examined using the Mant and Hicks cumulative relative benefit approach: relative benefit$=1-[(1-\text{treatment A})\times(1-\text{treatment B})\times\ldots$.[17]

Treatment Compliance and Overlaps

To avoid double counting, potential overlaps between different groups of patients were identified and adjustments were made (see Appendix 6 in the online-only Data Supplement). For example, $\approx$50% of the patients having CABG surgery have a previous myocardial infarction.

Compliance, the proportion of treated patients actually taking therapeutically effective levels of medication, was assumed to be 100% in hospital patients, 70% in symptomatic community patients, and 50% in asymptomatic community patients.[18]

Deaths Prevented or Postponed in 1981

A number of effective therapies were already in limited use in 1981. These included CABG surgery, cardiopulmonary resuscitation, β-blockers for acute myocardial infarction, diuretics for acute left ventricular heart failure, and therapy for moderate and severe hypertension (defined as a diastolic blood pressure $>$105 mm Hg). Precise patient data for some of these interventions, such as CABG, and eligible hypertensives were available from the data sources detailed above. Others were estimated after consultation with cardiologists in practice in 1981.

Risk Factor Trends and Mortality Benefits

For risk factor changes, the model uses regression (β) coefficients obtained from large cohort studies and MONICA analyses (Appendix 8 in the online-only Data Supplement). Each β coefficient quantifies the independent relationship between population change in a specific CHD risk factor (such as smoking, cholesterol, or blood pressure) and the consequent change in population mortality rate from CHD. These coefficients were reviewed and updated[8]). The subsequent reduction in deaths produced by the decrease in each major risk factor was then estimated as the product of 3 variables: the number of CHD deaths observed in 1981 (the base year), the relative reduction in that risk factor, and the β coefficient.

TABLE 1. Deaths Prevented or Postponed by Medical and Surgical Treatments in England and Wales in 2000

Treatment	Patients Eligible	Treatment Uptake, %	Absolute Risk Reduction	Deaths Prevented or Postponed			Proportion of Overall Deaths Prevented or Postponed, %, Best Estimate
				Best Estimate	Minimum Estimate	Maximum Estimate	
Acute myocardial infarction	66 196			4779	3118	7928	7.7
Community resuscitation	3045	48	0.110	799	742	958	1.3
Hospital resuscitation	7282	99	0.208	1453	680	2185	2.4
Thrombolysis		46	0.033	1321	493	1636	2.1
Aspirin		94	0.024	1949	1132	2780	3.2
Primary angioplasty		1	0.057	38	13	207	0.1
β-Blockers		4	0.008	21	11	38	0.0
ACE inhibitors		19	0.011	172	47	123	0.3
Total secondary prevention				6899	4587	12 670	11.2
Secondary prevention after infarction	313 378			3844	2850	5059	6.2
Aspirin		56	0.009	1263	641	1991	2.0
β-Blockers		34	0.014	969	569	1636	1.6
ACE inhibitors		19	0.014	442	336	1439	0.7
Statins		25	0.018	459	432	1341	0.7
Warfarin		4	0.009	100	58	233	0.2
Rehabilitation		23	0.017	673	304	1231	1.1
Secondary prevention after revascularization	315 680		0.028	3055	1737	7610	4.9
Chronic angina				3424	1907	5889	5.5
CABG surgery (1990–2000)	187 416	100	0.009	1935	1124	2375	3.0
Angioplasty (1990–2000)	112 404	100	0.005	559	160	814	0.8
Aspirin in community	1 763 633	55	0.001	1104	627	2117	1.6
Unstable angina	67 376			912	620	1622	1.5
Aspirin and heparin		59	0.012	467	334	718	0.8
Aspirin alone		30	0.013	234	127	657	0.4
Platelet IIb/IIIa inhibitors		48	0.007	211	158	247	0.3
Heart failure			...	7760	5957	17 356	12.6
Hospital	34 689	62	...	4756	4228	11 762	7.5
Community	242 088	56		3211	1802	5997	5.0
Hypertension treatment	13 352 868	53	0.001	1888	875	3166	3.1
Statins for primary prevention	7 630 759	3	0.002	143	47	410	0.2
Total treatment effects, 2000				25 805	17 110	49 042	41.8

A separate method was used for obesity, diabetes, physical activity, and socioeconomic deprivation, given the absence of suitable β coefficients (Appendix 5 in the online-only Data Supplement).[11,12] Population-attributable risk fraction (PAR) was calculated by use of the conventional formula: PAR=prevalence×(relative risk−1)/[prevalence×(relative risk−1)]+1.

The number of CHD deaths attributable to each specific risk factor was then calculated for 1981 and for 2000. The difference between the two values then represented the deaths prevented or postponed because of the change in that specific risk factor in the population.

Model Validation: Comparison With Observed Mortality Decreases

The model estimate for the total deaths prevented or postponed by all treatments plus all risk factor changes was summed and then compared with the observed decreases in mortality for men and women in each specific age group. On an a priori basis, any shortfall in the overall model estimate was then formally attributed to other, unmeasured risk factors.[8,11]

Sensitivity Analyses

Because of the uncertainties surrounding many of the values, a multiway sensitivity analysis was performed using the analysis-of-extremes method.[19] Illustrative examples of specific analyses and calculations are shown in Appendix 5 in the online-only Data Supplement.

Results

In England and Wales between 1981 and 2000, CHD mortality rates decreased by 62% in men and 45% in women 35 to 84 years old. There were 68 230 fewer CHD deaths than expected from baseline mortality rates in 1981.

Medical and Surgical Treatments

Medical and surgical treatments together prevented or postponed ≈25 805 deaths (minimum estimate, 17 110; maximum estimate, 49 042) (Table 1). This represented ≈42% of

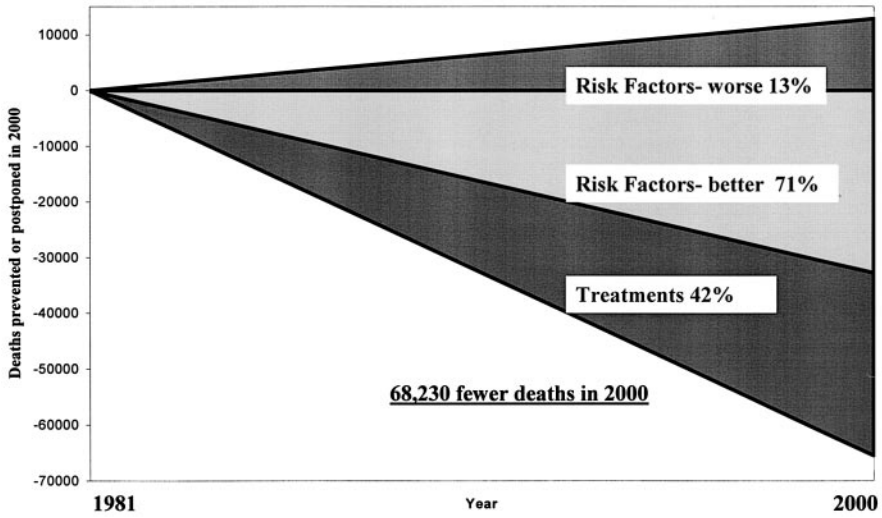

Figure 2. CHD deaths prevented or postponed by treatments and risk factor changes in England and Wales population, 1981 to 2000.

the total mortality decrease, after allowance for treatments given in 1981 (Figure 2). Substantial contributions came from specific treatments in individuals for secondary prevention (11.2%), heart failure (12.6%), acute myocardial infarction (7.7%), angina (7.0%), and hypertension (3.1%).

Approximately 4779 deaths were prevented or postponed by immediate treatments for acute myocardial infarction; the biggest contributions came from cardiopulmonary resuscitation, aspirin, and thrombolysis (Table 1). Coronary artery bypass surgery and angioplasty were estimated to prevent or postpone ≈1935 and 559 deaths, respectively, accounting for 3.8% of the total (Table 1).

Adjustment for Polypharmacy in Individual Patients

Applying the Mant and Hicks equation to the uptake of multiple medications in individual patients would reduce the total deaths prevented or postponed (25 830) by ≈2118 (395 in acute myocardial infarction, 800 in heart failure patients, and 923 in secondary prevention) (Appendix 7 in the online-only Data Supplement).

Major Cardiovascular Risk Factors

Changes in the major cardiovascular risk factors together produced a best estimate of 35 944 fewer deaths (minimum estimate, 23 123; maximum, 62 195) (Table 2). This therefore accounted for some 58% of the total mortality decrease between 1981 and 2000. The biggest contribution came from the reduction in smoking (48.1%), along with decreases in serum total cholesterol levels (9.6%), blood pressure (9.5%), and deprivation (3.4%) (Figure 3). These mortality reductions reflected a substantial decline in smoking prevalence and smaller reductions in mean blood pressure, total cholesterol, and deprivation (Table 2).

Adverse trends were seen for obesity, physical activity, and diabetes. They together caused ≈7650 additional CHD deaths (Table 2). The prevalence of obesity increased by 186%, resulting in an estimated additional 2095 CHD deaths. Diabetes prevalence increased by 66% with ≈2890 additional CHD deaths, and indirect evidence suggested a 30% decrease in physical activity, with some 2660 additional deaths (Table 2).

Sensitivity Analyses, Validation, and Model Fit

Figure 3 demonstrates the results of the sensitivity analysis. The proportional contributions of specific treatments and risk factor changes to the overall decrease in CHD mortality in England and Wales between 1981 and 2000 remained relatively consistent (Figure 3). Thus, all secondary prevention

TABLE 2. Deaths Prevented or Postponed as a Result of Population Risk Factor Changes in England and Wales 1981–2000

Risk Factors	% Change in Risk Factor 1981–2000	β Coefficient	Deaths Prevented or Postponed (No.)			Proportion of Overall Deaths Prevented or Postponed, %, Best Estimate
			Best Estimate	Minimum Estimate	Maximum Estimate	
Smoking	−34.0	0.51	29 715	20 037	44 677	48.1
Population blood pressure	−7.7	1.67	5868	4246	15 469	9.5
Cholesterol	−4.2	2.46	7900	5284	16 692	9.6
		Relative Risk				
Deprivation	−6.6	1.24	2126	1063	3189	3.4
Physical activity	−30.6	0.50	−2662	−1491	−3460	−4.3
Obesity	+186.2	1.57	−2097	−1339	−2587	−3.4
Diabetes	+65.6	4.24	−2888	−2567	−4685	−4.7
Total risk factor effects	...	...	35 944	23 123	62 195	58.2

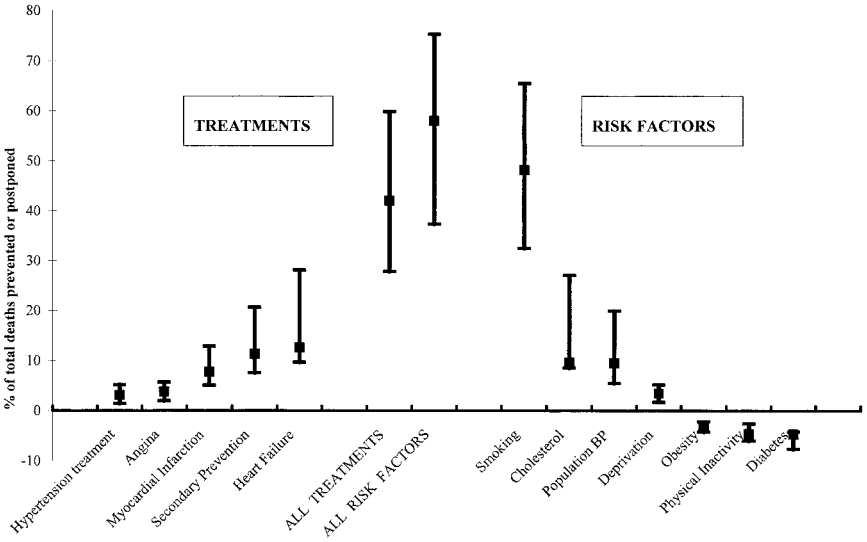

Figure 3. Proportional contributions of specific treatments and risk factor changes to CHD mortality reduction in England and Wales, 1981 to 2000: results of a sensitivity analysis. ■ Best estimate; –, minimum and maximum estimates.

treatments together accounted for ≈11% of the total mortality decrease of 68 230. The minimum contribution was 7% and the maximum, 21%. This contribution therefore remained consistently larger than that for acute myocardial infarction or hypertension (Figure 3).

The agreement between the estimated and observed mortality decreases for men and women in each age group was generally good (Table 3). Overall, the model accounted for 89% of the total mortality decrease in England and Wales between 1981 and 2000 (95% in men and 77% in women). As planned, the remaining 11% was attributed to other, unmeasured factors such as dietary changes and life-course effects.

Discussion

CHD mortality decreased by more than 50% between 1981 and 2000 in England and Wales. Approximately 40% of the UK decrease was attributable to the combined effects of modern cardiological treatments and almost 60% to reduction in major risk factors, particularly smoking. This is consistent with the majority of other studies in the United States,[20] Europe,[21] Scotland,[12] and New Zealand.[11] Although Hunink et al[9] attributed 71% of the recent US decline to "treatments," this exception was more apparent than real. It principally reflected the categorization of risk factor decreases in individual patients with recognized CHD as "treatment benefits." In the entire US population, 50% of the CHD mortality decline was actually explained by risk factor reductions. Furthermore, Hunink et al did not report on specific medical therapies.

Modern cardiological treatments together prevented or postponed ≈26 000 deaths in 2000. Irrespective of whether best, minimum, or maximum estimates were used, the most substantial contributions came from secondary prevention and heart failure treatments. However, although heart failure treatments resulted in >7700 deaths prevented or postponed because of the relatively short life expectancy in these patients, this gained only ≈25 360 life-years (just 2% of the total life years gained by cardiological treatments and population risk factor changes in England and Wales in 2000).[22]

TABLE 3. Model Validation: Estimated vs Observed Changes in CHD Deaths in England and Wales 1981–2000

	Age Group, y						
	25–34	35–44	45–54	55–64	65–74	75–84	Total
Men							
Observed fall in CHD deaths	168	1314	5571	10 685	15 342	11 740	44 822
Estimated fall in CHD deaths	165	1305	5582	10 452	13 349	11 689	42 542
Discrepancy	−3	−10	10	−234	−1993	−51	−2280
Model fit: estimated fall/observed fall in CHD deaths	98%	99%	100%	98%	87%	100%	95%
Women							
Observed fall in CHD deaths	28	155	998	3054	7479	11 695	23 409
Estimated fall in CHD deaths	21	151	1011	3212	7411	6246	18 053
Discrepancy	−7	−4	13	158	−68	−5449	−5356
Model fit: estimated fall/observed fall in CHD deaths	75%	98%	101%	103%	99%	53%	77%

Revascularization from CABG surgery and angioplasty together accounted for only 4% of the total mortality decrease, much as in the United States.[23,24] This is a disappointingly small contribution, particularly when considering the large financial and political resources being consumed.[13,24,25]

Thrombolysis likewise accounted for only 25% of the deaths prevented by initial treatments for acute myocardial infarction. This was much less than aspirin and cardiopulmonary resuscitation, as in other studies.[26] Furthermore, treating angina patients with aspirin in the community prevented almost twice as many deaths as treating unstable angina patients in hospitals, principally reflecting the far greater numbers involved (Table 1).

Treatment uptake levels were often poor (Table 1). Earlier work suggested that if even 80% of eligible patients had received appropriate therapy, ≈30 000 additional deaths might have been prevented or postponed each year[33] in the United Kingdom, equivalent to 100 000 fewer deaths in the United States.

Reductions in the major risk factors between 1981 and 2000 accounted for ≈35 000 fewer deaths in England and Wales in 2000. The biggest single contribution reflected a large decrease in smoking prevalence, from 39% to 28% overall. Almost 10% of the mortality decrease came from a relatively small reduction (4.2%) in population total cholesterol level. This emphasizes the large β coefficient (1.9 to 5.4, depending on age[27]) and highlights the potential gains from larger reductions in population cholesterol.

The adverse trends in obesity, diabetes, and physical inactivity together contributed ≈8000 additional deaths in 2000. These canceled out 2 decades of improvement in cholesterol. Furthermore, continuing deteriorations are expected.[13,14,28]

We used relatively conservative β coefficients for smoking, cholesterol, and blood pressure. Even so, there was relatively little space left in the model, ≈11%, for potential mortality benefits from other, unquantified factors such as life-course effects, alcohol. and other dietary improvements.[29]

All the β coefficients and relative risk values used in the model were independent, being obtained from multiple regression analyses. The interaction between the major risk factors should therefore have been accounted for. However, these estimates may still overestimate, because most models, of necessity, entered data into the model on only a limited range of risk factors. For the MONICA study, for instance, these are smoking (yes or no), systolic blood pressure, total cholesterol, and body mass index.[4] There are many other potentially important risk factors for CHD, including diet (such as consumption of fish oils, antioxidants, and alcohol) and life-course factors. Some novel risk factors may be highly correlated with the 7 risk factors measured and considered in the model. It is therefore possible that the calculated coefficients contain the effects of some of these other, unmeasured risk factors.

Modeling studies have a number of potential strengths. They transparently integrate and simultaneously consider huge amounts of data from many sources. Explicit assumptions can then be tested by sensitivity analyses.[8]

Modeling studies also have limitations. They are dependent on the variable quality and extent of data available on CHD risk factor trends and treatment uptakes.[30] Assumptions and robust sensitivity analyses therefore become essential.[19] However, the relative contribution of each risk factor and treatment to the overall CHD mortality decline was little changed whether considering best, minimum, or maximum estimates (Figure 2). The model included only those 25 to 84 years old because of very limited data in older groups. We considered only deaths from CHD and ignored "competing causes" such as cancer.[6] However, reductions in smoking would actually decrease deaths from lung cancer and other cancers.[2,7] This analysis focused on mortality rather than symptomatic relief, "life-years-gained," or disease incidence.[22,31] These all merit attention in future work.

The IMPACT model assumes that estimates of efficacy from randomized controlled trials can usually be generalized to effectiveness in clinical practice. This seems reasonable.[32] Further development work is clearly needed.[8] Finally, although lag times were not explicitly considered, they may be relatively unimportant over a 20-year analysis. Substantial mortality reduction occurs within 1 to 4 years of quitting smoking or reducing cholesterol.[27,34]

In conclusion, more than 50% of the recent CHD mortality decrease in England and Wales was attributed to reductions in major risk factors, and some 40% to medical therapies. These findings might be cautiously generalizable to the United States and other comparable industrialized countries. Comprehensive CHD strategies should therefore actively promote primary prevention as well as maximizing the population coverage of effective treatments.

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TRENDS IN THE INCIDENCE OF CORONARY HEART DISEASE AND CHANGES IN DIET AND LIFESTYLE IN WOMEN

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ABSTRACT

Background Previous studies have found concurrent declines in blood pressure, serum cholesterol levels, and the incidence of and mortality from coronary disease. However, the effects of changes in diet and lifestyle on trends in coronary disease are largely unknown.

Methods We followed 85,941 women who were 34 to 59 years old and had no previously diagnosed cardiovascular disease or cancer from 1980 to 1994 in the Nurses' Health Study. Diet and lifestyle variables were assessed at base line and updated during follow-up.

Results After adjustment for the effect of age, the incidence of coronary disease declined by 31 percent from the two-year period 1980–1982 to the two-year period 1992–1994. From 1980 to 1992, the proportion of participants currently smoking declined by 41 percent, the proportion of postmenopausal women using hormone therapy increased by 175 percent, and the prevalence of overweight, defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 25 or more, increased by 38 percent. During the study period, diet improved substantially. Statistically, changes in these variables — when considered simultaneously — explained a 21 percent decline in the incidence of coronary disease, representing 68 percent of the overall decline from 1980–1982 to 1992–1994. Taken individually, the reduction in smoking explained a 13 percent decline in the incidence of coronary disease; improvement in diet explained a 16 percent decline; and increase in postmenopausal hormone use explained a 9 percent decline. On the other hand, the increase in body-mass index explained an 8 percent increase in the incidence of coronary disease.

Conclusions Reduction in smoking, improvement in diet, and an increase in postmenopausal hormone use accounted for much of the decline in the incidence of coronary disease in this group of women. An increasing prevalence of obesity, however, appears to have slowed the decline in the incidence of coronary disease. (N Engl J Med 2000;343:530-7.)

MORTALITY from coronary heart disease in the United States has declined substantially in the past three decades.[1] It is unclear, however, how much of the decline is due to a reduction in the incidence of disease and how much is due to improved survival.[2,3] Although most studies show improvement in survival among patients with myocardial infarction, trends in incidence are uncertain.[2-5] In the Atherosclerosis Risk in Communities Study,[5] a stable or slightly increasing incidence of hospitalization for acute myocardial infarction was observed from 1987 to 1994, despite a decrease in mortality from coronary disease. The recent lack of decline in the incidence of coronary disease suggests that the change attributable to prevention may have stagnated, but the lack of data on changes in particular risk factors precludes detailed analyses.

In this study, we examined trends in the incidence of coronary disease from 1980 to 1994 among women in the Nurses' Health Study cohort. The large sample, high rate of follow-up, and detailed data on dietary and other lifestyle factors provided an opportunity to examine trends over time in the incidence of coronary disease and the degree to which changes in diet and lifestyle might account for these trends.

METHODS

The Nurses' Health Study Cohort

The Nurses' Health Study was established in 1976, when 121,700 female nurses 30 to 55 years old completed a mailed questionnaire on their medical history and lifestyle. Every two years, follow-up questionnaires are sent to obtain updated information on risk factors and to identify newly diagnosed diseases. In 1980 a 61-item food-frequency questionnaire was included to assess the intake of specific fats and other nutrients. In 1984 the dietary questionnaire included 116 items. Similar questionnaires were used to update dietary information in 1986 and 1990.

After up to four mailings, 98,462 women returned the 1980 diet questionnaire. We excluded questionnaires with 10 or more items blank, those reporting implausibly high or low values for total food or energy intake (less than 500 or more than 3500 kcal per day), and those from women with previously diagnosed can-

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cer or cardiovascular disease (including those who had undergone coronary-artery bypass surgery or angioplasty). We obtained data on the incidence of coronary disease among the remaining 85,941 women during the subsequent 14 years of follow-up. The follow-up rate for nonfatal events was 98 percent of the total potential person-years.

End Points

The end point for this study was nonfatal myocardial infarction or fatal coronary disease occurring after the return of the 1980 questionnaire but before June 1, 1994. We sought to review medical records for all myocardial infarctions reported by the women. The records were reviewed by physicians who had no knowledge of the self-reported risk factors. Myocardial infarction was considered confirmed when the criteria of the World Health Organization were met: symptoms plus either diagnostic electrocardiographic changes or elevated cardiac-enzyme levels.[6] Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable (17 percent of the total).

Deaths were identified from state vital records and the National Death Index or were reported by next of kin and the postal system. Follow-up for the deaths was over 98 percent complete.[7] Fatal coronary disease was considered to have been present if fatal myocardial infarction was confirmed by hospital records or autopsy or if coronary disease was listed as the cause of death on the certificate, coronary disease was the underlying and most plausible cause, and evidence of previous coronary disease was available. We designated as deaths due to presumed myocardial infarction (15 percent of the cases of fatal coronary disease) deaths for which coronary disease was listed on the death certificate as the underlying cause but for which no records were available. We also included sudden death within one hour after the onset of symptoms if there was no plausible cause other than coronary disease (12 percent of the cases of fatal coronary disease).

Assessment of Diet

A detailed description of the semiquantitative food-frequency questionnaires has been published elsewhere.[8] A common unit or portion size for each food (e.g., one egg or one slice of bread) was specified, and the participants were asked how often, on average, they had consumed that amount during the previous year. The nine responses ranged from "never or less than once per month" to "six or more times per day." Nutrient intake was computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portions, taking into account the type of fat used in preparation.[9] In validation studies in subsamples of the Nurses' Health Study participants, the correlations between the intake of specific fatty acids as calculated from the questionnaire and the proportions of the same fatty acids in adipose tissue were 0.34 for linolenic acid, 0.37 for linoleic acid,[10] and 0.51 for trans fatty acids.[11] Among men in the Health Professionals' Follow-up Study who were given the same questionnaire, the correlation was 0.47 for eicosapentaenoic acid intake as assessed with the questionnaire and values measured in adipose tissue.[12] In addition, the correlation between folate intake as calculated from the questionnaire and plasma folate levels was 0.56.[13]

Assessment of Nondietary Factors

Every two years, we update the participants' smoking status (never smoked, smoked in the past, or smoke currently, with the number of cigarettes per day), menopausal status and postmenopausal hormone use, and body weight. In validation studies, self-reported weights were highly correlated with measured weights ($r=0.96$).[14] Although increasing levels of physical activity were clearly associated with a lower risk of coronary disease in this cohort,[15] we could not examine the effects of trends over time because of the different measurements used. During the period when physical activity was assessed with the same questionnaire (from 1986 to 1994), there was no appreciable change in levels of physical activity. We also did not include alcohol use in these analyses, because consumption was stable over time. Additional analyses that included physical activity and alcohol consumption had little effect on the estimates of trends in coronary disease.

Statistical Analysis

The person-time for each participant was calculated from the date of return of the 1980 questionnaire to the date of the first coronary disease event, death, or June 1, 1994. We did not exclude women who had undergone coronary-artery bypass surgery or angioplasty during follow-up, because exclusion of these women might artificially lower the calculated incidence of coronary disease. Moreover, it is not certain that these procedures reduce rates of reinfarction or mortality.[16,17]

Trends in diet and lifestyle variables over time were standardized according to the age distribution of the total number of person-years of follow-up in the cohort. We computed the age-specific incidence of coronary disease in different periods to examine trends. The incidence was calculated by dividing the number of coronary disease events by person-time of follow-up in each two-year period. The relative risk was computed as the rate in a specific period divided by that in the period from 1980 to 1982. Tests for trend were conducted by assigning an ordinal value (from 1 to 7) to each of the periods. A multivariate pooled logistic model,[18] which allows the exposure variables to change over the different periods, was used to estimate the effects of time. The basic model included only period and age; updated information on cigarette smoking, diet, postmenopausal hormone use, and body-mass index (the weight in kilograms divided by the square of the height in meters) was then added separately to the model. The changes in estimates of trends in the incidence of coronary disease were used to indicate the degree to which the trends could be explained statistically by changes in each of the exposure variables. Specifically, we calculated the decline in the rate of coronary disease that was explained statistically by changes in a risk factor as the difference between the estimated percent decline in incidence from the two-year period 1980–1982 to the two-year period 1992–1994 from the age-adjusted analysis and the decline derived from a model including age and the updated risk factor. Further adjustment, in a secondary analysis, for base-line values of each exposure variable had no appreciable effect on the estimated percentage of the declines that were explained by the variables.

To reflect trends in overall dietary pattern over time, we calculated a priori a single composite dietary score based on six dietary components: a low intake of trans fat; a low glycemic load (a measure of the ability of a diet to raise the blood glucose level)[19,20]; a high intake of cereal fiber, marine n−3 fatty acids, and folate; and a high ratio of polyunsaturated to saturated fat. For each of these six dietary factors, we calculated the distribution according to quintile within the cohort and assigned each woman the score corresponding to the quintile of intake. For each participant, the quintile value for each nutrient (a higher quintile score represents a lower risk) was summed and the totals were used to recategorize the participants according to quintiles. Previous analyses have documented the importance of trans fat,[21,22] cereal fiber,[23] glycemic load,[24] marine n−3 fatty acids (unpublished data), folate,[25] and the ratio of polyunsaturated to saturated fat[26] in relation to the risk of coronary disease in the Nurses' Health Study.

RESULTS

Trends in the Incidence of Coronary Disease

During 14 years of follow-up, from 1980 to 1994, we documented 1304 newly diagnosed cases of coronary disease: 946 nonfatal myocardial infarctions and 358 cases of fatal coronary disease. The age-specific incidence rates of coronary disease (Fig. 1) indicate an

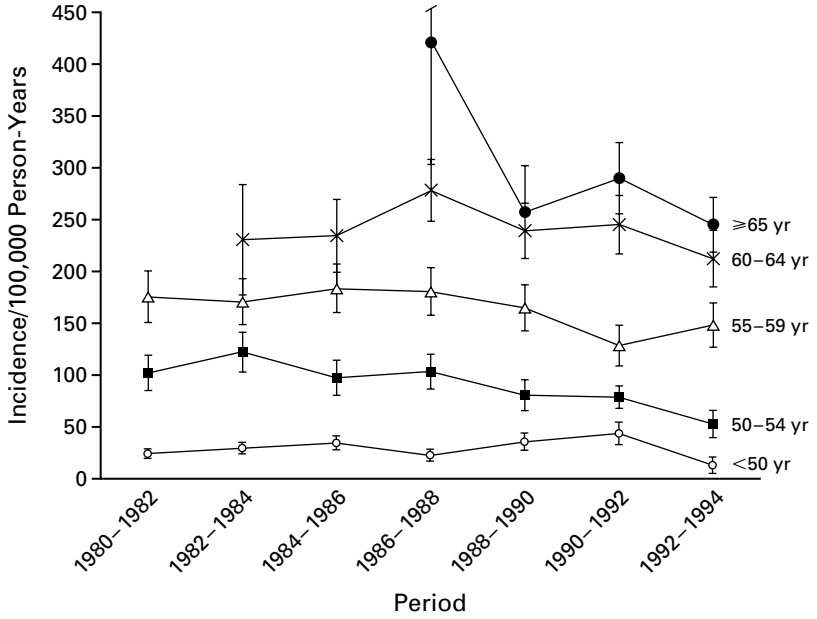

Figure 1. Trends in the Incidence of Coronary Disease According to Age Group in the Nurses' Health Study, 1980 to 1994.
The I bars indicate the standard errors.

overall decline in the incidence of coronary disease over time for all age groups; most of the change appears to have occurred in the second half of the 14-year follow-up period. Between 1980–1982 and 1992–1994, the annual rate declined from 25 to 13 cases per 100,000 person-years for women 49 years of age or younger, from 103 to 53 per 100,000 for women 50 to 54 years of age, and from 177 to 149 per 100,000 for women 55 to 59 years of age. Among older women, the follow-up was slightly shorter, since none of the women in the cohort reached 60 years of age until 1982; the annual rate declined from 242 to 214 per 100,000 between 1982–1984 and 1992–1994 for women 60 to 64 years of age and from 422 to 244 per 100,000 between 1986–1988 and 1992–1994 for women 65 years of age or older.

Trends in Lifestyle and Diet

Figure 2 shows the age-adjusted trends in current smoking, overweight (defined as a body-mass index of at least 25), and current postmenopausal hormone use. The percentage of women who were currently smoking declined from 27 percent in 1980 to 16 percent in 1992 (a decline of 41 percent), whereas the percentage of women who were overweight increased from 37 percent in 1980 to 51 percent in 1992 (an increase of 38 percent). The average age-adjusted body-mass index increased from 24.5 in 1980 to 26.1 in 1992. The percentage of postmenopausal women who were currently using hormone therapy increased from 16 percent in 1980 to 44 percent in 1992 (an increase of 175 percent).

The composite dietary score increased steadily over time (Table 1). Among the six components of the dietary score, the average daily intake of trans fat decreased by 31 percent from 1980 to 1990, the ratio of polyunsaturated to saturated fat increased by 69 percent, the average daily intake of cereal fiber increased by 90 percent, the average daily intake of marine n−3 fatty acids increased by 180 percent, and the average daily intake of folate increased by 12 percent. Of the six dietary factors considered, only one, glycemic load, showed an adverse trend; it increased over time by 22 percent.

From 1980 to 1990, the average consumption of red meat (beef, pork, and lamb) declined from 1.11 to 0.69 serving per day, whereas the consumption of poultry and fish increased from 0.43 to 0.69 serving per day (Fig. 3). The consumption of high-fat dairy products decreased from 1.42 to 0.81 serving per day, whereas the consumption of low-fat dairy products increased from 0.94 to 1.11 servings per day.

Analyses of Diet and Lifestyle in Relation to Trends in the Incidence of Coronary Disease

In age-adjusted analyses, there was a significant trend toward a lower risk of coronary disease over time (Table 2). The relative risk of all coronary disease in 1992–1994 as compared with 1980–1982 was 0.69 (95 percent confidence interval, 0.54 to 0.88; P for

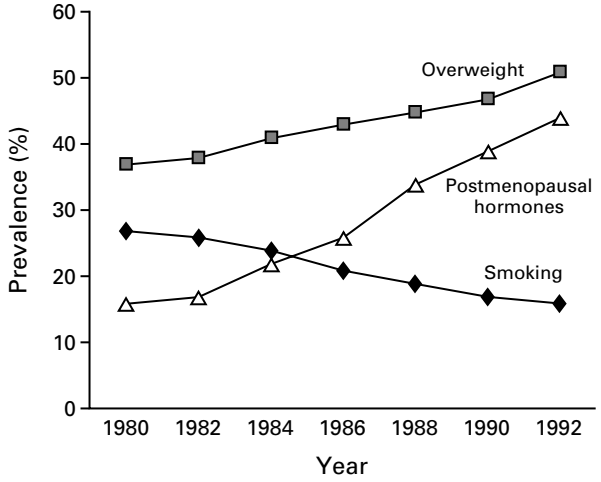

Figure 2. Age-Adjusted Trends in the Prevalence of Smoking, Overweight (Body-Mass Index ≥25), and Postmenopausal-Hormone Use.

Prevalences are standardized according to age distribution for the entire number of person-years of follow-up. The prevalence of postmenopausal hormone use was calculated for postmenopausal women only. All standard errors were less than 0.25 percent and thus would not be visible on the graph.

TABLE 1. AGE-ADJUSTED VALUES FOR DIETARY FACTORS OVER TIME IN THE NURSES' HEALTH STUDY.*

DIETARY FACTOR	1980	1984	1986	1990	P VALUE FOR TREND
Trans fat (% of total energy)	2.20	1.90	1.68	1.52	<0.001
Ratio of polyunsaturated to saturated fat	0.29	0.48	0.47	0.49	<0.001
Cereal fiber (g/day)	2.63	4.21	4.45	4.99	<0.001
Glycemic load†	120.4	138.6	138.0	147.0	<0.001
Marine n−3 fatty acids (% of total energy)	0.05	0.11	0.12	0.14	<0.001
Folate (μg/day)	377	387	403	421	<0.001
Dietary score‡	9.30	13.0	14.0	14.7	<0.001

*Means were standardized according to age distribution for the entire number of person-years of follow-up.

†Glycemic load was calculated by multiplying the carbohydrate content of each food by its glycemic-index value and the frequency of consumption and summing the results for all food items. Each unit of glycemic load represents the equivalent glycemic effect of 1 g of carbohydrate from white bread. Dietary glycemic load represents a diet's overall ability to raise the blood glucose level.

‡Intakes of trans fat, cereal fiber, marine n−3 fatty acids, and folate, the glycemic load, and the ratio of polyunsaturated to saturated fat were categorized into quintiles, and for each participant, the quintile values for the nutrients were summed to generate the composite dietary score (a higher quintile score represents a better diet).

trend <0.001), indicating a 31 percent overall decline in the incidence of coronary disease. In this analysis, we excluded women with previously diagnosed cardiovascular disease or cancer, since the development of these conditions might have led to changes in diet and lifestyle. An analysis including these women did not materially alter the results (age-adjusted relative risk of coronary disease in 1992–1994 as compared with 1980–1982, 0.64).

To address whether trends over time in diet and lifestyle explained the coronary-disease trend, we added updated information on cigarette smoking, dietary score, postmenopausal hormone use, and body-mass index to the age-adjusted model. After simultaneous adjustment for these variables, the relative risk was 0.90 (95 percent confidence interval, 0.70 to 1.16); the similarity of this relative risk to that calculated with diet and lifestyle variables included in the model suggests that these factors can explain much of the observed decline in the incidence of coronary disease. Together, these variables statistically explained a 21 percent decline (31 percent minus 10 percent) in the incidence of coronary disease; this amounts to 68 percent of the total decline.

To examine the contribution of these variables individually to the change in the incidence of coronary disease, we added them one at a time to the age-adjusted model. After adjustment for age and smoking, the relative risk of coronary disease in 1992–1994 as compared with 1980–1982 was 0.82 (95 percent confidence interval, 0.64 to 1.04), indicating an 18 percent decline after the effect of the reduction in smoking was taken into account. Thus, we estimated that reduction in smoking statistically explained a 13 percent decline in the age-adjusted incidence of coronary disease (31 percent minus 18 percent). Similarly, we estimated that improvement in diet explained a 16 percent decline and increase in postmenopausal hormone use explained a 9 percent decline. On the other hand, the increase in body-mass index explained an 8 percent increase in the incidence of coronary disease. Because the risk factors are correlated, the sum of the individual percentages does not equal the percentage from the analysis that included all of the risk factors.

To examine further the relation of change in diet and lifestyle to the risk of coronary disease, we fitted models that included base-line or updated values for these variables and an additional model that included both base-line and updated values (Table 3). Base-line values for smoking, body-mass index, postmenopausal hormone use, and dietary score were all significantly associated with the risk of coronary disease (model 1). In the model using updated values for these variables (model 2), the associations with dietary score and postmenopausal hormone use became stronger. When both base-line and updated variables were modeled simultaneously (model 3), the fit was significantly

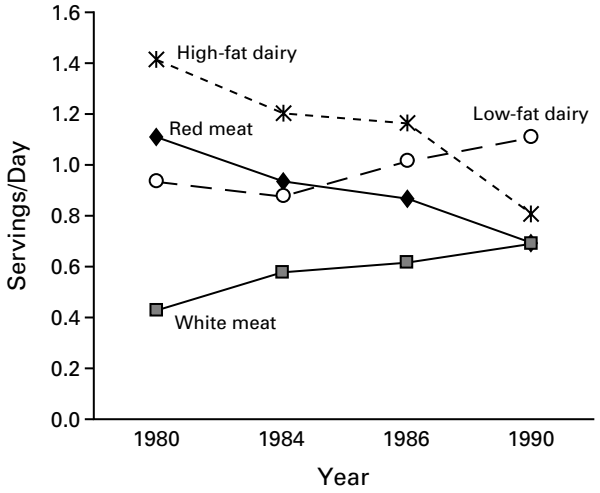

Figure 3. Age-Adjusted Trends in Intake of Major Food Groups. Intake has been standardized according to age distribution for the entire number of person-years of follow-up. The score for red meat is the composite score for the following foods: beef, pork, or lamb as main dish; beef as sandwich or mixed dish; hamburger; hot dog; processed meat; and bacon. White meat includes fish and poultry. High-fat dairy includes whole milk, hard cheese or cream cheese, ice cream, and butter. Low-fat dairy includes skim or low-fat milk, yogurt, and cottage cheese. All standard errors were less than 0.005 serving per day and thus would not be visible on the graph.

better than with model 1 ($P<0.001$). In that model, the association with updated variables can be interpreted as the effects of individual changes in these variables on the risk of coronary disease. Individual changes in diet and postmenopausal hormone use were significantly associated with lower risk of coronary disease. The associations with change in smoking independent of base-line values were consistent with the expected direction, although the confidence intervals were wide. For body-mass index, the association was slightly inverse but not significant.

DISCUSSION

We found that the age-standardized incidence of coronary disease declined by 31 percent from 1980 to 1994 among women in the Nurses' Health Study; the decline was evident in all age groups. From 1980 to 1992, the prevalence of current smoking declined by 41 percent, the proportion of women with postmenopausal hormone use increased by 175 percent, and the prevalence of overweight increased by 38 percent. Meanwhile, diet improved substantially. Multivariate analyses suggest that changes in cigarette smoking, diet, and postmenopausal hormone use statistically explain much of the reduction in the incidence of coronary disease. In contrast, the increase in obesity adversely affected the trend.

Over the past three decades, mortality from coronary disease in the United States has declined substantially.[27] It is unclear, however, how much of the decline in mortality is due to a decline in incidence and how much is due to improved survival.[5,28] Although several studies have suggested a decline in the case fatality rate for coronary disease,[4,5,29,30] the trends in incidence in these studies have been inconsistent.[3,4,29,30] Recently, the Atherosclerosis Risk in Communities Study[5] found a stable or slightly increasing incidence of hospitalization for acute myocardial infarction from 1987 to 1994 in four U.S. communities. We observed an overall decline in the incidence of coronary disease, primarily in nonfatal myocardial infarction. This discrepancy may be due to a greater adoption of health-promoting forms of behavior by women in the Nurses' Health Study. In addition, the power of the study to examine the trend in mortality from coronary disease is limited.

In our cohort, a decline in cigarette smoking contributed substantially to the reduction in the incidence of coronary disease, as might be expected.[31,32] Also associated with the decline in coronary disease was the increase in postmenopausal hormone use. Such hormone use has been related to a lower risk of coronary disease in numerous prospective studies,[33] although a recent secondary-prevention trial failed to find an overall benefit during four years of follow-up.[34]

Few studies have systematically monitored trends in diet concurrently with trends in cardiovascular disease.[35] In our cohort, the intake of saturated and trans fats declined over time, whereas the intake of polyunsaturated fat (in relation to saturated fat), cereal fiber, marine n−3 fatty acids, and folate increased. However, the dietary glycemic load also increased because of high intake of refined carbohydrates, which may have adverse effects on type 2 diabetes,[19,20] coronary disease,[24] and perhaps obesity.[36] Nevertheless, the overall diet score improved substantially, and this appeared to contribute markedly to the decline in the incidence of coronary disease in our cohort.

In a finding that was consistent with national data,[37] obesity increased substantially in our cohort. Because obesity is a strong risk factor for type 2 diabetes and cardiovascular disease,[38] its increasing prevalence slowed the decline in coronary disease. The incidence of coronary disease would probably have declined even more if body-mass index had not increased over time.

Overall, trends in diet and lifestyle explained much of the decline in the incidence of coronary disease. These results, however, do not imply that other factors, such as levels of blood pressure and serum cholesterol, are unimportant or do not contribute to this decline, because the effects of diet and lifestyle are partially mediated by their effects on blood pressure and serum cholesterol. Previous studies[4,29] have observed concurrent declines in blood pressure, serum cholesterol levels, the incidence of coronary disease, and mortality from coronary disease. In the Framingham Study,[39] the increasing use of antihypertensive

TABLE 2. RELATIVE RISK OF CORONARY DISEASE ACCORDING TO PERIOD, FROM 1980 TO 1994, IN THE NURSES' HEALTH STUDY.

PERIOD	ADJUSTED FOR AGE*	ADJUSTED FOR AGE AND SMOKING†	ADJUSTED FOR AGE AND DIET SCORE‡	ADJUSTED FOR AGE AND POSTMENOPAUSAL HORMONE USE§	ADJUSTED FOR AGE, SMOKING, DIET SCORE, AND POSTMENOPAUSAL HORMONE USE§	ADJUSTED FOR AGE AND BODY-MASS INDEX¶	ADJUSTED FOR AGE, SMOKING, DIET, POSTMENOPAUSAL HORMONE USE, AND BODY-MASS INDEX
				relative risk (95% confidence interval)			
Total coronary disease							
1980–1982	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1982–1984	1.02 (0.80–1.31)	1.05 (0.82–1.34)	1.02 (0.80–1.30)	1.02 (0.80–1.31)	1.04 (0.82–1.33)	0.97 (0.76–1.24)	1.01 (0.79–1.29)
1984–1986	0.98 (0.77–1.25)	1.02 (0.80–1.30)	1.11 (0.87–1.42)	0.99 (0.78–1.26)	1.14 (0.90–1.46)	0.89 (0.70–1.14)	1.07 (0.83–1.36)
1986–1988	1.06 (0.84–1.34)	1.14 (0.90–1.45)	1.26 (1.00–1.60)	1.09 (0.86–1.38)	1.34 (1.06–1.70)	0.95 (0.75–1.20)	1.22 (0.96–1.55)
1988–1990	0.90 (0.71–1.14)	1.00 (0.79–1.27)	1.07 (0.84–1.36)	0.96 (0.76–1.22)	1.19 (0.94–1.52)	0.79 (0.62–1.01)	1.07 (0.84–1.37)
1990–1992	0.85 (0.67–1.08)	0.97 (0.76–1.23)	1.04 (0.82–1.32)	0.93 (0.73–1.18)	1.21 (0.95–1.54)	0.78 (0.61–0.99)	1.08 (0.85–1.38)
1992–1994	0.69 (0.54–0.88)	0.82 (0.64–1.04)	0.85 (0.66–1.08)	0.78 (0.61–0.99)	1.03 (0.80–1.32)	0.61 (0.48–0.79)	0.90 (0.70–1.16)
P value for trend	<0.001	0.04	0.11	0.02	0.65	<0.001	0.46
Fatal coronary disease							
1980–1982	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1982–1984	1.08 (0.61–1.92)	1.11 (0.63–1.95)	1.08 (0.61–1.91)	1.07 (0.60–1.88)	1.08 (0.61–1.91)	0.87 (0.49–1.54)	0.91 (0.51–1.61)
1984–1986	1.32 (0.77–2.25)	1.37 (0.80–2.34)	1.51 (0.89–2.59)	1.29 (0.75–2.20)	1.48 (0.87–2.54)	0.96 (0.56–1.65)	1.12 (0.65–1.93)
1986–1988	1.16 (0.68–1.97)	1.23 (0.72–2.10)	1.39 (0.82–2.38)	1.16 (0.68–1.98)	1.42 (0.83–2.42)	0.80 (0.46–1.37)	1.00 (0.58–1.73)
1988–1990	1.14 (0.67–1.93)	1.25 (0.74–2.12)	1.37 (0.81–2.33)	1.20 (0.71–2.04)	1.48 (0.87–2.51)	0.75 (0.44–1.29)	1.00 (0.58–1.72)
1990–1992	1.09 (0.65–1.84)	1.23 (0.72–2.08)	1.35 (0.80–2.29)	1.19 (0.71–2.02)	1.52 (0.90–2.59)	0.91 (0.54–1.53)	1.23 (0.72–2.09)
1992–1994	0.81 (0.47–1.38)	0.93 (0.54–1.60)	1.00 (0.58–1.72)	0.91 (0.53–1.57)	1.18 (0.68–2.04)	0.62 (0.36–1.07)	0.89 (0.51–1.54)
P value for trend	0.14	0.47	0.67	0.52	0.54	0.08	0.96
Nonfatal myocardial infarctions							
1980–1982	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1982–1984	1.01 (0.77–1.33)	1.04 (0.79–1.36)	1.01 (0.77–1.33)	1.02 (0.78–1.34)	1.04 (0.79–1.37)	1.01 (0.77–1.33)	1.06 (0.80–1.39)
1984–1986	0.90 (0.68–1.18)	0.94 (0.72–1.24)	1.02 (0.77–1.34)	0.92 (0.70–1.21)	1.07 (0.81–1.40)	0.89 (0.67–1.16)	1.07 (0.81–1.41)
1986–1988	1.05 (0.81–1.36)	1.14 (0.87–1.48)	1.25 (0.96–1.62)	1.09 (0.84–1.42)	1.34 (1.03–1.75)	1.03 (0.79–1.34)	1.34 (1.02–1.75)
1988–1990	0.84 (0.64–1.10)	0.94 (0.72–1.23)	1.00 (0.76–1.31)	0.90 (0.69–1.18)	1.13 (0.86–1.48)	0.82 (0.63–1.08)	1.12 (0.85–1.47)
1990–1992	0.79 (0.60–1.03)	0.91 (0.69–1.19)	0.96 (0.73–1.26)	0.86 (0.66–1.13)	1.13 (0.85–1.48)	0.75 (0.57–0.98)	1.05 (0.79–1.38)
1992–1994	0.67 (0.51–0.89)	0.80 (0.60–1.06)	0.82 (0.62–1.09)	0.75 (0.57–0.99)	1.00 (0.75–1.33)	0.63 (0.47–0.83)	0.92 (0.69–1.22)
P value for trend	<0.001	0.05	0.11	0.02	0.87	<0.001	0.48

*Age was entered into the model in five-year categories.

†The smoking categories were never smoked, smoked in past, and currently smoking 1 to 14, 15 to 24, or ≥25 cigarettes per day. Information on cigarette smoking was updated every two years.

‡The intakes of trans fat, cereal fiber, marine n−3 fatty acids, and folate, the glycemic load, and the ratio of polyunsaturated to saturated fat were categorized into quintiles, and for each participant, the quintile values for the nutrients (a higher quintile score represents a better diet) were summed to generate the composite dietary score. Dietary scores were updated in 1984, 1986, and 1990.

§The categories of postmenopausal hormone use were premenopausal, postmenopausal without hormone use, and postmenopausal with hormone use. Information was updated every two years.

¶Body-mass index was divided into four categories: <23, 23 to 24.9, 25 to 29.9, and ≥30. Information was updated every two years.

TABLE 3. MULTIVARIATE RELATIVE RISK OF CORONARY DISEASE ACCORDING TO BASE-LINE AND UPDATED RISK FACTORS IN THE NURSES' HEALTH STUDY, 1980 TO 1994.*

RISK FACTOR	MODEL 1: BASE-LINE VALUES	MODEL 2: UPDATED VALUES†	MODEL 3: UPDATED VALUES ADJUSTED FOR BASE-LINE VALUES‡
	relative risk (95% confidence interval)		
Cigarette smoking			
Never	1.0	1.0	1.0
Past	1.24 (1.06–1.47)	1.47 (1.27–1.70)	1.10 (0.27–4.47)
Current			
1–14 cigarettes/day	1.99 (1.59–2.48)	2.56 (2.08–3.16)	1.43 (0.35–5.87)
15–24 cigarettes/day	4.10 (3.52–4.79)	4.51 (3.84–5.31)	1.90 (0.46–7.81)
≥25 cigarettes/day	4.66 (3.96–5.47)	4.64 (3.86–5.57)	1.75 (0.42–7.22)
Body-mass index			
<23	1.0	1.0	1.0
23–24.9	1.49 (1.27–1.76)	1.22 (1.01–1.47)	0.92 (0.75–1.15)
25–29.9	2.04 (1.76–2.36)	1.62 (1.38–1.91)	0.88 (0.71–1.09)
≥30	3.86 (3.30–4.51)	2.57 (2.16–3.06)	0.83 (0.64–1.08)
Postmenopausal hormone use			
Premenopausal	0.72 (0.61–0.83)	0.67 (0.54–0.83)	0.78 (0.62–0.99)
Postmenopausal			
Never used or used in past	1.0	1.0	1.0
Currently using	0.81 (0.66–1.00)	0.68 (0.58–0.91)	0.73 (0.60–0.88)
Composite diet score§			
Lowest quintile	1.0	1.0	1.0
Second quintile	0.89 (0.76–1.04)	0.79 (0.67–0.94)	0.79 (0.66–0.95)
Third quintile	0.80 (0.65–0.98)	0.78 (0.67–0.90)	0.77 (0.64–0.93)
Fourth quintile	0.76 (0.64–0.90)	0.59 (0.49–0.71)	0.57 (0.45–0.71)
Fifth quintile	0.64 (0.53–0.78)	0.43 (0.35–0.52)	0.40 (0.31–0.53)

*Variables were entered into the model simultaneously. Age was adjusted for in five-year categories.

†Data on smoking, body-mass index, and postmenopausal hormone use were obtained in 1980, 1982, 1984, 1986, 1988, 1990, and 1992. Data on diet were obtained in 1980, 1984, 1986, and 1990.

‡The associations for the updated variables can be interpreted as the effects of changes in these variables over time on the risk of coronary disease.

§The intakes of trans fat, cereal fiber, marine n−3 fatty acids, and folate, the glycemic load, and the ratio of polyunsaturated to saturated fat were categorized into quintiles, and for each participant, the quintile values for the nutrients (a higher quintile score represents a better diet) were summed to generate the composite dietary score.

medication from 1950 to 1989 was associated with a downward trend in the prevalence of hypertension and a concomitant decline in left ventricular hypertrophy. In the Nurses' Health Study cohort, much of the benefit of pharmacologic treatment of hypertension was probably realized before 1980.

One strength of our study is the use of regularly collected, detailed data on dietary and other lifestyle factors; this data base permits us to estimate the degree to which trends in coronary disease are explained by changes in diet and lifestyle. However, assessing the effects of individual changes in body-mass index and smoking is difficult, because these variables are highly correlated over time. In addition, our analyses did not take into account the potential effect of a time lag between the change in a risk factor (e.g., an improvement in diet) and the resulting reduction in the risk of coronary disease.

Furthermore, the observed dietary change between 1980 and 1984 may in part reflect changes in the dietary questionnaires. This may be especially true for the calculated intakes of marine n−3 fatty acids and cereal fiber, because more food items containing these nutrients were included in the later questionnaire. However, most of the observed changes are generally consistent with dietary-records data from two validation studies conducted in 1980 and 1986 in the Nurses' Health Study (Sampson L: personal communication). For example, during this period, according to the dietary records, intake of saturated fat decreased by 12 percent and intake of polyunsaturated fat increased by 13 percent.

Finally, because our participants were all registered nurses, the trends over time cannot be extrapolated to women in the general population. However, the observed associations between diet and lifestyle variables and changes in the incidence of coronary disease should apply broadly.

In conclusion, we observed a substantial decline in the incidence of coronary disease from 1980 to 1994 among women in the Nurses' Health Study. Reduction in smoking, improvement in diet, and an increase in postmenopausal hormone use accounted for much of the decline in coronary disease. The increase in obesity, however, appears to have prevented a further decline in the incidence of coronary disease. These findings underscore the importance of diet and lifestyle in the primary prevention of coronary disease.

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PRIMARY PREVENTION OF CORONARY HEART DISEASE IN WOMEN THROUGH DIET AND LIFESTYLE

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ABSTRACT

Background Many lifestyle-related risk factors for coronary heart disease have been identified, but little is known about their effect on the risk of disease when they are considered together.

Methods We followed 84,129 women participating in the Nurses' Health Study who were free of diagnosed cardiovascular disease, cancer, and diabetes at base line in 1980. Information on diet and lifestyle was updated periodically. During 14 years of follow-up, we documented 1128 major coronary events (296 deaths from coronary heart disease and 832 nonfatal infarctions). We defined subjects at low risk as those who were not currently smoking, had a body-mass index (the weight in kilograms divided by the square of the height in meters) under 25, consumed an average of at least half a drink of an alcoholic beverage per day, engaged in moderate-to-vigorous physical activity (which could include brisk walking) for at least half an hour per day, on average, and scored in the highest 40 percent of the cohort for consumption of a diet high in cereal fiber, marine n−3 fatty acids, and folate, with a high ratio of polyunsaturated to saturated fat, and low in trans fat and glycemic load, which reflects the extent to which diet raises blood glucose levels.

Results Many of the factors were correlated, but each independently and significantly predicted risk, even after further adjustment for age, family history, presence or absence of diagnosed hypertension or diagnosed high cholesterol level, and menopausal status. Women in the low-risk category (who made up 3 percent of the population) had a relative risk of coronary events of 0.17 (95 percent confidence interval, 0.07 to 0.41) as compared with all the other women. Eighty-two percent of coronary events in the study cohort (95 percent confidence interval, 58 to 93 percent) could be attributed to lack of adherence to this low-risk pattern.

Conclusions Among women, adherence to lifestyle guidelines involving diet, exercise, and abstinence from smoking is associated with a very low risk of coronary heart disease. (N Engl J Med 2000;343:16-22.)

DESPITE dramatic declines, coronary heart disease remains the leading cause of death among men and women in the United States. Much effort has focused on the pharmacologic management of hypertension and blood lipid levels and on improved therapy for acute myocardial infarction and congestive heart failure. These treatments have proven benefit but are costly, may have side effects, and require medical intervention. Diet and lifestyle can also affect the incidence of coronary heart disease. Typically, behavioral risk factors are studied individually, but these types of behavior are often correlated, because people follow common lifestyle patterns.

In the present study, we assessed the effect of a combination of lifestyle practices on the risk of coronary heart disease. Specifically, we estimated the proportion of coronary events that could potentially be prevented by adherence to a set of dietary and behavioral guidelines. In secondary analyses, we also evaluated the effect of the practices on the risk of stroke.

METHODS

Population

The Nurses' Health Study cohort was established in 1976, when 121,700 U.S. female registered nurses 30 to 55 years of age provided detailed information by questionnaire. Every two years, we send follow-up questionnaires to update our information on potential risk factors and to identify newly diagnosed cases of various diseases.

Ascertainment of Risk and Preventive Factors

The 1976 questionnaire inquired about the nurses' height and weight and about myocardial infarction in a parent before the age of 60 years. Each follow-up questionnaire asked for updated information on weight for calculation of the body-mass index (the weight in kilograms divided by the square of the height in meters) as a measure of obesity.[1] Each questionnaire also inquired about cigarette smoking (including past smoking and the number of cigarettes smoked per day for current smokers), menopausal status (including the use of postmenopausal hormones), and physician-diagnosed hypertension and high cholesterol levels; self-reports of these diagnoses were quite accurate as compared with medical records.[2]

Information on physical activity was first obtained in 1980 and was updated in 1982, 1986, 1988, and 1992 with a previously validated questionnaire on the frequency of activity.[3-5] We estimated the amount of time per week spent in moderate-to-vigorous ac-

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tivities requiring 3 or more MET per hour; this excluded walking at an easy or normal pace but included brisk walking at 5 km (3 mi) or more per hour.

In 1980 we assessed diet with a 61-item food-frequency questionnaire. In 1984 the questionnaire was expanded to 116 food items, and similar questionnaires were used to update information on diet in 1986 and 1990. The questionnaires also assessed the intake of multivitamin and single-vitamin supplements. The reproducibility and validity of the food-frequency questionnaires are high when compared with multiple one-week diet records and a variety of biochemical markers, as described in detail elsewhere.[6]

To calculate the intake of specific nutrients, we specified a common unit or portion size for each food on the questionnaire and asked the participant how often, on average, she had consumed that amount during the previous year. The nine response categories ranged from "never" to "six or more times per day." The intake of nutrients was computed by multiplying the frequency of consumption of each unit of food by its nutrient content. Beer, wine, and liquor were included in each of the food-frequency questionnaires to permit calculation of alcohol intake.

Definition of Low-Risk Groups

Our aim in this analysis was to estimate the effect of diet and lifestyle on the risk of coronary heart disease. Therefore, we did not consider the additional effect of pharmacologic agents, including aspirin or postmenopausal hormones, or medical conditions, such as hypertension and high cholesterol levels. However, all analyses were adjusted for those factors. We sought to limit the number of lifestyle and dietary variables, and we included only those with reasonable evidence supporting their effect on coronary heart disease, while recognizing that most such variables have never been tested in randomized trials.

For smoking, the low-risk group was defined as those who had stopped smoking or had never smoked. Cigarette smoking is a major risk factor for coronary heart disease[7] and stroke.[8] The risk declines after the cessation of smoking and approximates the level of those who have never smoked after 10 to 14 years.[9-11]

Moderate alcohol consumption is associated with a lower risk of coronary heart disease[12-14] and ischemic stroke[15] but can raise the risk of hemorrhagic stroke.[16] We considered women as being at low risk if they consumed an average of 5 g or more per day (a typical glass of wine has 11 g of alcohol). For simplicity, and because so few women in this cohort drank heavily (1.2 percent reported drinking more than 45 g of alcohol per day), we did not define an upper limit for alcohol consumption, although clearly this would be necessary in establishing public health guidelines.

For physical activity, we considered subjects to be at low risk if they engaged in an average of at least one half-hour per day of vigorous or moderate activity, including brisk walking. This cutoff point is consistent with various guidelines.[17,18] We have found that this level of activity is associated with a substantial reduction in the risk of coronary heart disease[5] and stroke (unpublished data).

Women with a body-mass index of less than 25, the standard cutoff point for overweight, were considered to be at low risk. We have previously found a significantly higher risk of coronary heart disease among women with a body-mass index of 23 to 24.9, as compared with women with a body-mass index of less than 21.[19] The cutoff point of 25 represents a higher-than-optimal level.

We considered subjects to be at low risk if they scored in the highest 40 percent of the cohort on a composite measure based on a diet low in trans fat and glycemic load (which reflects the extent to which diet raises blood glucose levels), high in cereal fiber, marine n−3 fatty acids, and folate, and with a high ratio of polyunsaturated to saturated fat. For each of these six dietary factors, we calculated the distribution according to quintiles within the cohort and assigned each woman a score of 1 to 5 corresponding to the quintile of intake, with 5 representing the most favorable quintile. The cutoff points for the most favorable quintile for each dietary factor were as follows: less than 1.56 percent of energy supplied by trans fat, a ratio of polyunsaturated to saturated fat of more than 0.43, consumption of more than 4.2 g of cereal fiber per day, a glycemic load of less than 723 units per day, more than 0.1 percent of energy from marine n−3 fatty acids, and consumption of more than 525 μg of folate per day. For each participant, the quintile value for each nutrient was summed (with a higher score representing a lower risk), and the participants with dietary scores in the highest 40 percent were defined as the low-risk group with respect to diet. We and others have previously demonstrated the importance of each of these factors for the risk of coronary disease.[20-26]

Population for Analysis

We excluded women who left 10 or more items blank on the 1980 diet questionnaire, those with implausibly low or high scores for total food or energy intake (below 500 or above 3500 kcal per day), and those with previously diagnosed cancer, angina, myocardial infarction, stroke, or other cardiovascular diseases. We did not exclude women who reported high cholesterol levels or hypertension. Because diabetes increases the risk of coronary heart disease and can induce changes in diet and lifestyle, we excluded women who had diabetes at base line. Women given a diagnosis of diabetes during follow-up were included, but we used only the dietary information collected before the diagnosis. The final 1980 base-line population consisted of 84,129 women.

Ascertainment of End Points

We tried to review medical records for all reports of major coronary events (nonfatal myocardial infarction or death due to coronary heart disease) that occurred between the return of the 1980 questionnaire and June 1, 1994. The records were reviewed by study physicians who had no knowledge of the subjects' self-reported risk factors. Myocardial infarction was confirmed according to World Health Organization criteria, as follows: symptoms plus either diagnostic electrocardiographic changes or elevated cardiac-enzyme levels. Infarctions that required hospital admission and for which confirmatory information was obtained, but for which no medical records were available, were designated as probable (these amounted to 17 percent of all infarctions). We included all confirmed and probable cases. Deaths were identified from state vital records and the National Death Index or were reported by the subject's family or postal authorities. Information on the cause of death was available for more than 98 percent of deaths.

Confirmed deaths from coronary heart disease were defined as those caused by myocardial infarction according to hospital records or autopsy, or those for which coronary heart disease was listed as the cause of death and evidence of previous coronary disease was available. In addition to confirmed deaths from coronary heart disease, we included the deaths in which coronary heart disease was listed as the underlying cause but no records were available (15 percent of all deaths from coronary heart disease). We also included sudden deaths with no plausible cause other than coronary heart disease (12 percent of deaths from coronary heart disease). Analyses limited to confirmed cases yielded similar results, although with less precision.

Strokes were considered confirmed if they met the criteria of the National Survey of Stroke.[27] We excluded subdural hematomas and strokes caused by infection or neoplasia. Nonfatal strokes for which medical records were unavailable were defined as probable strokes and included in the analysis if they required hospitalization and were corroborated by letter or interview. Fatal strokes were confirmed by review of autopsy records, hospital records, or death certificates listing stroke as the underlying cause. In secondary analyses, strokes were added to coronary events to form the broader end point of cardiovascular events.

Statistical Analysis

The person-time for each participant was calculated from the date of return of the 1980 questionnaire to the date of the first coronary (or cardiovascular) event, death, or June 1, 1994, whichever came first. Women were classified in risk categories as described above. In multivariate models with pooled logistic regression, each

two-year interval was treated as an independent observation; we simultaneously adjusted for age, time period (seven time periods), presence or absence of a parental history of myocardial infarction before the age of 60 years, menopausal status and postmenopausal use or nonuse of hormones, presence or absence of hypertension, and the presence or absence of high cholesterol levels. In initial analyses, we calculated relative risks and 95 percent confidence intervals for categories within each factor of the low-risk profile, adjusting for the other coronary risk factors listed above, but not for the other components of the low-risk index. We then examined the low-risk group, with the various factors taken together.

We began by including only diet, smoking, and exercise. We then added body-mass index and, finally, alcohol use to examine all five factors simultaneously. In those analyses, we compared women in the low-risk category for each of the component variables with all other women, following a method previously used by Wacholder et al.[28] We calculated the population attributable risk,[29] an estimate of the percentage of coronary heart disease in this population that would not have occurred if all women had been in the low-risk group, on the assumption that there was a causal relation between the risk factors and coronary heart disease. We repeated the analysis among nonsmokers to estimate the proportion of coronary heart disease that could be prevented by adherence to the remainder of the guidelines.

To obtain the best estimate of long-term dietary intake, we used the cumulative-update method,[21] which takes the average of all previous dietary data. For example, for the interval from 1980 to 1984 we used the 1980 dietary data, and for the interval from 1984 to 1986 we used the average of 1980 and 1984. We used the same method for physical activity, which was updated in 1982, 1986, 1988, and 1992. For all other risk variables and covariates apart from diet and exercise, we used the most recent information. Body-mass index and smoking status were updated every two years, and alcohol intake was updated in 1984, 1986, and 1990.

RESULTS

During 14 years of follow-up, we documented 1128 coronary heart disease events (832 nonfatal myocardial infarctions and 296 deaths from coronary heart disease) in the study cohort. We also documented 705 strokes. Table 1 shows the estimates of the relative risk of a coronary event for each of the five factors considered in the low-risk profile and the proportion of the cohort in each risk category. These estimates have been adjusted for the other covariates but not for the other elements of the low-risk index. The most important single factor was cigarette smoking, with a relative risk of 5.48 for those smoking 15 or more cigarettes per day, as compared with nonsmokers. Even smoking 1 to 14 cigarettes per day tripled the risk. In this population, 41 percent of the coronary events could be attributed to current smoking.

In addition, each individual component of the low-risk profile showed a significant and substantial association with risk; each of the components of the dietary score was independently significant (data not shown). A gradient of risk was present within the categories of each variable that were included as low risk. For example, we included former smokers and those who had never smoked in the low-risk category, although former smokers were at significantly higher risk than those who had never smoked. Likewise, we included women who consumed more than 5 g of alcohol daily as being at low risk, although women consuming 5 to 9 g of alcohol daily were at higher risk than those consuming 10 g or more a day. We included all women with dietary scores in the highest 40 percent as being at low risk, but within that group, those with higher scores had lower risk.

Table 2 provides estimates of the reduction in risk for women in the low-risk category for three, four, or five of the modifiable risk factors. Women in the low-risk category for all five factors considered together, as compared with all other women, had a relative risk of 0.17 (95 percent confidence interval, 0.07 to 0.41). The population attributable risk was 82 percent (95 percent confidence interval, 58 to 93), suggesting that 82 percent of the coronary events in this cohort might have been prevented if all women had been in the low-risk group.

TABLE 1. DISTRIBUTIONS OF INDIVIDUAL MODIFIABLE RISK FACTORS AND RELATIVE RISK OF CORONARY EVENTS IN THE NURSES' HEALTH STUDY, 1980 TO 1994.

FACTOR	RELATIVE RISK (95% CI)*	PERCENTAGE IN EACH CATEGORY†
Dietary score (quintile)‡		
1	1.90 (1.55–2.34)	20
2	1.50 (1.21–1.88)	17
3	1.57 (1.29–1.91)	28
4	1.23 (0.98–1.55)	16
5	1.0 (reference)	20
Exercise (hr/wk)§		
<1.0	1.41 (1.15–1.75)	20
1.0–2.2	1.23 (0.99–1.53)	15
2.3–3.5	1.18 (0.94–1.47)	18
3.6–5.5	1.05 (0.82–1.34)	18
>5.5	1.0 (reference)	17
Body-mass index		
≥30.0	1.57 (1.30–1.91)	12
25.0–29.9	1.33 (1.12–1.57)	24
23.0–24.9	1.16 (0.95–1.41)	18
<23.0	1.0 (reference)	33
Smoking (cigarettes/day)		
≥15	5.48 (4.67–6.42)	15
1–14	3.12 (2.50–3.90)	7
Former smoker	1.55 (1.31–1.82)	34
Never smoked	1.0 (reference)	44
Alcohol consumption (g/day)		
0	1.65 (1.39–1.95)	34
0.1–5.0	1.41 (1.18–1.68)	33
5.1–10.0	1.26 (1.00–1.60)	11
>10.0	1.0 (reference)	22

*Relative risk was estimated from a multiple logistic-regression model and adjusted for age (in five-year categories), time periods (seven time periods), presence or absence of a parental history of myocardial infarction before the age of 60 years, menopausal status and use or nonuse of postmenopausal hormones, presence or absence of a history of hypertension, and presence or absence of a history of high cholesterol levels. CI denotes confidence interval.

†Percentages may not add to 100 because of rounding and missing values.

‡The intakes of trans fat, cereal fiber, marine n−3 fatty acids, and folate (including supplements), glycemic load, and the ratio of polyunsaturated fat to saturated fat were categorized in quintiles. For each participant, the quintile values for each nutrient were summed (a higher quintile score represented a lower risk), and the sum was recategorized into quintiles.

§Activities included vigorous sports, jogging, brisk walking, heavy gardening, heavy housework, and activities "strenuous enough to build up a sweat."

TABLE 2. RISK OF CORONARY EVENTS IN LOW-RISK GROUPS DEFINED ACCORDING TO DIFFERENT CONSTELLATIONS OF MODIFIABLE RISK FACTORS FOR CORONARY DISEASE IN THE NURSES' HEALTH STUDY, 1980 TO 1994.*

GROUP	PERCENTAGE OF WOMEN IN GROUP	NO. OF CORONARY HEART DISEASE EVENTS	RELATIVE RISK (95% CI)†	POPULATION ATTRIBUTABLE RISK (95% CI)‡
				%
Three low-risk factors§ Diet score in upper 2 quintiles Nonsmoking Moderate-to-vigorous exercise ≥30 min/day	12.7	62	0.43 (0.33–0.55)	54 (42–64)
Four low-risk factors¶ Diet score in upper 2 quintiles Nonsmoking Moderate-to-vigorous exercise ≥30 min/day Body-mass index <25	7.2	24	0.34 (0.23–0.52)	64 (46–76)
Five low-risk factors Diet score in upper 2 quintiles Nonsmoking Moderate-to-vigorous exercise ≥30 min/day Body-mass index <25 Alcohol ≥5 g/day	3.1	5	0.17 (0.07–0.41)	82 (58–93)

*CI denotes confidence interval.

†Relative risk was estimated from a multiple logistic-regression model and adjusted for age (in five-year categories), time periods (seven time periods), presence or absence of a parental history of myocardial infarction before the age of 60 years, menopausal status and use or nonuse of postmenopausal hormones, presence or absence of a history of hypertension, and presence or absence of a history of high cholesterol.

‡The population attributable risk is the percentage of coronary disease events in the population that are attributable to the nonadherence to the particular combination of lifestyle characteristics. Women with missing values were considered to be in the high-risk group.

§The model was also adjusted for body-mass index and alcohol use.

¶The model was also adjusted for alcohol use.

As shown in Table 3, we repeated this analysis with only the 78 percent of women who were not currently smoking. Women who were in the low-risk category for the remaining four risk factors, as compared with all other current nonsmokers, had a relative risk of 0.25 (95 percent confidence interval, 0.10 to 0.60). The population attributable risk was 74 percent (95 percent confidence interval, 39 to 90 percent), suggesting that among the nonsmokers, 74 percent of the coronary disease events might have been prevented by compliance with the remaining components of the low-risk index.

To adjust for possible confounding according to socioeconomic status, we conducted further analyses in which we controlled for the parents' occupation and husband's education. This had no substantial effect on the estimates (for example, the relative risk in the low-risk group went from 0.17 to 0.19).

Only about 3 percent of the population met the criteria for low risk. To address the possibility that these women represented a unique and peculiar subgroup, we performed further analyses, successively relaxing the criteria. We observed a graded effect on the population attributable risk. For example, if women at low risk were defined as those not currently smoking, having dietary scores among the highest 45 percent, exercising at least 25 minutes a day, having a body-mass index under 26, and drinking at least 4 g of alcohol a day (a group that constituted 5.1 percent of the population), the population attributable risk would be 72 percent (95 percent confidence interval, 47 to 83 percent). Further relaxation of the criteria to include 10 percent of the population (at least 15 minutes of exercise a day, consumption of more than 2 g of alcohol a day, and a body-mass index of less than 28) yielded a relative risk of 0.36 (95 percent confidence interval, 0.26 to 0.50) and a population attributable risk of 62 percent (95 percent confidence interval, 47 to 72 percent).

Table 4 shows the results for analyses of major cardiovascular disease (coronary events plus stroke). Women in the low-risk group had a relative risk of 0.25 (95 percent confidence interval, 0.14 to 0.44), with a population attributable risk of 74 percent (95 percent confidence interval, 55 to 86 percent).

DISCUSSION

In this population of middle-aged women, those who did not smoke cigarettes, were not overweight, maintained the healthful diet described above, exer-

TABLE 3. RISK OF CORONARY EVENTS IN LOW-RISK GROUPS DEFINED ACCORDING TO DIFFERENT CONSTELLATIONS OF MODIFIABLE RISK FACTORS FOR CORONARY DISEASE AMONG CURRENT NONSMOKERS IN THE NURSES' HEALTH STUDY, 1980 TO 1994.*

GROUP	PERCENTAGE OF WOMEN IN GROUP	NO. OF CORONARY HEART DISEASE EVENTS	RELATIVE RISK (95% CI)†	POPULATION ATTRIBUTABLE RISK (95% CI)‡
				%
Two low-risk factors§	16.4	62	0.68 (0.52–0.88)	28 (10–44)
Diet score in upper 2 quintiles				
Moderate-to-vigorous exercise ≥30 min/day				
Three low-risk factors¶	9.4	24	0.54 (0.36–0.82)	43 (17–62)
Diet score in upper 2 quintiles				
Moderate-to-vigorous exercise ≥30 min/day				
Body-mass index <25				
Four low-risk factors	4.0	5	0.25 (0.10–0.60)	74 (39–90)
Diet score in upper 2 quintiles				
Moderate-to-vigorous exercise ≥30 min/day				
Body-mass index <25				
Alcohol ≥5 g/day				

*CI denotes confidence interval.

†Relative risk was estimated from a multiple logistic-regression model and adjusted for age (in five-year categories), time periods (seven time periods), presence or absence of a parental history of myocardial infarction before the age of 60 years, menopausal status and use or nonuse of postmenopausal hormones, presence or absence of a history of hypertension, and presence or absence of a history of high cholesterol levels.

‡The population attributable risk is the percentage of coronary disease events in the population that are attributable to the nonadherence to the particular combination of lifestyle characteristics.

§The model was also adjusted for body-mass index and alcohol use.

¶The model was also adjusted for alcohol use.

cised moderately or vigorously for half an hour a day, and consumed alcohol moderately had an incidence of coronary events that was more than 80 percent lower than that in the rest of the population. Closer adherence to a more healthful lifestyle might reduce the risk of coronary heart disease still further.

This analysis has several important limitations. Despite the large numbers of subjects and the long follow-up, the estimates were somewhat imprecise, largely because there were few cases of coronary heart disease among women in the low-risk categories. Indeed, we could not provide reliable estimates on which to base more stringent recommendations because of the small number of cases. The fact that the incidence of coronary events increases in a graded fashion as the criteria for low risk are relaxed supports the robustness of the findings, and suggests that the results do not apply solely to a select group of peculiarly health-conscious persons. Some of the lifestyle characteristics (especially diet and physical activity) were measured with error, which undoubtedly caused some misclassification. However, with the prospective design, such misclassification would tend to lead to an underestimate of the true effect. Some factors we considered have not been tested in randomized trials with clinical end points. However, ample observational data support their use. For some variables, there probably will never be randomized trials of primary prevention, so we must make decisions on the basis of the best available information.

For simplicity, we considered only a limited set of variables. For example, we did not include consumption of nuts,[30,31] linolenic acid,[32] vitamin B_6,[23] or vitamin E[33-35] or the use of aspirin or postmenopausal hormones.[36,37] Larger reductions in risk might be possible with these added preventive factors. Some of these factors may be especially worthy of consideration for women who avoid alcohol to minimize the risk of breast cancer[38] or because of a personal or family history of alcoholism.

We also did not consider pharmacologic treatment of hypertension and of lipid levels, which has proved efficacious in the prevention of coronary heart disease. However, we did adjust for these factors in the analysis. Since part of the effect of diet and lifestyle is mediated through improvements in lipid levels and blood pressure, adjustment for those conditions might lead to an underestimate of the overall benefit of the factors we considered. Our nurse participants are more likely to receive treatment for these conditions than the general population. However, not all participants are receiving optimal therapy; there is thus a greater potential for prevention, if all treatments are considered. Our results complement those of Stamler et al.,[39] who found that the relative risk of death from coronary heart disease ranged from 0.08 to 0.23

TABLE 4. RISK OF CORONARY EVENTS OR STROKE (CARDIOVASCULAR EVENTS) IN LOW-RISK GROUPS DEFINED ACCORDING TO DIFFERENT CONSTELLATIONS OF MODIFIABLE RISK FACTORS FOR MAJOR CARDIOVASCULAR DISEASE IN THE NURSES' HEALTH STUDY, 1980 TO 1994.*

GROUP	PERCENTAGE OF WOMEN IN GROUP	NO. OF CARDIOVASCULAR EVENTS	RELATIVE RISK (95% CI)†	POPULATION ATTRIBUTABLE RISK (95% CI)‡
				%
Three low-risk factors§	12.7	106	0.46 (0.37–0.55)	51 (42–60)
Diet score in upper 2 quintiles				
Nonsmoking				
Moderate-to-vigorous exercise ≥30 min/day				
Four low-risk factors¶	7.2	44	0.38 (0.28–0.51)	60 (47–70)
Diet score in upper 2 quintiles				
Nonsmoking				
Moderate-to-vigorous exercise ≥30 min/day				
Body-mass index <25				
Five low-risk factors	3.1	12	0.25 (0.14–0.44)	74 (55–86)
Diet score in upper 2 quintiles				
Nonsmoking				
Moderate-to-vigorous exercise ≥30 min/day				
Body-mass index <25				
Alcohol ≥5 g/day				

*CI denotes confidence interval.

†Relative risk was estimated from a multiple logistic-regression model and adjusted for age (in five-year categories), time periods (seven time periods), presence or absence of a parental history of myocardial infarction before the age of 60 years, menopausal status and use or nonuse of postmenopausal hormones, presence or absence of a history of hypertension, and presence or absence of a history of high cholesterol.

‡The population attributable risk is the percentage of major cardiovascular events in the population that are attributable to the nonadherence to the particular combination of lifestyle characteristics.

§The model was also adjusted for body-mass index and alcohol use.

¶The model was also adjusted for alcohol use.

in low-risk persons, defined as nondiabetic subjects with no history of coronary disease who were not current smokers and who had cholesterol levels of less than 200 mg per deciliter (5.17 mmol per liter) and blood pressure of 120/80 mm Hg or less.

By simultaneously examining the effect of several lifestyle variables, we took into account the clustering of healthful types of behavior within individual women. In addition, we adjusted for many coronary risk factors. Nevertheless, confounding by other variables, particularly socioeconomic status, could have affected our results. However, all the participants were registered nurses with some college education. Analysis of home addresses according to census-tract data found substantial economic homogeneity (Laden F: personal communication). Furthermore, adjustment for parental occupation and the husband's education had little effect on the findings. Indeed, at least some of the health benefits of higher socioeconomic status are mediated through the lifestyle variables we studied.

Thus, although vigorous pharmacologic treatment of hypertension and lipid levels (when necessary) has been proved effective, these data support the hypothesis that adopting a more healthful lifestyle could prevent a substantial majority of coronary disease events in women.

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A PROSPECTIVE STUDY OF WALKING AS COMPARED WITH VIGOROUS EXERCISE IN THE PREVENTION OF CORONARY HEART DISEASE IN WOMEN

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Abstract

Background The role of walking, as compared with vigorous exercise, in the prevention of coronary heart disease remains controversial, and data for women on this topic are sparse.

Methods We prospectively examined the associations between the score for total physical activity, walking, and vigorous exercise and the incidence of coronary events among 72,488 female nurses who were 40 to 65 years old in 1986. Participants were free of diagnosed cardiovascular disease or cancer at the time of entry and completed serial detailed questionnaires about physical activity. During eight years of follow-up, we documented 645 incident coronary events (nonfatal myocardial infarction or death from coronary disease).

Results There was a strong, graded inverse association between physical activity and the risk of coronary events. As compared with women in the lowest quintile group for energy expenditure (expressed as the metabolic-equivalent [MET] score), women in increasing quintile groups had age-adjusted relative risks of 0.77, 0.65, 0.54, and 0.46 for coronary events (P for trend <0.001). In multivariate analyses, the inverse gradient remained strong (relative risks, 0.88, 0.81, 0.74, and 0.66 for women in increasing quintile groups as compared with those in the lowest quintile group; P for trend=0.002). Walking was inversely associated with the risk of coronary events; women in the highest quintile group for walking, who walked the equivalent of three or more hours per week at a brisk pace, had a multivariate relative risk of 0.65 (95 percent confidence interval, 0.47 to 0.91) as compared with women who walked infrequently. Regular vigorous exercise ($\geq$6 MET) was associated with similar risk reductions (30 to 40 percent). Sedentary women who became active in middle adulthood or later had a lower risk of coronary events than their counterparts who remained sedentary.

Conclusions These prospective data indicate that brisk walking and vigorous exercise are associated with substantial and similar reductions in the incidence of coronary events among women. (N Engl J Med 1999;341:650-8.)

In epidemiologic studies, physical activity has been associated with a decrease in the risk of coronary heart disease,[1,2] but data on women have been sparse. Moreover, the specific role of walking, the most common form of exercise among women,[3] has not been fully elucidated. The most recent federal guidelines from the Centers for Disease Control and Prevention and the American College of Sports Medicine,[4] as well as the Surgeon General's report on physical activity and health,[3] endorse at least 30 minutes of moderate-intensity physical activity on most, and preferably all, days of the week, whereas earlier guidelines recommended vigorous endurance exercise for at least 20 minutes three or more times per week.[5] Although the current guidelines encourage a level of activity that is safe, achievable, and feasible for most Americans (60 percent of whom do not engage in regular physical activity),[6,7] the potential benefits of moderate-intensity activity in preventing coronary heart disease remain unclear.

We therefore assessed the comparative roles of walking and vigorous exercise in the prevention of coronary events in a large cohort of women enrolled in the prospective Nurses' Health Study. Detailed and repeated assessments of physical activity were performed to examine the degree to which total physical activity, walking time and pace, vigorous exercise, and change in activity level were associated with the incidence of coronary events in this cohort.

METHODS

Study Population

The Nurses' Health Study was initiated in 1976, when 121,700 female registered nurses 30 to 55 years old who were residing in 11 large U.S. states completed a mailed questionnaire on their medical history and lifestyle. Every two years, follow-up questionnaires have been sent to obtain updated information on potential risk factors and to identify newly diagnosed cases of coronary heart disease or other illnesses. For the primary analyses in the

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present study, the base-line data were those gathered in 1986, when detailed information on physical activity was first collected, and the duration of follow-up was eight years. After women who reported a diagnosis of cardiovascular disease or cancer at base line were excluded, the population for analysis was made up of 72,488 women 40 to 65 years old in 1986.

Assessment of Physical Activity

Detailed information on physical activity was first collected in 1986 and was updated in 1988 and 1992. Participants were asked to report the average amount of time spent per week during the previous year in walking or hiking outdoors (including walking to work or while playing golf), jogging (at a speed slower than 10 minutes per mile [6 minutes per kilometer]), running (at 10 minutes per mile or faster), bicycling (including the use of a stationary bicycle), swimming laps, playing tennis or squash, or participating in calisthenics, aerobics, or aerobic dance; in addition, the women were asked to report the average number of flights of stairs they climbed each week. Women also reported their usual walking pace: easy or casual (<2.0 miles per hour [mph] [3.2 km per hour]), average (2.0 to 2.9 mph [3.2 to 4.6 km per hour]), brisk (3.0 to 3.9 mph [4.8 to 6.2 km per hour]), or very brisk (≥4.0 mph [6.4 km per hour]). Using a standardized classification of the energy costs of physical activities,[8] we calculated a weekly metabolic-equivalent (MET) score for total physical activity, vigorous activity (≥6 MET per hour), nonvigorous activity (<6 MET per hour), and walking (2.5 to 4.5 MET per hour, depending on the pace). One MET is the caloric need per kilogram of body weight per hour of activity, divided by the caloric need per kilogram per hour at rest. Physical-activity scores were expressed as MET-hours per week. Validation of the questionnaire for assessing physical activity has been described previously in a similar cohort[9]; the overall correlation between physical activities reported on the questionnaire and those recorded in four one-week diaries was 0.62, and the correlation was 0.79 for activities reported on the questionnaire and those recalled after one week.[9]

For secondary analyses, we used data from a shorter questionnaire about physical activity that was administered in 1980 and 1982. On the 1980 questionnaire, women were asked to report the average number of hours they spent each week during the previous year engaged in moderate or vigorous recreational activities, including vigorous sports, jogging, bicycling, brisk walking, heavy gardening, or heavy housework. On the 1982 questionnaire, women were asked the question: "For how many hours per week, on average, do you engage in activity strenuous enough to build up a sweat?" To analyze this information, we calculated the cumulative average number of hours per week spent in moderate or vigorous recreational activities (all the activities listed above except for walking at a casual or average pace), as assessed in 1980, and (with updated information) in 1982, 1986, 1988, and 1992.

Ascertainment of End Points

The primary end points for this study were coronary events (defined as nonfatal myocardial infarction or death due to coronary disease) that occurred after the return of the 1986 questionnaire and before June 1994. We requested permission to review the medical records of women who reported a nonfatal myocardial infarction on a follow-up questionnaire. Study physicians who had no knowledge of the women's self-reported risk factors reviewed the records. Nonfatal myocardial infarction was confirmed if data in the medical records met World Health Organization criteria for this condition — namely, symptoms and either diagnostic electrocardiographic changes or elevated cardiac-enzyme levels.[10] Myocardial infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter but for which no medical records were available were designated as probable infarctions (and constituted 17 percent of all reported nonfatal infarctions). We included all confirmed and probable cases of infarction in the analyses because the results were the same whether probable cases were included or excluded. Follow-up information for nonfatal infarction was obtained for more than 95 percent of the potential person-time of follow-up.

Deaths were reported by family members or the Postal Service or were ascertained through state registries or the National Death Index. We estimate that follow-up for deaths was more than 98 percent complete.[11] Fatal coronary disease (codes 410 through 414 of the *International Classification of Diseases, 8th Revision*[12]) was confirmed by review of the hospital or medical autopsy records or by review of the death certificate if coronary disease was the stated cause of death and evidence of previous coronary disease was available. We designated deaths for which coronary disease was listed as the underlying cause on the death certificate, but for which no records were available, as due to presumed fatal coronary disease. These cases constituted 14.7 percent of all fatal coronary events. We also included sudden deaths (12.3 percent of all fatal coronary events). Analyses limited to confirmed cases yielded results similar to those in which confirmed and presumed cases of fatal coronary disease were combined.

Statistical Analysis

For primary analyses, we used the detailed assessment of physical activity performed in 1986 as the base line. Person-time for each participant was calculated from the date of her return of the 1986 questionnaire to the date of an incident coronary event, death from any cause, or June 1, 1994, whichever came first. Data on women who had a coronary event or who died from any cause were censored with respect to subsequent analysis during follow-up. The relative risk of a coronary event was computed as the incidence of the event in each quintile group for MET score, divided by the incidence in the lowest quintile group, with adjustment for five-year age categories. Tests of linear trend for increasing quintiles of MET scores were performed by treating the score as a continuous variable and designating the median score for the category as its value. To represent long-term levels of physical activity for individual women as accurately as possible and to reduce measurement error, we calculated cumulative averages of the MET scores from all the questionnaires available up to the start of each two-year follow-up interval. A similar method for analyzing repeated dietary measurements has been described in detail elsewhere.[13]

For secondary analyses, we used data gathered in 1980 as the base line. We used the continuous values of hours of activity per week to compute the cumulative averages at the start of each interval and grouped the average hours per week of moderate or vigorous exercise into five categories (<1, 1 to 1.9, 2 to 3.9, 4 to 6.9, and ≥7 hours per week). To examine the association between a change in physical activity and the risk of coronary events, we related the change between 1980 and 1986 in hours spent engaged in moderate or vigorous activity to coronary events occurring between 1986 and 1994.

We used pooled logistic regression[14] to adjust simultaneously for potential confounding variables, including age (in five-year categories), period during the study (four two-year periods), smoking status (never smoked, previously smoked, or currently smokes 1 to 14, 15 to 24, or ≥25 cigarettes per day), body-mass index (the weight in kilograms divided by the square of the height in meters, in five categories), alcohol consumption (0, 1 to 4, 5 to 14, or ≥15 g per day), menopausal status (premenopausal, postmenopausal without hormone-replacement therapy, postmenopausal with previous hormone-replacement therapy, or postmenopausal with current hormone-replacement therapy), history of diabetes, history of hypercholesterolemia, history of hypertension, parental history of myocardial infarction before the age of 60 years, use of multivitamin supplements, use of vitamin E supplements, and use of aspirin (none, one to six doses per week, or seven or more doses per week). Covariates were updated according to questionnaire information every two years. The population attributable risk was calculated from multivariate models with use of the following formula: ([1 − relative risk] ÷ relative risk) × (proportion of inactive cases) (×100).[15]

TABLE 1. DISTRIBUTION OF INDICATORS OF CORONARY RISK ACCORDING TO QUINTILE GROUP FOR TOTAL PHYSICAL-ACTIVITY SCORE AT BASE LINE (1986).*

VARIABLE	QUINTILE GROUP FOR TOTAL PHYSICAL ACTIVITY†				
	1	2	3	4	5
No. of women	13,859	15,065	14,598	14,326	14,640
Total physical-activity score (MET-hr/wk)					
Median	0.8	3.2	7.7	15.4	35.4
Range	0–2.0	2.1–4.6	4.7–10.4	10.5–21.7	>21.7
			percentage of group		
Risk indicator					
Currently smoking	28.2	23.7	19.6	17.4	17.5
History of hypertension	26.1	25.1	24.0	22.4	21.0
History of diabetes	4.2	3.3	3.7	2.8	2.6
History of hypercholesterolemia	12.0	11.4	11.7	11.6	10.6
Parent with myocardial infarction before age of 60 yr	14.0	14.4	13.9	14.2	14.0
Current postmenopausal hormone-replacement therapy‡	19.5	21.5	23.1	23.8	24.1
Use of multivitamin supplement	36.9	39.9	43.0	45.0	47.2
Use of vitamin E supplement	12.8	13.9	15.8	17.5	19.4
			mean		
Age (yr)	52.1	52.3	52.2	52.2	52.3
Alcohol consumption (g/day)	5.9	5.8	6.0	6.4	7.0
Body-mass index	25.1	24.6	24.2	23.9	23.5
Waist-to-hip ratio	0.79	0.79	0.78	0.78	0.77
Saturated fat (% of caloric intake)	12.3	11.9	11.7	11.5	11.2
Polyunsaturated fat (% of caloric intake)	6.2	6.1	6.2	6.1	6.1
Trans fat (% of caloric intake)	1.8	1.7	1.7	1.6	1.5
Dietary cholesterol (mg/1000 cal)	154	152	151	149	148

*Percentages and means for variables other than age have been standardized according to the age distribution of the overall study group.

†The total physical-activity score was expressed as MET-hours per week, calculated as the average time per week spent in each of eight activities, multiplied by the MET value of each activity. The MET value is the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram per hour at rest.

‡Values are percentages of postmenopausal women who used hormone-replacement therapy among all the postmenopausal women in each quintile group.

RESULTS

The distribution at base line of several indicators of coronary risk varied according to quintile group for total physical-activity score (expressed as MET-hours per week) in this cohort (Table 1). Women who were more physically active were less likely to be current smokers and, as expected, were leaner and had a lower prevalence of reported hypertension, diabetes, and hypercholesterolemia than less active women. More physically active women were also more likely to use postmenopausal hormone-replacement therapy, multivitamin and vitamin E supplements, and alcohol. In contrast, the activity level was not appreciably related to age, parental history of myocardial infarction, or dietary intake of fats or cholesterol.

The eight years of follow-up, from 1986 to 1994, included 559,435 person-years. During this follow-up period we documented 645 coronary events (475 nonfatal myocardial infarctions and 170 deaths from coronary disease) among the 72,488 women who in 1986 were 40 to 65 years old, had neither cardiovascular disease nor cancer, and completed a detailed physical-activity questionnaire. The total physical-activity score (expressed as MET-hours per week) in 1986 was strongly inversely related to the risk of coronary events during the eight-year follow-up (Table 2). In age-adjusted analyses from 1986 to 1994 (in which MET scores, first computed in 1986, were calculated as cumulative updated averages in 1988 and 1992), the risk of coronary events decreased monotonically with increasing quintiles for MET score (relative risks, 0.77, 0.65, 0.54, and 0.46 as compared with the risk in the lowest quintile group; P for trend <0.001). In multivariate analyses, after simultaneous control for age, smoking status, body-mass index, and other covariates (Table 2), the total physical-activity score remained a powerful predictor of the subsequent risk of coronary events; relative risks for increasing quintile groups for physical activity, as compared with the lowest quintile group, were 0.88, 0.81, 0.74, and 0.66 (P for trend $=0.002$). There was a significant risk reduction for the two highest quin-

TABLE 2. RELATIVE RISK OF CORONARY EVENTS ACCORDING TO QUINTILE GROUP FOR TOTAL PHYSICAL-ACTIVITY SCORE.*

VARIABLE	QUINTILE GROUP FOR TOTAL PHYSICAL ACTIVITY					P FOR TREND
	1	2	3	4	5	
MET-hr/wk						
Median	0.8	3.2	7.7	15.4	35.4	
Range	0–2.0	2.1–4.6	4.7–10.4	10.5–21.7	>21.7	
No. of coronary events	178	153	124	101	89	
Person-yr of follow-up	106,252	116,175	112,703	110,886	113,419	
	relative risk (95% CI)					
Type of analysis						
Age-adjusted	1.0	0.77 (0.62–0.96)	0.65 (0.52–0.82)	0.54 (0.42–0.69)	0.46 (0.36–0.60)	<0.001
Multivariate†	1.0	0.88 (0.71–1.10)	0.81 (0.64–1.02)	0.74 (0.58–0.95)	0.66 (0.51–0.86)	0.002
Multivariate, excluding first 2 yr†‡	1.0	0.91 (0.71–1.16)	0.79 (0.61–1.03)	0.69 (0.52–0.92)	0.66 (0.49–0.88)	0.004
Multivariate, excluding biologic intermediates†§	1.0	0.85 (0.69–1.06)	0.78 (0.62–0.99)	0.69 (0.54–0.88)	0.60 (0.46–0.77)	<0.001

*The total physical-activity score was computed as the cumulative updated average number of MET-hours per week for 1986, 1988, and 1992. The primary end point, events due to coronary heart disease, included nonfatal myocardial infarction and death due to coronary causes. In each type of analysis, the women in the lowest quintile group served as the reference group. CI denotes confidence interval.

†The model included variables for age (in five-year categories), period during the study (four two-year periods), smoking status (never smoked, previously smoked, or currently smokes 1 to 14, 15 to 24, or ≥25 cigarettes per day), body-mass index (in five categories), menopausal status (premenopausal, postmenopausal without hormone-replacement therapy, postmenopausal with previous hormone-replacement therapy, or postmenopausal with current hormone-replacement therapy), parental history with respect to myocardial infarction before the age of 60 years, multivitamin-supplement use, vitamin E supplement use, alcohol consumption (0, 1 to 4, 5 to 14, or ≥15 g per day), history of hypertension, history of diabetes, history of hypercholesterolemia, and aspirin use (none, one to six doses per week, or seven or more doses per week).

‡In this analysis, data from the first two years of follow-up after the completion of the physical-activity questionnaire were excluded in order to minimize potential bias due to subclinical disease.

§In this analysis, biologic intermediary covariates that may have had a role in mediating the effect of exercise (body-mass index, hypertension, high cholesterol level, and diabetes) were excluded from the model.

tile groups, with a total of 10.5 MET-hours per week or more (the equivalent of ≥3 hours per week of brisk walking or 1.5 hours per week of vigorous exercise). In a separate analysis in which data from the first two years of follow-up after completion of the activity questionnaires were excluded (to minimize potential bias due to the influence of subclinical disease on activity level), the results were not materially altered (Table 2). Exclusion of biologic variables that may have a role in mediating the effect of activity (e.g., body-mass index) strengthened the inverse association between physical-activity level and risk of a coronary event (relative risk, 0.60 [95 percent confidence interval, 0.46 to 0.77] for the highest vs. the lowest quintile group for total physical-activity score) (Table 2).

To assess the potential modifying effects of cigarette-smoking status, body-mass index, and parental history with respect to premature myocardial infarction on the relation between physical activity and coronary events, analyses were repeated within subgroups defined by these variables (Fig. 1). Physical activity was inversely related to the risk of coronary events in all strata for smoking (never, previously, and currently), for both nonobese and obese women, and for women with and those without a parental history of premature myocardial infarction.

We next used the 1980 questionnaire to assess the long-term association between moderate and vigorous recreational activity (from data updated in 1982, 1986, 1988, and 1992) and the incidence of coronary events from 1980 to 1994. The activities included were vigorous sports, jogging, bicycling, brisk walking, heavy gardening, heavy housework, and activities "strenuous enough to build up a sweat." The number of hours per week of moderate or vigorous activity were strongly inversely related to the risk of coronary events. In multivariate analyses, averages of 4.0 to 6.9 and 7 or more hours per week spent in these activities were associated with risk reductions of 31 percent and 37 percent, respectively, as compared with an average of less than 1 hour per week (P for trend <0.001).

To assess the role of changes in activity level during the follow-up period, we categorized information from women according to their activity in 1980 relative to that in 1986. In an analysis restricted to women who were sedentary (exercised less than once per week) in 1980 (54 percent of the cohort at that time), women who remained sedentary in 1986 had substantially higher rates of coronary events than women who became active. As compared with the risk among women who remained sedentary, the multivariate risks of coronary events from 1986 to 1994 for women in increasing quintile groups for total phys-

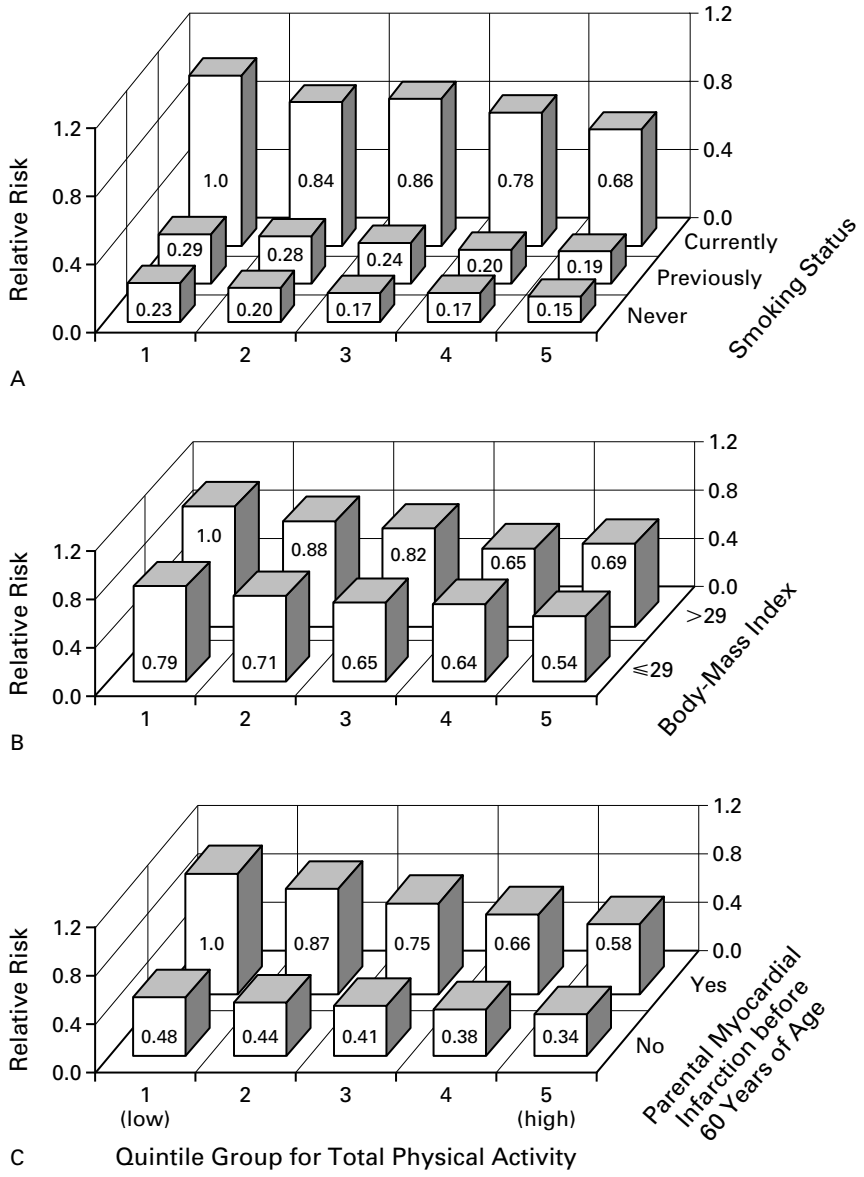

Figure 1. Multivariate Relative Risk of Coronary Events (Nonfatal Myocardial Infarction or Death from Coronary Causes) According to Quintile Group for Total Physical Activity within Subgroups Defined According to Smoking Status (Panel A), Body-Mass Index (Panel B), and Presence or Absence of a Parental History of Premature Myocardial Infarction (Panel C).

For each risk factor, the reference group is the category at highest risk. Relative risks have been adjusted for the variables in the full multivariate model (listed in Table 2).

ical activity (MET score) in 1986 were 0.85, 0.79, 0.67, and 0.71 (P for trend=0.03).

Detailed information about walking (duration and pace) was first obtained in 1986 and was updated in 1988 and 1992. Approximately 60 percent of the cohort of 72,488 women reported in 1986 that they walked for at least one hour per week, whereas only 26 percent engaged in vigorous exercise (≥6 MET) for at least one hour per week. To address the association between walking and the risk of coronary events while minimizing the potential confounding effect of vigorous activity, we restricted the study population to the women who reported no vigorous exercise (47 percent of the cohort). Women in the two highest quintile groups for walking score (a composite of walking time and pace) had a significantly reduced risk of coronary events as compared with the risk in the lowest quintile group (Table 3). As compared with sedentary women, women who had a walking score of 3.9 to 9.9 MET-hours per week —

TABLE 3. RELATIVE RISK OF CORONARY EVENTS AMONG WOMEN WHO DID NOT ENGAGE IN VIGOROUS EXERCISE, ACCORDING TO QUINTILE GROUP FOR WALKING.*

VARIABLE	QUINTILE GROUP FOR WALKING					P FOR TREND
	1	2	3	4	5	
MET-hr/wk						
Median	0	1.7	3	7.5	20	
Range	≤0.5	0.6–2.0	2.1–3.8	3.9–9.9	≥10	
No. of coronary events	92	78	73	77	57	
Person-yr of follow-up	46,900	51,934	45,413	62,011	51,162	
	relative risk (95% CI)					
Type of analysis						
Age-adjusted	1.0	0.69 (0.50–0.93)	0.71 (0.53–0.97)	0.52 (0.38–0.70)	0.46 (0.33–0.63)	<0.001
Multivariate†	1.0	0.78 (0.57–1.06)	0.88 (0.65–1.21)	0.70 (0.51–0.95)	0.65 (0.47–0.91)	0.02

*The walking score was computed as the cumulative updated average number of MET-hours per week spent walking for 1986, 1988, and 1992. These analyses excluded women who engaged in vigorous exercise. Coronary events included nonfatal myocardial infarction and death due to coronary causes. In each type of analysis, the women in the lowest quintile group served as the reference group. CI denotes confidence interval.

†The model included variables for age (in five-year categories), period during the study (four two-year periods), smoking status (never smoked, previously smoked, or currently smokes 1 to 14, 15 to 24, or ≥25 cigarettes per day), body-mass index (in five categories), menopausal status (premenopausal, postmenopausal without hormone-replacement therapy, postmenopausal with previous hormone-replacement therapy, or postmenopausal with current hormone-replacement therapy), parental history with respect to myocardial infarction before the age of 60 years, multivitamin-supplement use, vitamin E supplement use, alcohol consumption (0, 1 to 4, 5 to 14, or ≥15 g per day), history of hypertension, history of diabetes, history of hypercholesterolemia, and aspirin use (none, one to six doses per week, or seven or more doses per week).

the equivalent of 1 to 2.9 hours of walking per week at a brisk pace ≥3 mph — had a multivariate relative risk of 0.70 (95 percent confidence interval, 0.51 to 0.95) for subsequent coronary events, and those with scores of 10 or more MET-hours per week — the equivalent of 3 or more hours of walking per week at a brisk pace — had a multivariate relative risk of 0.65 (95 percent confidence interval, 0.47 to 0.91) for subsequent coronary events (P for trend=0.02). For those who walked five or more hours per week, the risk reduction exceeded 40 percent (data not shown). Exclusion of the small number of women who reported that they were "unable to walk" on the 1990 or 1992 questionnaire (2 percent of the cohort) did not alter these results.

Walking pace was also an important determinant of the risk of coronary events (Fig. 2). In multivariate analyses that also included control for time spent walking (in MET-hours per week), walking pace emerged as an independent predictor of the risk of coronary events. As compared with women who walked at an easy or casual pace (<2.0 mph), women who usually walked at an average pace (2.0 to 2.9 mph) had a multivariate relative risk of 0.75 (95 percent confidence interval, 0.59 to 0.96), whereas those who walked briskly or very briskly (≥3.0 mph) had a relative risk of 0.64 (95 percent confidence interval, 0.47 to 0.88).

To assess the comparative roles of walking and

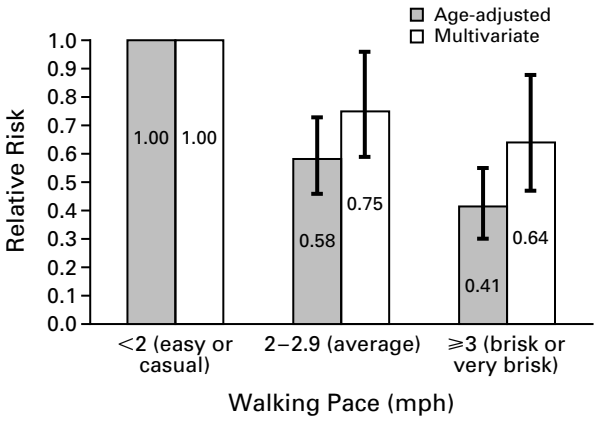

Figure 2. Age-Adjusted and Multivariate Relative Risks of Coronary Events (Nonfatal Myocardial Infarction or Death from Coronary Causes) According to Walking Pace.

These analyses excluded women who engaged in vigorous exercise. Multivariate relative risks have been adjusted for the variables in the full multivariate model, as listed in Tables 2 and 3, and for MET score for walking. Women who walked at an easy or casual pace served as the reference group. I bars indicate 95 percent confidence intervals. To convert miles per hour to kilometers per hour, multiply by 1.6.

TABLE 4. MULTIVARIATE RELATIVE RISKS OF CORONARY EVENTS ACCORDING TO CATEGORIES OF VIGOROUS EXERCISE AND WALKING.*

SCORE FOR WALKING (MET-HR/WK)	SCORE FOR VIGOROUS EXERCISE (MET-HR/WK)†		
	0	0.1–6.9	≥7.0
	relative risk (95% CI)		
0–0.6	1.0	0.78 (0.55–1.09)	0.76 (0.49–1.17)
0.7–6.9	0.84 (0.67–1.06)	0.86 (0.65–1.13)	0.59 (0.42–0.82)
≥7.0	0.74 (0.57–0.97)	0.56 (0.36–0.88)	0.70 (0.51–0.95)

*The model included variables for age (in five-year categories), period during the study (four two-year periods), smoking status (never smoked, previously smoked, or currently smokes 1 to 14, 15 to 24, or ≥25 cigarettes per day), body-mass index (in five categories), menopausal status (premenopausal, postmenopausal without hormone-replacement therapy, postmenopausal with previous hormone-replacement therapy, or postmenopausal with current hormone-replacement therapy), parental history with respect to myocardial infarction before the age of 60 years, multivitamin-supplement use, vitamin E supplement use, alcohol consumption (0, 1 to 4, 5 to 14, or ≥15 g per day), history of hypertension, history of diabetes, history of hypercholesterolemia, and aspirin use (none, one to six doses per week, or seven or more doses per week). Coronary events included nonfatal myocardial infarction and death due to coronary causes. The women with the lowest score for each type of activity served as the reference group. CI denotes confidence interval.

†Vigorous exercise was defined as participation in activities that required at least 6 MET per hour and included jogging, running, bicycling, lap swimming, tennis, squash, and calisthenics.

vigorous exercise in relation to coronary risk, we examined the incidence of coronary events according to the joint distribution of MET-hours per week spent in these activities (Table 4). Women who engaged in both walking and vigorous exercise had greater reductions in coronary events than those who participated in either type of activity alone. When examined simultaneously in a multivariate model, walking and vigorous exercise were each associated with a risk reduction. For every 5 MET-hours per week spent walking (the equivalent of 1.5 hours of walking per week at a brisk pace), the multivariate relative risk of coronary events was 0.86 (95 percent confidence interval, 0.74 to 0.99; β coefficient, −0.157), and for every 5 MET-hours per week spent in vigorous exercise (the equivalent of jogging, bicycling, swimming laps, or playing tennis for 45 minutes per week), the multivariate risk was 0.94 (95 percent confidence interval, 0.89 to 0.99; β coefficient, −0.059). Thus, we did not observe a greater magnitude of risk reduction with vigorous exercise than with walking in this cohort when we compared those who walked with those who exercised vigorously a similar number of MET-hours per week. However, our ability to assess the role of vigorous exercise was limited because of the small number of women in this study population (26 percent of the cohort) who engaged regularly in vigorous exercise.

DISCUSSION

These prospective data from a large cohort of women indicate that both walking and vigorous exercise are associated with substantial reductions in the incidence of coronary events. We observed that in this cohort, the magnitudes of risk reduction associated with brisk walking and vigorous exercise were similar when total energy expenditures were similar. These findings lend further support to current federal exercise guidelines, which endorse moderate-intensity exercise for at least 30 minutes on most (preferably all) days of the week.[3,4] Our results suggest that such a regimen (e.g., brisk walking for three or more hours per week) could reduce the risk of coronary events in women by 30 to 40 percent. Increasing walking time or combining walking with vigorous exercise appears to be associated with even greater risk reductions. Given the high prevalence in the United States of a sedentary lifestyle (78 percent of adults engage in less physical activity than currently recommended),[3] we estimate, on the basis of our multivariate relative-risk analyses, that one third of coronary events among middle-aged women in the United States are attributable to physical inactivity.

The strengths of the current study include the prospective design, the large size of the cohort, the long-term follow-up, repeated measures of physical activity, and the uniform and strict criteria for coronary events. Women with diagnosed cardiovascular disease or cancer at base line were excluded from the analyses. These exclusions and the prospective design minimized any influence that underlying disease may have had on physical-activity levels and decreased the potential for biased reporting of activity. Moreover, in our secondary analyses, the first two years of follow-up were excluded in order to minimize bias related to subclinical disease. The repeated measures of physical activity enabled us to calculate more stable, cumulative, and updated classifications of activity status as well as to assess the role of changes in activity level over time. Other advantages include the level of detail of information gathered about walking time and pace on the survey first administered in 1986, the high rate of participation during follow-up, and the collection of information about a large number of potential confounders, including cigarette smoking, body-mass index, family history of myocardial infarction, postmenopausal hormone use, alcohol consumption, diet, and other coronary risk factors. The substantial reduction in the risk of coronary events among women who increased their activity level, as compared with women who remained sedentary, and the strong dose–response gradient observed in each analysis lend credence to the interpretation that there is a causal relation between physical activity and a reduced risk of coronary events and that the risk may be modified through increased activity, even when it is begun in later adulthood.

Because our multivariate analyses controlled for several factors that could be considered intermediate biologic variables (such as body-mass index and a history of hypertension, hypercholesterolemia, or diabetes),[3] the analyses provide a conservative estimate of the relation between physical activity and coronary disease. In analyses that excluded these biologic intermediates, the inverse association between physical activity and coronary events was strengthened (Table 2).

Limitations of the current study must also be considered. Physical activity was assessed by a self-administered questionnaire and, despite the use of repeated measures, there was undoubtedly some misclassification. However, in a validation study, conducted in a separate cohort of nurses, the correlations between physical activity as reported on the questionnaire and as recorded in four one-week diaries or recalled after one week were reasonably high ($r=0.62$ and $r=0.79$, respectively).[9] Random misclassifications would be expected to lead to underestimation of the true association and to bias the estimate of risk toward unity; therefore, misclassification cannot explain the strong inverse associations in our cohort between physical-activity level and the incidence of coronary events. Nevertheless, despite the control for many potential confounding variables in our multivariate analyses, residual confounding by lifestyle factors cannot be excluded. In this regard, it should be noted (Table 1) that the more active women had more favorable risk profiles. Finally, our study population, consisting of registered nurses, is not representative of the general population. The relative homogeneity of the cohort in educational attainment and socioeconomic status may actually serve to enhance the internal validity of this study; confounding by these factors has posed an important problem in many previous studies of physical activity and coronary disease.

More than 40 epidemiologic studies have addressed the relation between exercise and coronary disease,[1,2] but few have included women and presented data on women separately.[16-24] In those that did, results in women were generally similar to those in men, indicating that risk reductions were 30 to 50 percent in both sexes with regular physical activity. Most of these studies were small, however, and did not collect detailed information about walking or report repeated measures of activity. The evidence that moderate-intensity activity is associated with a reduction in the risk of coronary disease, however, has been mounting. In a recent report from the Iowa Women's Health Study, both moderate activity and vigorous activity were inversely related to overall mortality and mortality due to cardiovascular causes,[20] although walking was not assessed separately. In two recent studies among elderly women[24] and men,[25] walking at least four hours per week was associated with substantial reductions in cardiovascular risk.

Even moderate levels of physical fitness (assessed by treadmill testing) have been associated with substantial reductions in mortality due to cardiovascular events and in total mortality.[23] It is unlikely that genetic and constitutional differences in fitness levels and in the ability to exercise explain these findings: in a study of nearly 16,000 men and women in the Finnish Twin Cohort, leisure-time physical activity was associated with reduced mortality, even after the analyses had accounted for genetic, familial, and behavioral factors.[26]

It is also biologically plausible that both moderate exercise and vigorous exercise have an important role in reducing coronary risk. Increasing the intensity or duration of exercise has a graded relation to improvements in lipid concentrations[3,27] and insulin sensitivity.[28] Randomized trials of the effects of different intensities of exercise on blood pressure suggest that moderate- and vigorous-intensity activity may confer similar reductions in diastolic blood pressure and that moderate-intensity activity may confer even greater reductions in systolic blood pressure than vigorous-intensity exercise.[3] In the Insulin Resistance Atherosclerosis Study, both vigorous and nonvigorous levels of physical activity were directly associated with insulin sensitivity.[28] Moreover, equivalent expenditures of energy in moderate or vigorous exercise will lead to similar reductions in adipose mass.[3] A recent study indicated that moderate-intensity exercise reduces the secretion of atherogenic cytokines.[29] Finally, physical activity of all intensities has been linked to improvement in emotional well-being and reduction in anxiety and stress.[3]

In conclusion, these prospective data from a study of a large cohort of women indicate that both walking and vigorous exercise are associated with substantial reductions in the risk of coronary events. We observed a strong, graded inverse relation between energy expenditure in either walking or vigorous activity and the incidence of coronary disease. Among women who either walked briskly at least 3 hours per week or exercised vigorously for 1.5 hours per week, the risk was reduced by 30 to 40 percent. These findings lend support to current federal guidelines that endorse moderate-intensity exercise, which is safe, achievable, and feasible for the majority of the population. Although vigorous exercise should not be discouraged for those who choose a higher intensity of activity, our results indicate that enormous public health benefits would accrue from the adoption of regular moderate-intensity exercise by those who are currently sedentary.

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