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Lifelong benefits on myocardial infarction mortality: 40-year follow-up of the randomized Oslo diet and antismoking study

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Abstract

Background. The effects of saturated fat on atherosclerotic vascular disease are currently debated.

Objectives. In the Oslo cardiovascular study initiated in 1972/1973, a 5-year randomized intervention was conducted in healthy middle-aged men at high risk of coronary heart disease to compare the effects on coronary heart disease incidence of diet and antismoking advice versus control (no intervention). A significant reduction (47%) in first myocardial infarction incidence was observed. We have followed mortality up to 40 years to determine whether there was a lifelong benefit of the intervention on mortality risk after first myocardial infarction.

Methods. A total of 16,203 men (63% of those invited), aged 40–49 years, participated in a screening examination. Overall, 1232 men with total serum cholesterol levels of 6.9–8.9 mmol/L (80% smokers) were included in the study. The dietary intervention consisted of mainly decreasing the intake of saturated fats and increasing fish and vegetable products, as well as weight reduction in overweight subjects. Smokers were advised to stop smoking. Cox regression analysis was used for statistical analyses.

Results. The intervention group showed a sustained reduced risk of death at first myocardial infarction (hazard ratio 0.71, 95% confidence interval 0.51 to 1.00; $P = 0.049$), compared to control subjects up to 40 years. During follow-up the beneficial effect developed proportionally up to about 15 years after randomization. Later, the curves were parallel. All-cause mortality decreased in the period 8 to 20 years after randomization, but not thereafter.

Conclusions. Receiving advice about a healthy lifestyle led to a long-term reduced risk of coronary mortality during the following 40 years. Our results suggest that systematically providing effective counselling for a healthy lifestyle for 5 years can lead to lifelong benefits.

Keywords: coronary heart disease, diet, mortality, prevention, smoking.

Word count: 250

Introduction

The role of reducing saturated fat in the diet to promote health is debated [1, 2]. Interpretation of results from large prospective cohort studies differs regarding the association between intake of saturated fat and incidence of cardiovascular disease [3]. In the field of nutrition, however, very few randomized controlled trials (RCTs) have had enough statistical power to investigate all-cause mortality as an outcome. This lack of mortality data from RCTs has contributed to ambiguity in the literature. In the present study we report data on all-cause mortality and death from acute myocardial infarction in an RCT initiated 40 years ago.

During the period 1972–1973, 1232 healthy men at high risk of coronary heart disease were randomly assigned to intervention or control groups. Results from this 5-year intervention trial have previously been reported in detail [4]. The intervention consisted of half-yearly control and advice to reduce the amount of saturated fats in the diet and to increase the intake of fish products, vegetables and fruit. Overweight men were advised to reduce weight and reduce their intake of sugar. Smokers in the intervention group were also advised to quit smoking. Men in the control group were not given any such specific advice until the end of the 5-year intervention. Neither the intervention group nor the control group received advice regarding physical activity.

 The purpose of this study was to present results up to 40 years with respect to death at first myocardial infarction (MI) and all-cause mortality, to determine whether lifelong benefits were obtained from the original 5-year intervention. To our knowledge this is the longest survival observation in an RCT in this field. This study provides insight into historical aspects of coronary heart disease primary prevention.

Methods

All 25,915 men born in Oslo during the period 1923–1932 were invited in 1972/1973 to a cardiovascular disease (CVD) screening examination; of these, 16,203 (63%) men participated in the

screening. Participants were asked to complete a questionnaire about prevalent CVD and diabetes. Men without these diseases were considered healthy, and subsequently took part in two examinations to select suitable participants for the randomized Oslo diet and antismoking study [5]. Men with total serum cholesterol levels of 6.9–8.9 mmol/L were included provided they had a coronary risk score in the upper quartile of a distribution based on the classical risk factors blood pressure, total cholesterol and cigarette smoking [4]. Men with higher total serum cholesterol levels than those in the diet and antismoking trial were referred to a lipid clinic. After 8.5 years, all surviving men were recalled for a follow-up examination and the same measurements as carried out at the final trial examination were performed in all except 26 men [6]. At this timepoint, all men in the control group were given the same advice about dietary change and smoking cessation as given to the men in the intervention group, as supported by the positive findings of the trial.

Among survivors ($n = 12,764$) only 47.2% met to a second screening examination in the year 2000 [7] and among the trial groups only 25.8% and 22.3% attended in the active and control group respectively.

The present study is an extended survey to 31 December 2011, including the complete cohort of all participants ($n = 1232$) with respect to mortality at first MI, established through death certificates, and total mortality. Men who emigrated were censored at the date of emigration. Statistics Norway provided mortality data to the Oslo study data file through the national unique 11-digit personal number, following permission from the Data Inspectorate, tax authorities and Department of Health. The project was approved by the regional ethics committee for medical research.

Statistical analysis

Rates per 1000 observation years and differences between rates with 95% confidence limits were calculated. Cox proportional hazards regression models were used; time to death or time to death at first MI were included as dependent variables and group codes, age, total cholesterol, systolic blood pressure and smoking were exposure factors. Hazard ratios were calculated with 95% confidence limits. The log rank test was used to test for differences between groups (intervention and control)

with respect to survival. Kaplan–Meier curves were generated, and mean survival times were estimated, using STATA 13 software.

Results

Table 1 shows the levels of the major CVD risk factors at screening by group. According to the inclusion criteria of the study, the prevalence of smoking and the levels of total serum cholesterol were high whereas blood pressure was not raised. The average age of participants was 45 years. These men were of normal weight but had somewhat elevated levels of non-fasting serum triglycerides.

The use of antihypertensive medication (45%) and use of statins (45%) were similar between the intervention and control groups at follow-up in the year 2000, as were other risk factors including total serum cholesterol levels, smoking and the prevalence of diabetes and CVD (Tables 2 and 3). Thus, the major CVD risk factors seem to have developed equally after about 10 years.

At the end of the trial, a total of 19 coronary events had been reported in the intervention group and 36 in the control group ($P = 0.028$). Fatal myocardial infarction and sudden deaths were six and 14 respectively ($P = 0.086$) whereas total mortality were 16 and 24 ($P = 0.246$), as previously reported [4].

At 40 years of follow-up there was a nominally significant reduction in the risk of death at first MI in the intervention group versus control (hazard ratio 0.71, 95% confidence interval 0.51 to 1.00, $P = 0.049$; Fig. 1 and Table 4). After adjusting for baseline risk factors such as age, total cholesterol, systolic blood pressure and smoking, the P-value was slightly lower (0.038). A proportional development of risk until about 15 years of follow-up took place and thereafter the curves went parallel. There was no significant difference in total mortality at 40 years (Fig. 2); however, there was a nominally significant reduction in total mortality at 15 years of follow- up (Fig. 3). The net difference in number of deaths between the two groups varied from 12 at 8.5 years to 20 at 40 years of follow-up. Mean survival time increased by 0.5 years (restricted due to censorship) in the intervention

versus control group and by 0.9 years if an exponential distribution of survival time was modelled for the remaining lifetime among survivors.

Discussion

The intervention was successful in that major dietary changes were made such as a reduction in intake of saturated fat from 18.3 to 8.2 energy percentage as measured in representative subgroups, with an average net reduction of 0.8 mmol/L (10%) in serum total cholesterol between groups [4]. The beneficial effects of the intervention on death at first MI peaked at about 15 years of follow-up, long after the end of the trial. Thereafter, survival curves in the two groups were parallel until 71% of the participants had died at study end, indicating a lifelong benefit of the intervention. At 15 years, 24 deaths due to CVD had occurred in the intervention group and 48 in the control group (nominal $P = 0.004$), while the corresponding values for all-cause mortality were 58 and 82 (nominal $P = 0.027$). Interestingly, the West of Scotland Coronary Prevention Study (WOSCOPS) researchers reported continued beneficial effects of statin therapy on all-cause mortality up to 14 years after study end [8, 9]. They speculated that a reduction in serum cholesterol over 6 years may reduce the development of atherosclerosis during that period resulting in clinical benefit long after the end of the trial. Much of the effect in our study was probably mediated through the dietary lowering of serum cholesterol and triglyceride levels and weight reduction, whereas the effects of smoking cessation were smaller as relatively few men stopped smoking completely in the two groups (16% and 21% in the control and intervention groups respectively). However, smoking reduction by smokers was greater in the intervention group than in the control group [4] and, because the 40-year follow-up of the population showed a strong dose–response relationship between amount of cigarette smoking and both MI and total mortality [10], it is conceivable that the smoking intervention also played a role in the continued positive effect on mortality at first MI in the early years after the end of the intervention.

Based on an extensive statistical analysis conducted at the end of the trial [4], it was estimated that the changes in smoking explained at most 25% of the difference in MI incidence, whereas the remaining

difference was due to dietary intervention and chance variations. However there was a clear dose–response relationship between early reduction in total serum cholesterol and subsequent reduction in risk of MI.

There was an almost complete follow-up of surviving trial participants at about 8.5 years [6]. This showed that the number of cigarettes smoked per day increased in the intervention group and was almost equal to that in the control group. The net difference between groups in total serum cholesterol was reduced from 0.8 mmol/L during the 5-year trial to about 0.3 mmol/L. Thus, from the time-point of 8.5 years of follow-up and until 40 years of follow-up, the exposure of the intervention factors seemed to be about equal, also underlined by the results after 21 years of follow-up [7].

In 2000, all participants in the Oslo diet and antismoking study were invited to a second screening examination, Oslo II [11]. Unfortunately the attendance rate was low (45%) and among men in the diet and antismoking trial only 140 (out of 628) and 156 (out of 604) participated, partly due to a higher mortality than average. Levels of total serum cholesterol, and other coronary risk factors, were similar in the two groups (intervention and control). There were 37 (26.4%) and 34 (21.8%) daily smokers in the two groups, i.e. a difference of about 5% as observed at the end of the trial. Nevertheless, the smoking prevalence was higher than found among all Oslo II participants (17.6%) [11]. It is difficult, however, from this highly selected group to explain the continuing benefit on MI mortality observed in the intervention group by the effects on these CVD risk factors.

A systematic review and meta-analysis of RCTs investigating the effect of increasing polyunsaturated fat in place of saturated fat provided evidence of reduced coronary heart disease [12], however these results were not consistent with the findings of a more recent meta-analysis [1]. Replacement of saturated fats in the diet with other fats, such as omega 6 linoleic acid, showed an increased risk of CVD and total mortality [13], in contrast to our results. Furthermore, an intervention study of screening and lifestyle counselling in the general population failed to show a beneficial effect on incidence of ischaemic heart disease, possibly due to the low net difference in major lifestyle changes between intervention groups [14, 15].

Ambiguity in the literature regarding these important issues clearly underlines the need for more data from RCTs. The intervention in the present RCT was to replace saturated fats in the diet with vegetables, fruits, fish and bread rich in fibre, and in addition overweight participants were instructed to reduce weight and reduced intake of sugar and alcohol. This study provides new data on well-defined endpoints; to our knowledge, no other trial has demonstrated such lifelong MI mortality benefit after the end of the study.

The success of our trial may be due to the criteria of high levels of serum total cholesterol and high smoking prevalence for selecting participants. Thus the trial design provided high prevention potential with good ability for proof of concept. Very high serum total cholesterol (>9.5 mmol/L) was, however, an exclusion criteria; all men with such levels were referred for active treatment [4].

Study limitations

This study was not designed to differentiate between the two intervention modalities: antismoking and dietary advice. The evidence that dietary changes were mainly responsible for the mortality outcomes is thus only observational. Participation at the second screening in the year 2000 was rather low, so biases of medication use and in levels of risk factors among participants in the two groups cannot be excluded. The decision to stop follow-up at almost 40 years was arbitrary but made without knowledge of mortality outcomes. These results are only applicable to the relatively small population of male smokers with high levels of total serum cholesterol. Of note, this risk profile was far more prevalent 40 years ago than nowadays.

Conclusions

The randomized Oslo diet and antismoking study maintained a beneficial effect of intervention regarding death at first MI up to 40 years of follow-up, indicating that half-yearly diet and healthy lifestyle advice over a 5-year period can provide lifelong benefits on MI mortality.

Conflict of interest statement

The authors declare that they have no competing interests related to this study. No specific funding was required for this study.

Figure legends

Fig. 1 Time to death at first myocardial infarction (MI) by intervention group in the Oslo diet and antismoking study. The log rank test was used to test for differences between groups.

Fig. 2 Time to death by intervention group in the Oslo diet and antismoking study. The log rank test was used to test for differences between groups.

Fig. 3 Absolute and relative reductions in risk of total mortality in the intervention versus the control group throughout the observation period, analysed by Z score statistics for proportions. CI, confidence interval.

Table 1 Cardiovascular disease risk factors at screening in 1972–1973[a]

	Intervention ($n = 604$)	Control ($n = 628$)
Systolic blood pressure, mmHg	136.6 (12.0)	136.5 (11.9)
Diastolic blood pressure, mmHg	87.1 (9.0)	87.1 (9.1)
Body weight, kg	78.5 (10.4)	79.1 (10.4)
Daily smoking, n (%)	482 (79.8)	498 (79.3)
Serum total cholesterol, mmol/L	8.00 (0.44)	8.01 (0.44)
Serum triglycerides, mmol/L	2.80 (1.5)	2.84 (1.5)

[a]Number of valid measurements for some variables may vary due to incompleteness.

Data are presented as mean (SD) unless stated otherwise.

Table 2 Cardiovascular disease risk factors at follow-up in the year 2000[a]

	Intervention ($n = 140$)	Control ($n = 156$)
Participants, n (%)	140 (23.2)	156 (24.7)
Systolic blood pressure, mmHg	147.4 (17.7)	148.6 (17.9)
Diastolic blood pressure, mmHg	86.8 (10.2)	88.3 (10.5)
Body weight, kg	81.1 (11.0)	81.8 (12.1)
Total serum cholesterol, mmol/L	6.51 (1.19)	6.55 (1.04)
Triglycerides, mmol/L	1.76 (0.81)	1.76 (0.95)
High-density cholesterol, mmol/L	1.45 (0.39)	1.55 (0.48)
Serum glucose, mmol/L	6.03 (2.01)	5.91 (1.23)
Daily smoking, n (%)	37 (26.4)	34 (21.8)
Previous smoking, n (%)	82 (58.6)	101 (64.7)
Never smoking, n (%)	21 (15.0)	21 (13.5)

[a]Number of valid measurements for some variables may vary due to incompleteness.

Data are presented as mean (SD) unless stated otherwise.

Table 3 Disease prevalence and drug use at follow-up in the year 2000

	Intervention ($n = 140$)	Control ($n = 156$)
Diabetes	14 (10.5)	15 (10.3)
Myocardial infarction	29 (22.0)	26 (17.3)
Cerebral stroke	8 (5.9)	14 (9.9)
Use of antihypertensive drugs	56 (41.5)	72 (48.6)
Use of cholesterol-lowering drugs	60 (44.4)	65 (44.5)

Table 4 First MI and total death risk over 40 years in the Oslo diet and antismoking study

Group	MI deaths	Rate per 1000 observation years	Number of deaths	Death rate per 1000 observation years
Interventon ($n = 604$)	57	3.5	430	26.2
Control ($n = 628$)	82	4.5	450	24.6
Difference (95% CI)		1.0 (0.0 to 2.3)		-1.6 (-5.0 to -1.7)

MI, myocardial infarction; CI, confidence interval.

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