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Increased Mortality Despite Successful Multifactorial Cardiovascular Risk Reduction in Healthy Men

40-year follow-up of the Helsinki Businessmen Study intervention trial

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Abstract

Objective In a 5-year multifactorial risk reduction intervention for healthy men with at least one cardiovascular disease (CVD) risk factor, mortality was unexpectedly higher in the intervention than the control group during the first 15-year follow-up. In order to find explanations for the adverse outcome, we have extended mortality follow-up and examined in greater detail baseline characteristics that contributed to total mortality.

Design Long-term follow-up of a controlled intervention trial.

Setting The Helsinki Businessmen Study Intervention Trial.

Participants and Intervention The prevention trial between 1974-1980 included 1,222 initially healthy men (born 1919-1934) at high CVD risk, who were randomly allocated into intervention (n=612) and control groups (n=610). The 5-year multifactorial intervention consisted of personal health education and contemporary drug treatments for dyslipidemia and hypertension. In the present analysis we used previously unpublished data on baseline risk factors and lifestyle characteristics.

Main outcome measures 40-year total and cause-specific mortality through linkage to nation-wide death registers.

Results The study groups were practically identical at baseline in 1974, and the 5-year intervention significantly improved risk factors (body mass index, blood pressure, serum lipids and glucose), and total CVD risk by 46% in the intervention group. Despite this, total mortality has been consistently higher up to 25 years post-trial in the intervention group than the control group, and converging thereafter. Increased mortality risk was driven by CVD and accidental deaths. Of the newly-analysed baseline factors, there was a significant interaction for mortality between intervention group and yearly vacation time (P=0.027): shorter vacation was associated with excess 30-year mortality in the intervention (hazard ratio 1.37, 95% CI 1.03-1.83, P=0.03), but not in the control group (P=0.5). This finding was robust to multivariable adjustments.

Conclusion After a multifactorial intervention for healthy men with at least one CVD risk factor, there has been an unexpectedly increased mortality in the intervention group. This increase was especially observed in a subgroup characterised by shorter vacation time at baseline. Although this adverse response to personal preventive measures in vulnerable individuals may be characteristic to men of high social status with subclinical CVD, it clearly

deserves further investigation.

Key words: Multifactorial prevention, mortality, vacation

Introduction

Unexpected findings in the 5-year intervention period and the 15-year mortality follow-up of the Helsinki multifactorial primary prevention trial (Helsinki Businessmen Study, HBS [1-4]) seemed to defy current knowledge as to the treatment of cardiovascular risk factors in middle-aged men. Despite significant decreases in traditional cardiovascular risk factors during the intervention period, 1974-1980, mortality up to 1990 was 46% higher in the intervention group than in the control group (2). This result has puzzled investigators in the field (5-8), especially as no plausible explanation for such results emerged from previous analyses. For example, the multidrug treatments – including cholesterol and blood pressure lowering medications -- used in the intervention group could not be related to excess mortality (1,2). It has, however, been speculated that intense lifestyle intervention might have had psychologically detrimental effects on the participants (2,7). If so, the results of this particular trial would have broader implications for multifactorial prevention in healthy middle-aged men.

The aim of the current report is to explore possible explanations for the unexpected finding. Because mortality difference seemed to be increasing even 10 years after the HBS trial (2) we have now extended the mortality follow-up to 40 years (through 31 December, 2014). We have also re-examined original data along with formerly neglected baseline information on lifestyle characteristics and related them to the long-term mortality. These previously unanalyzed factors included vacation time -- which in the Multiple Risk Factor Intervention Trial (MRFIT, 9) was inversely related to follow-up mortality -- working hours that have been related to cardiovascular disease (10), and sleep duration that has been related to total mortality (11). The analyses are hypothesis-generating, but may give new perspectives to intensive individual health education in healthy middle-aged people at risk of CVD.

Methods

Study Design, Participants and Procedures

Details and structure of the HBS have been described in previous reports (1-4). In brief, participants of the prevention trial were recruited from healthy volunteers from a background population of 3,490 businessmen and executives born between 1919-1934 who had attended health check-ups with risk factor measurements and received some health education during 1964-1973. In 1974-1975, healthy volunteers from this population with no clinical CVD, no diabetes, no regular drug treatment for CVD risk factors but at least one cardiovascular risk factor (smoking, hypertension, hypercholesterolemia, hypertriglyceridemia, glucose intolerance, overweight) were randomly allocated to form an intervention group (n=612) and a control group (n=610) (1). According to the traditional risk factor levels, the groups were well balanced at baseline indicating successful randomisation (1). The average number of CVD risk factors in both groups was 2.1.

During the five trial years (1974-1980), the members of the intervention group were planned to visit the investigators every fourth month, whereupon they received individual – oral and written -- health instructions according to contemporary concepts of preventive medicine. They were given information about their risk factors and repeatedly advised to engage in aerobic physical activity; consume a healthy diet emphasising intake of vegetables, fruits, and whole grains, and limiting intake of saturated fats, sweets, and sugar-sweetened beverages; maintain a healthy weight; and stop smoking. In addition, antihypertensive drugs (mainly beta-blockers and diuretics) and lipid-lowering drugs (mainly probucol and clofibrate; statins did not exist at that time) were frequently used, when health education alone was not sufficiently effective (1). The members of the control group received standard health care and were not seen by the investigators.

Intervention led to a substantial reduction in most risk factors in the intervention group (1), and in the coronary risk score for hard criteria (46% reduction) calculated according to Keys

et al (12). At the end of the trial in 1979-1980, the prevalence of participants on antihypertensive treatment was 32% in the intervention group and 15% in the control group ($P<0.05$ between groups). The corresponding figures for lipid-lowering treatment were 37% and 0%, respectively ($P<0.05$ between groups).
At the end of the trial in 1979-1980, all survivors were re-examined, where after they have all been treated by their own physicians as needed.

The first post-trial evaluation using questionnaires and laboratory examinations was performed five years later in 1985-1986 (4). By that time the risk-factor differences (except mean body mass index) between the intervention and control groups had largely levelled off. The prevalence of participants on antihypertensive treatment was 27% in the intervention group and 22% in the control group. The corresponding figures for lipid-lowering treatment were negligible, 2.4% and 1.8%, respectively. The prevalencies of drug treatments were no more significantly different five years post-trial.

For the present analyses, information about total mortality of the study population up to December 31, 2014, was extracted from the National Population Information System, which keeps registry of all Finnish citizens. According to the register, assessment of vital status is very reliable for people having their permanent place of residence in Finland (over 95% of the present cohort) irrespective whether they die in Finland or abroad. Moreover, the assessment of the vital status is also reliable for Finnish citizens living permanently abroad. Causes of death, analysed up to 31 December, 2004, were determined from the nationwide computerized Cause-of-Death Register of Statistics Finland in which trained nosologists code the causes of death. The causes were categorised in 6 groups: cardiac, stroke, other CVD, cancer, violent (accidents and suicides separately), and other causes.

In the present analyses, we have also used previously unpublished data from questionnaires filled in by the participants at baseline in 1974-75. These questionnaires included data about lifestyle (vacation, sleep, work), and the men were also asked questions on self-rated health

(SRH) and physical fitness on a 5-point scale (”very good”, ”good”, ”average”, ”fairly poor”, ”very poor”). This wording of SRH was similar to that used in the Whitehall study (13). Because there were very few men perceiving their status as ‘very poor’, they were combined with ‘fairly poor’ as ‘poor’. The participants were asked to report their usual working hours (median 47 h/week, interquartile range [IQG] 40-52), vacation time (median 30 working days/year, IQR 21-30) and sleep duration (median 50 h/week, IQR 48-55). In the intervention and control groups 154 and 166 men, respectively, reported having $\leq$ 21 working days of vacation annually. In the analyses, this cutpoint, representing the 25th percentile, was used to categorise vacation time.

During the 1970s when the trial was performed, the patients consented to the trial but no formal ways to register the trial were available nor required. All follow-up results of the trial have been published before 1997 when US Congress passed law (FDAMA) requiring trial registration. The extended follow-up of the cohort was approved by the ethical committee of the Department of Medicine, Helsinki University Central Hospital and was registered as ClinicalTrials.gov identifier NCT02526082.

Statistical Analysis

NCSS statistical software (www.ncss.com) was used for the analyses. In the analyses, t-tests, nonparametric tests and analyses of covariance (ANCOVA) were used where appropriate to compare continuous variables between the intervention and control group. Chi-square and trend tests were used to compare proportions. Differences in mortality curves were analysed with the log rank test. Requirements for proportional hazards were checked and hazard ratios (HR) with their 95 % confidence intervals (CI) for mortality were calculated using Cox proportional hazards regression with covariates. Besides the 40-year follow-up, we also analysed causes of deaths during the first 30 years of follow-up, because mortality curves

were parallel after that thus diluting intervention effects. To study whether work, sleep or vacation time would modify the intervention effect, an interaction term (intervention-control group* time) was included in the model. A flexible parametric proportional-hazards model was fitted using restricted cubic splines. In statistical analyses 2-tailed tests were used and P values < 0.05 were taken as statistically significant.

Results

In-trial changes

Baseline risk factors and lifestyle characteristics of the two groups in year 1974 are shown in Table 1. This comparison shows that the groups were well balanced at baseline. Furthermore, there was no significant difference in the distributions of self-rated health (P=0.81) or self-rated physical fitness (P=0.54) between the intervention and control groups at baseline. The principal risk factors after the 5-year intervention period (between 1974-1980) are shown in Table 2. Body mass index (BMI), blood pressure, serum lipids and one-hour glucose were significantly improved in the intervention group as compared to the control group. However, the absolute reductions were not large, for example, BMI was 3% lower, systolic blood pressure 5% lower, and cholesterol 6% lower in the intervention than in the control group at end of the intervention. There was no significant difference in smoking, because it was reduced both in the intervention and control groups.

Mortality during the 40-year follow-up

Total mortality data during various phases of follow-up have been reported earlier (1-4). During the 5-year intervention period there were 10 and 5 deaths in the intervention and control groups, respectively (HR = 2.00, 95% CI, 0.63-6.66, P = 0.3). During the first 15 years from start of the intervention there were significantly more deaths in the intervention

than in the control group (67 vs. 46, HR = 1.45, 95% CI, 1.01-2.08, P = 0.048). Crude mortality curves for the entire 40-year follow-up are shown in Fig 1. The difference between the groups is no longer statistically significant (434 vs 409 deaths, HR (Keys adjusted) 1.08 (95% CI: 0.94 to 1.23) P=0.28), because the mortality curves have converged for several years, but a "bulge" between curves during 10 to 25 years of follow-up can be discerned (Fig. 1).

Because mortality converged with increasing follow-up, causes of death were analysed during the first 30 years, up to 31 December, 2004, and could be retrieved for 221 and 210 deaths in the intervention and control groups, respectively (Table 3). Age-adjusted HR was 1.23 (95% CI 0.85-1.80, P=0.27) for cardiac deaths, and 2.56 (95% CI, 1.13-5.82, P = 0.025) for violent deaths (including accidents), so that a higher mortality characterized the intervention group. Perusal of death certificates with narratives suggested that it was impossible in most cases of accidental deaths to rule out a potential disease attack as the primary cause.

Subgroup analyses

Preliminary analyses showed that of the reported baseline work, vacation and sleep times, only shorter yearly vacation time separated the study groups, and adjusted interaction between group and annual length of vacation time (but not with work and sleep time) was significant (P=0.013). Crude 40-year mortality curves (Fig. 2) according to annual vacation time (cutpoint 21 working days) were different between intervention (HR 1.17, 95% 0.94 to 1.45; P=0.15) and control groups (HR 0.86, 95% CI 0.69 to 1.07; P=0.18). If follow-up was restricted to 30 years, the respective HRs were 1.37 (95% CI 1.03 to 1.83; P=0.03) for intervention group, and 0.90 (95% CI 0.66 to 1.22; P=0.50) for the control group.

Multivariate analyses were performed to resolve whether the shorter annual vacation time was an independent predictor of 40-year total mortality. As a covariate we used the baseline log-transformed Keys' risk score (includes age, smoking, BMI, cholesterol, and systolic blood pressure), which predicted 40-year mortality (HR per SD 1.44, 95% CI 1.31 to 1.58, P<0.001). In this analysis there was a significant interaction between the treatment group and

vacation time (HR 1.61, 95% CI 1.06 to 2.47, P=0.027), suggesting that excess mortality in the intervention group was modified by vacation time. Annual differences in mortality up to 30 years according to vacation time (≤21 days vs >21 days) in the intervention and control groups are summarised in Fig. 3 demonstrating the constant difference between the 2 groups starting early and widening during the long-term follow-up.

Finally, we compared baseline characteristics of the men with short vs longer annual vacation time (men in both groups combined). Men with short vacation worked more (P<0.001), slept less (P=0.04), and had worse self-rated health (P=0.018) than men with longer vacation, but there were no significant differences in BMI, CVD risk factors (smoking, blood pressure, serum lipids), and alcohol consumption.

Discussion

Despite improvements of cardiovascular risk factors during intervention, multifactorial primary prevention was associated with more deaths during the first two decades after the start of the trial among middle-aged high-risk men. The forms of the mortality curves in the control and intervention groups are in keeping with a harm induced by the intervention, peaking at 15-20 years post-trial and weakening thereafter. Excess deaths seemed to be mainly due to cardiac and accidental deaths. The significant interaction between the intervention group and vacation time further suggests that the harm induced by intervention was concentrated in a vulnerable subgroup of men characterized by shorter yearly vacation time. We speculate that adverse psychological effects of intervention in certain individuals are at least partly the explanation for the excess deaths.

Both the American Heart Association policy statement for CVD prevention at worksites (14), and the European 2016 Clinical Guideline for CVD prevention in clinical practice (15) recommend stress management/reduction for individuals at high CVD risk or with an established CVD. This was not part of the concepts of preventive medicine used in the multifactorial prevention during the late 1970s. Prospective studies have linked coronary heart disease with various psychosocial factors. These include work, home/marital, and other

acute or chronic stressors (16-19), various personality characteristics, emotional factors and mood disorders (20,21), shorter vacation (9), and longer work time (10). Even a doctor's round in hospital may acutely increase myocardial infarcts (22), and daily hassles predict mortality (23).

Already during the 1990s various pathogenetic mechanisms for these associations were presented, including stress-induced adverse changes in risk factors (lipids, fibrinogen, coagulation factors, 24,25), and direct effects on factors related to myocardial infarction and sudden death, such as endothelial function (26) and cardiac autonomic control (27). The concept of allostatic load (28,29), i.e. long-term environmental challenge leading to chronic fluctuations in bodily responses – with a growing list of extra- and intracellular mediators (30) -- may help to understand further the pathways to disease onset and poor outcomes. In the cardiovascular system this might involve repeated bouts of endothelial damage and accelerating atherosclerosis through neuroendocrine mediators as well as inflammatory, hemostatic, and autonomic processes that trigger a cardiac event in individuals with atherosclerotic burden (31). It is also evident that these middle-aged men with CVD risk factors – albeit clinically healthy – already had subclinical CVD and advanced lesions in their coronary tree (32). Sudden cardiac deaths may also mask as accidental deaths, when due to fatal arrhythmia.

If omission of stress management in the intervention encouraged participants to ignore chronic stress as part of healthy lifestyle, this could have long-term adverse effects. One may argue that if psychological factors have true pathogenetic influence, the adverse effect on mortality should only be seen during the intervention period. However, the intervention period lasted for 5 years, and effects of psychological influence may last longer, in particularly, if inducing an attitude that management of body mass index, blood pressure, serum lipids and glucose is enough to minimize CVD risk. For example, in the study of Rosengren et al (33), stressful life events were associated with mortality during 7 years' follow-up, and in the study of Carroll et al (34) up to 16 years of follow-up. Similarly to a positive legacy, also a negative one may take place long-term.

Our speculations must not be taken to signify that individual health education as such is harmful. Although Cochrane reviews have suggested limited benefit from multifactorial primary prevention (35,36), several individual studies using personal lifestyle modifications have definitely shown benefit in the prevention of CVD (37-40) or diabetes (41,42). On the other hand, despite the beneficial effect on several CVD risk factors in the Look AHEAD (Action for Health in Diabetes) trial, CVD events were not reduced during median follow-up of almost 10 years (43). Modern preventive medications, such as statins, were used in both groups of the Look AHEAD trial, and overall, target populations in these trials have been quite different from the present one, which may be the decisive factor.

Turning to a more speculative area in the search of explanations, studies in nonhuman primates have revealed various effects of social position on biological functioning and health (44). Analogously, might the change of a dominant individual to a subordinate status in health care have made some executives more vulnerable to psychological distress? Moreover, feelings of a personal failure to modify lifestyle according to instructions – such as in the current intervention trial - can be especially frustrating for individuals concerned of their health. Indeed, shorter vacation in our cohort was associated with worse self-rated health, and tended to be associated with some mental components of quality of life (45). Also modern stress research has emphasized the effect of perceived – subjective, not objective – amount of stress in the pathway to health disorders (46,47).

The negative psychological effects of personal intervention were obviously not counteracted by the weak methods available for treatment of CVD risk factors during the 1970s (non-statin drugs for hyperlipidemia, beta-blockers for hypertension). This is further emphasized by the relatively high baseline risk factor levels (mean systolic blood pressure 148 mm Hg, mean plasma cholesterol 6.5 mmol/L). Therefore, at the mean age of 48 years subclinical CVD was likely to be present and much more efficient prevention would have been needed.

Limitations

Obviously, male sex and social class distribution limit generalizability of the study, but there

are also other important points to discuss. Baseline information on personal characteristics is sparse – after all the primary aim was not to study their influence -- and the discussion of their influence is necessarily speculative. However, we had information of vacation time, which in another multifactorial trial was associated with mortality (7). Also the play of chance must be taken into account in a relatively small trial. Still, the study groups were comparable at baseline, the mortality difference at its peak was highly statistically significant, and above all, the results were quite opposite to the one the investigators were hoping for.

Finally, the study and its results may be questioned, because it was performed 40 years ago. However, while preventive drug treatment has greatly developed during the last decades, the methods and aims of individual lifestyle modification – exercise, diet, weight reduction -- have largely remained the same.

Conclusions

The paradoxical increase of mortality after successful multifactorial prevention is provocative and may be neglected as an anomalous result. Nevertheless, we think that it is worthwhile to present these post-hoc analyses in a hypothesis-generating manner as they closely relate to the long-term debate and questions about the value of early intervention and risk-benefit ratios of intervention methods in primary prevention (48,49). The results raise the possibility that submitting middle-aged men at high risk of CVD to personal lifestyle modification - but with only modest concomitant risk factor changes - might for some men be harmful. Because personal lifestyle modifications are traditionally (and at times aggressively) advocated in primary prevention of CVD irrespective of the grade of subclinical disease, better recognition and better treatment strategies of vulnerable individuals clearly calls for further study.

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Conflict of Interest

All authors (Strandberg TE, Räikkönen K, Salomaa V, Strandberg A, Kautiainen H, Kivimäki M, Pitkälä K, Huttunen J) declare no conflict of interest related to this article.

Ethical Standards The follow-up described here complies with the current laws of Finland.

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Figure legends

Figure 1. Total mortality in the study groups during the 40-year follow-up.

Intervention group = solid line; Control group= dotted line.

Panel A: Adjusted cumulative mortality. Panel B: Difference in survival curves between the intervention and control groups.

Figure 2. Adjusted total mortality curves according to baseline vacation time in the intervention (Panel A) and control (Panel B) groups during the 40-year follow-up.

Solid line = annual vacation $\leq$ 21 days; dotted line = annual vacation > 21 days.

Fig. 3. Cumulative difference between shorter and longer vacation in the intervention and control groups during 30-year follow-up

Table 1. Comparison of the study groups at baseline in 1974-1975

Variable	Intervention group (n=612)	Control group (n=610)	P value between groups
Age, years	48 (4)	48 (4)	0.75
Body mass index, kg/m^2	26.4 (2.9)	26.6 (2.8)	0.30
Reported weight gain from 25 years of age to 1974, kg	11.5 (8.5)	11.4 (8.3)	0.91
Resting heart rate/min	66 (11)	66 (12)	0.54
Blood pressure, mmHg			
Systolic	148 (18)	146 (19)	0.17
Diastolic	96 (11)	94 (11)	0.01
Serum cholesterol, mmol/L*	6.5 (1.0)	6.5 (1.1)	0.63
Serum triglycerides, mmol/L	1.8 (1.0)	1.8 (1.0)	0.96
1-h blood glucose, mmol/L	7.4 (2.3)	7.5 (2.3)	0.22
Alcohol consumption, g/week	185 (184)	168 (146)	0.17
Smokers, n (%)	239 (39)	226 (37)	0.56
Keys' risk score, %+	2.6 (2.0)	2.5 (2.0)	0.34
Work time, hours/week	49 (10)	48 (9)	0.01
Sleep, hours/week	50 (7)	51 (6)	0.08
Vacation time, days/year	27 (10)	26 (10)	0.37

Mean (SD)

* Concentrations corrected to values with modern methods.

+ Calculated according to Keys et al (12).

Table 2. Risk factors at end of 5-year intervention in 1979-1980

Variable	Intervention group (n=575)	Control group (n=580)	P value between groups
Body mass index, kg/m^2	26.2 (2.9)	26.9 (2.8)	<0.0001
Blood pressure, mmHg			
Systolic	135 (13)	142 (17)	<0.0001
Diastolic	88 (9)	91 (10)	0.002
Serum cholesterol, mmol/L*	6.2 (0.9)	6.6 (1.1)	<0.0001
Serum triglycerides, mmol/L	1.6 (0.9)	1.8 (1.1)	<0.0001
1-h blood glucose, mmol/L	7.7 (2.6)	7.9 (2.5)	0.003
Alcohol consumption, g/week	136 (128)	144 (146)	0.6
Smokers, n (%)	163 (28.5)	171 (29.6)	0.7

* Concentrations corrected to values with modern methods.

Table 3. Numbers and causes of death up during the first 30-year follow-up in the study groups

Variable	Intervention group (n=612)	Control group (n=610)	HR (95% CI)*	P value between groups
All cardiovascular	91	78	1.17 (0.87-1.59)	0.30
- Cardiac	70	58	1.22 (0.86-1.72)	0.27
- Stroke	13	10	..	
- Other cardiovascular	8	10	..	
Neoplasms	66	83	0.88 (0.65-1.19)	0.41
Violent	20	8	2.56 (1.13-5.82)	0.025
- Accidents	17	5	..	
-Suicides	3	3	..	
Other	44	41	..	
Total	256	236	1.06 (0.88-1.28)	0.53

*HR indicates hazard ratio of age-adjusted cause-specific mortality (with 95% confidence interval)

Figure. 1

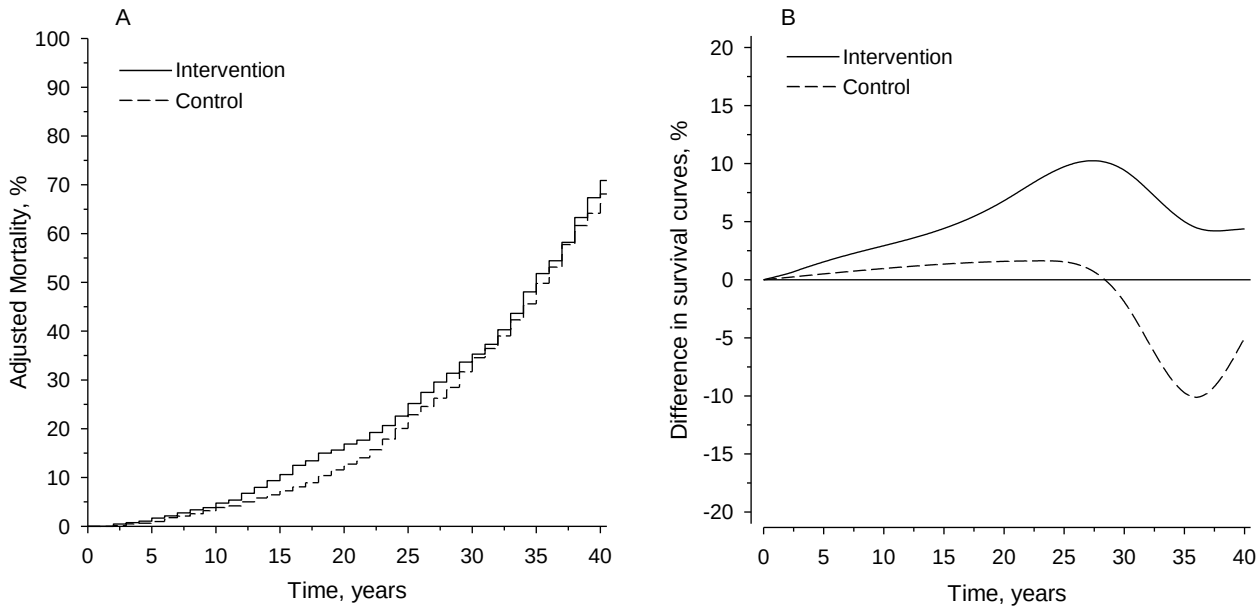
A
Intervention
Control
Adjusted Mortality, %
Time, years
B
Intervention
Control
Difference in survival curves, %
Time, years

Figure 2

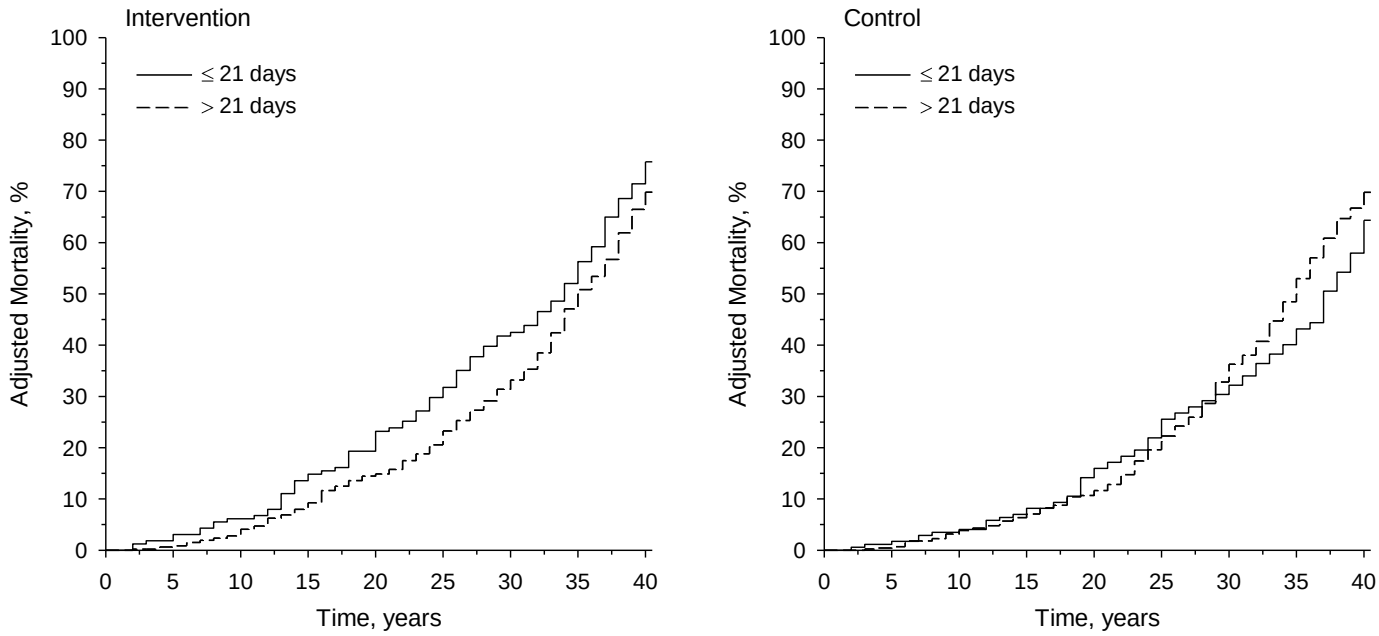
Intervention
≤ 21 days
> 21 days
Adjusted Mortality, %
Time, years
Control
≤ 21 days
> 21 days
Adjusted Mortality, %
Time, years

Figure 3

Difference between mortality according to vacation ≤21 vs >21 days/yr