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Rising adiposity curbing decline in incidence of myocardial infarction: 20-year follow-up of British men and women in the Whitehall II cohort

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Abstract (199 words)

Aims To estimate the contribution of risk factor trends to 20 year declines in myocardial infarction (MI) incidence in British men and women.

Methods and Results 6,379 men and 3,074 women in the Whitehall II cohort were followed for incident MI and risk factor trends from 1985 to 2004. Over 20 years the age-sex-adjusted hazard of MI fell by 74% (95% confidence interval 48-87%), corresponding to an average annual decline of 6.5% (3.2 to 9.7%). 34% (20-76%) of the decline in MI hazard could be statistically explained by declining non-HDL cholesterol levels, followed by increased HDL cholesterol (17%, 10-32%), reduced systolic blood pressure (13%, 7-24%), and reduced cigarette smoking prevalence (6%, 2-14%). Increased fruit and vegetable consumption made a non significant contribution of 6% (-2-23%). In combination these five risk factors explained 54% (34-105%). Rising BMI was counterproductive, reducing the scale of the decline by 11% (5-23%) in isolation. The MI decline and impact of the risk factors appeared similar for men and women.

Conclusion In men and women over half of the decline in MI risk could be accounted for by favourable risk factor time-trends. The adverse role of BMI emphasizes the importance of addressing rising population BMI.

Key words: **Myocardial infarction; Incidence; Time Trends; Population; Prevention; Risk factors**

INTRODUCTION

Coronary heart disease (CHD) incidence has declined appreciably in the UK (by almost two thirds among men in the last 25 years)(1), contributing to a substantial fall in CHD mortality(2). However the reasons for the decline in CHD incidence are not well understood. Furthermore the possible impact of rising adiposity in restraining the decline remains unknown. Addressing these uncertainties is important because despite the declines, CHD remains the leading cause of death in the UK(2), the USA and other wealthy countries(2) while control of the emerging CHD epidemic in the developing world is an increasing priority(3).

Although several studies have examined the contribution of risk factor trends to changes in incidence or mortality in the UK(1;4;5) and in other locations(6-8), most have used aggregate data sources and are subject to the limitations of ecological analyses. Few studies have used individual level data from single populations(1;6). The one previous UK-based investigation assessed major risk factors only twice and did not include women(1). The aim of this present analysis was therefore to estimate the contribution of risk factor trends to recent trends in the incidence of major CHD in the Whitehall II cohort of British men and women followed over a period of 20 years, with clinic visits every 5 years.

METHODS

The Whitehall II study

The Whitehall II study, described elsewhere(9), recruited 10,308 men and women, aged 35-55 years, from 20 civil service departments in London in 1985-88. At baseline (1985-8), phase 3 (1991-3), phase 5 (1997-9) and phase 7 (2002-4) the

participants completed clinical examinations and questionnaires on health and lifestyle. Participants were flagged at the National Health Service Central Registry, which provided information on the date and cause of death. Ethical approval for the Whitehall II study was obtained from the UCL Medical School Committee on the ethics of human research. Informed consent was obtained from the study participants.

Coronary events

The outcome was a first myocardial infarction (MI, fatal or non-fatal) between baseline and 2002-4 (end of phase 7), (mean follow-up of 15.4 (SD 4.2) and 9.0 (SD 4.5) years for participants who were censored, and those who experienced the outcome respectively). Participants who developed angina (either before baseline or during follow up) were retained for analysis. Fatal MI was identified as a record of death with CHD as the underlying cause, including sudden death of presumed cardiac origin (international classification of diseases, ninth revision, codes 410-414). Potential new cases of nonfatal MI were ascertained by questionnaire items on chest pain and the physician's diagnosis of heart attack in all four phases listed above. Only those cases confirmed according to MONICA criteria using electrocardiograms, markers of myocardial necrosis, and chest pain history from the medical records, were included(10).

Assessment of risk factors

At each of the three study phases: baseline (1985-8), phase 3 (1991-3), and phase 5 (1997-9), cigarette smoking status, physical activity levels, elements of diet, and alcohol consumption were ascertained by questionnaire, while fasting lipid levels, SBP and body mass index (BMI) were obtained from clinical examinations, using

consistent techniques on each occasion(11;12). At baseline, 9065 participants (88%) had no HDL cholesterol measurement, but serum apolipoprotein-A1 was available for almost 80% of participants(11). Age and gender-adjusted linear regression of the available HDL data on apolipoprotein-A1 was used to estimate the relationship between the two variables and then predict baseline HDL for those participants with no data (Appendix 1 in Online Supplementary Material). Alcohol consumption in the previous week was measured as units per week, then categorised as none, within recommended limit for gender (<21 units for men, <14 units for women), over recommended limit, and very heavy (>50 units for men and >35 units for women). Cigarette smoking categories were non-smoker, ex-smoker, and current smoker. Dietary data available was usual milk consumption (categorised as none, whole milk, semi-skimmed, skimmed and other), usual bread consumption (white, wholemeal, granary or wheatmeal, other brown bread, other) and usual fruit and vegetable consumption (<3 times/week, 3-4 times/week, 5-6 times/week, daily, ≥2 times/day). Physical activity levels were categorised as low (<2 hours per week of moderate activity and <1 hour of vigorous activity); high (≥2.5 hours per week of moderate activity or >1 hour of vigorous activity); or medium (levels in between low and high)(13).

Statistical analyses

   Cox regression was used to estimate associations between each risk factor at phase 1 and subsequent MI hazard to justify inclusion in the main analyses prior to computing attributable proportions. All risk factors except type of milk were significantly associated (positively or negatively) with MI hazard. To estimate secular time-trends in the risk factors and in MI the follow-up for each participant was

split into three consecutive periods, each of approximately five years, separated by the different examination phases: a first period from phase 1 to phase 3; a second from phase 3 to phase 5 and a third from phase 5 to phase 7. The MI incidence and risk factor levels in different periods are then compared, adjusting for age and gender, to assess secular trends over time. In particular, age-adjusted secular time-trends among men and women from phases 1 to 5 in the risk factors were estimated from regression of the risk factor on calendar time (of start of period), in this split dataset using generalised estimating equations with robust standard errors to take account of dependency between repeated measures for each participant. Poisson models were fitted for percentage change in prevalence of being a current cigarette smoker, having $\geq$medium physical activity levels, consuming alcohol over recommend limit, usually eating white bread, and usually eating fruit and vegetables $\geq$twice daily; and linear models for time-trend in mean BMI, SBP, HDL and non-HDL cholesterol. Cox regression on this split dataset was used to estimate the time-trend in the hazard of MI overall and by gender, again using robust standard errors to account for dependency between repeated observations for each participant. Age was used as the underlying time scale, enabling automatic adjustment for age[14]. There was no evidence of departure from the proportional hazards assumption of the Cox regression tested using Schoenfeld residuals[15].

The extent to which the secular time-trends in each of the risk factors statistically explained the trend in MI hazard were estimated by the expression $(\beta_0-\beta_1)/\beta_0$, where β_0 is the coefficient of calendar time in the Cox model with calendar time as the single covariate, and β_1 is the coefficient of calendar time in a Cox model adjusting additionally for the risk factor(s)[16]. Bias-corrected bootstrap resampling gave an

approximate 95% confidence interval (CI) for this estimate(17). Squared terms in the continuous risk factors (BMI, SBP and HDL and non-HDL cholesterol) were added to the models to test for non-linearity; squared-terms for HDL and non-HDL cholesterol were significant and so retained in the final models. The above analyses were applied to men and women combined, adjusting for gender. Further exploratory analyses were carried out to estimate risk factor contributions to the decline in MI in men and women separately. Participants missing data on ≥1 risk factors in a particular phase were excluded from that phase and the associated follow-up, but included in other phases. Participants missing data in all phases were excluded from analyses altogether. Numbers of participants included in each phase are given in Table 1. A p-value of 0.05 was used as the threshold for statistical significance and all tests were two-sided. Stata, version 11.1, (Stata Corp., College Station, Texas) was used for all analyses.

RESULTS

Time trends in MI incidence

Of 10,308 participants recruited, one had no follow-up data, 35 reported an MI before baseline, and 819 had missing data on ≥1 risk factor at all phases and were excluded from analysis. The remaining 9,453 participants included 6,379 (67%) men and 3,074 women. A total of 256 first MI events occurred during 107,892 person-years of follow-up; 208 first MI events occurred among men during 74,474 person-years of follow-up and 48 first MI events occurred during 33,418 person-years of follow-up among women. There was an average annual age-adjusted decline in MI hazard over the course of the follow-up of 6.5% (95% CI 3.2 to 9.7) corresponding to a 20-year fall from baseline (1985-8) of 74% (95% CI 48 to 87). Men experienced a

20-year fall of 73% (95% CI 42 to 87) and women experienced a 20-year fall of 82%

(-5 to 97). There was no evidence of a gender-time interaction (p=0.7).

Time trends in risk factors

The levels of each risk factor according to age-group and study phase for men and women are shown in Appendix 2 in the Online Supplementary Material. Favourable time-trends occurred in several risk factors between 1985-8 and 1997-9: adjusting for age, mean SBP fell, mean non-HDL cholesterol fell, mean HDL cholesterol rose, prevalence of consumption of fruit and vegetables ≥twice daily rose (comparable statistically significant changes for men and women); cigarette smoking prevalence fell (statistically significant among women only), and prevalence of at least moderate physical activity levels fell (statistically significant among men only) (Table 2). Bread consumption did not change among men or women. There were unfavourable increases in mean BMI and alcohol consumption, adjusting for age.

Role of risk factors trends in MI incidence trends

Four risk factor trends contributed in isolation to the 74% decline in MI hazard among all participants (Table 3). Percentage contributions of these risk factors in order of size were: declining non-HDL cholesterol 34% (bootstrap 95% CI 20 to 76), rising HDL cholesterol 17% (bootstrap 95% CI 10 to 32), declining SBP 13% (bootstrap 95% CI 7 to 24), and declining cigarette smoking 6% (bootstrap 95% CI 2 to 14). Together they explained a total of 54% (95%CI 34 to 105) of the decline (the upper bound of the CI indicates that the data are consistent at the 95% confidence level with the risk factors explaining a greater decline than that observed). The contribution of increased fruit and vegetable consumption did not reach statistical

significance (7%, bootstrap 95% CI -1 to 20), the combined contribution with the four other risk factors being 56% (bootstrap 95% CI 34 to 112). Trends in physical activity, alcohol consumption and bread consumption had no notable impact. The rise in mean BMI was adverse, explaining -11% (bootstrap 95% CI -23 to -5) of the decline in MI hazard in isolation. The proportion of the decline explained by the risk factors combined reduced from 56% to 48% (bootstrap 95% CI 27 to 96) with additional adjustment for the adverse trend in BMI. This suggests that the MI decline could be 8% greater in the absence of rising BMI.

Considering men and women separately, the relative contributions of each of the risk factors to the MI declines within each gender were generally similar to each other and to that in the combined analysis (Table 4). Exceptions were that among women, there was a smaller contribution from HDL cholesterol compared with SBP and the proportion explained by cigarette smoking was not significant. Further, among women, a negative impact of BMI was not as apparent. In secondary analyses considering fatal events only, results were similar (data not shown).

DISCUSSION

Over 20 years between 1985 and 2004 there was a substantial decline of 74% in the age-adjusted hazard of first MI among men and women the Whitehall II cohort. Over half of the MI decline could be explained by a combination of favourable time-trends in major risk factors, particularly non-HDL cholesterol, HDL cholesterol, SBP, and cigarette smoking. Rising adiposity had an adverse impact on the declining trend in MI, such that had other risk factor trends not occurred, rising BMI may have led to

an increase in MI incidence over the follow-up. The MI decline and the risk factor contributions were broadly similar for men and women.

Multiple repeated measurements of risk factors, using consistent techniques for measurement of the physical factors on each occasion, are a key strength of this study. We linked risk factor trends to coronary events at an individual-level, thus avoiding the limitation of ecological analyses predominantly used to study time-trends. Further, this is apparently the first analytical study of MI trends in a cohort following both men and women. We used consistent methods to identify MIs throughout the follow-up period to limit confounding of the estimate of the incidence trend by changes in diagnostic criteria. Silent MIs were not included and the outcome thus corresponds to major CHD events. Risk factor levels were related to MI events up to five years ahead, based on the interval between clinic phases, and there is evidence that the benefits of smoking cessation, changes in blood lipids and blood pressure are realised in this timeframe(19-21).

There are several limitations. The analyses were necessarily based on participants who re-attended after baseline, and provided complete risk factor data at one phase at least. This could introduce survival and response biases which might overestimate the favourable trends observed, due to a healthy participant effect. However, survivor bias is unlikely to be marked as survival in the cohort is high(9). Including those participants with missing risk factor data, the 20-years decline was smaller: 62% (95% CI 34 to 78) indicating some response bias. As we could arguably expect similar overestimation of the favourable risk factor trends, the percentage explained by each risk factor may still be comparable. HDL cholesterol values at baseline were derived

from serum apolipoprotein-A1 for a subgroup of the participants. The likely impact is underestimation of the variance associated with the baseline HDL measurements but without biasing the estimate of the contribution of HDL to the MI decline. Any measurement imprecision of the risk factors, particularly likely for the questionnaire-derived dietary factors, physical activity and alcohol consumption, may have led to underestimation of the contribution to the MI decline. Questions on physical activity at phase 5 were more detailed than those in the earlier phases, giving more opportunity to report activity, which could lead to underestimation of the physical activity decline and its counterproductive role. The analyses of the risk factor contributions by gender lack precision (confidence intervals for the percentage contributions are wide), particularly for women who experienced few events (48 in total), and should thus be considered exploratory. Diabetes was not considered in this analysis. It is likely that diabetes lies on the causal pathway between several of the risk factors considered here and major CHD risk. Including diabetes in the analysis would therefore be problematic and could lead to underestimation of the effects of the risk factors(22). The limitation of not considering diabetes is that we are unable to ascertain the extent to which the adverse effect of increasing BMI levels operates through an increase in diabetes (particularly type 2 diabetes) incidence. Effort was made to model carefully the relationship between the risk factors and MI incidence, for example by inclusion of squared terms in the continuous variables in the Cox regression models, where significant. However, if the relationship between the risk factors and MI incidence is not fully captured in the Cox models, this may have led to underestimation of the association between the risk factors and MI risk and in turn underestimation of the percentage of the decline in MI explained by the risk factors.

Trends in non-HDL cholesterol had the greatest single impact on the decline in MI incidence. The favourable time-trend in non-HDL cholesterol may reflect increasing use of lipid-regulating medication or lifestyle (e.g. diet) or some combination of factors. Statin use rose to 11% of the cohort (25% of those with high LDL-cholesterol) by the end of the follow-up in 2004 (Bouillon et al, submitted), suggesting that lipid-regulating medication may have made an appreciable contribution.

The combined contribution of the risk factors to the MI decline in the present study was similar to that found in a national cohort of men over a similar period (46%), but the individual relative impacts of the risk factors differed between the two cohorts(1). The decline in smoking prevalence had greater impact in the national cohort, possibly explained by the already lower prevalence of smokers at a later baseline in the present study (23% among men in Whitehall II compared with ~40% among men in the national cohort). The trend in and contribution of non-HDL cholesterol was smaller in the national cohort, (non-HDL cholesterol fell by 0.4mmol/L over 12 years in Whitehall II men, compared to 0.35mmol/L over 20 years in a national cohort(23)) possibly reflecting greater take-up of effective lipid lowering medication in the present study (Boullion et al in press). The differences may reflect the higher socioeconomic status in the present London-based cohort. Indeed, in results stratified by employment grade, the risk factor contributions in the lowest grades corresponded more closely to the national cohort findings (data not shown).

In a comparable analysis of US women, 68% of the decline in CHD incidence could be explained by combined trends in smoking, diet (decreased saturated fat,

increased fibre content) and post-menopausal hormone use(6). Dietary trends in isolation accounted for the largest part of the decline (52%). The greater contribution of diet in the US investigation is likely to reflect the influence of diet on risk factors such as blood pressure and cholesterol not available in that study, but included as explanatory variables in our analysis. Any protective effect of hormone therapy is doubtful in the light of recent evidence from the Women's Health Initiative(24). Finally, the WHO MONICA Project suggested that cigarette smoking, SBP and total cholesterol together explained approximately 38% of the variation in trends in coronary event rates from the mid-1980s to the mid-1990s in men in 27 different populations(7). The lower total percentage explained may reflect the ecological analysis, using aggregate data to study variations in trends between populations, rather than studying variation over time in individuals within one population as in the present study.

Implications

In this cohort of London civil servants there was a substantial decline in MI over two decades to 2004, more than half of which could be attributed to favourable risk factor trends, highlighting what can be achieved and emphasizing the value of measures to reduce exposure to these risk factors in the population. The risk factor trends were of comparable importance for men and women, suggesting that similar influences have operated to achieve declines in MI incidence, such that similar prevention strategies may be appropriate for both genders. Further research is needed to determine whether the residual unexplained portion of the decline in MI may be explained by early treatment, underestimated contributions of the major risk factors (reflecting imprecision in the analyses) or the influence of other risk factors. The

apparent lack of association of the decline in physical activity with the time-trend in MI may reflect the methodological limitations associated with quantifying activity levels or the measured decline in activity was insufficient to influence MI incidence.

While the negative contribution of rising mean BMI over recent decades appears to have been outweighed by the favourable trends in other vascular risk factors, continued increases in BMI may further reduce or even reverse the decline in MI incidence. The extent to which the rise in BMI may have influenced the time-trend in MI through an increase in incidence of diabetes cannot be evaluated from this analysis. The association between type 2 diabetes and CHD risk is well-established and previous studies suggest that a concurrent rise in incidence of type 2 diabetes has occurred which may be at least in part explained by rising BMI(25), supporting the influence of BMI on the time-trend in CHD operating to some extent through rising diabetes. Sharply rising trends in statin and BP lowering medication(2;23) may contribute to continuing favourable MI incidence trends in the UK and other rich countries but it is unlikely that the health care systems in emerging economies will have the necessary resources to provide the level of care needed to compensate for the increasing prevalence of overweight and obesity already taking place. The rising BMI in the UK and in other countries needs therefore urgent attention.

FUNDING

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Table 1. Numbers of participants contributing data in each study phase by age group (participants with complete risk factor data)

MEN		Age group, years							
		35-39	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-68*	*All*
Number of participants									
Phase	1 (1985-8)	1333	1354	928	1048	129	0	0	4792
	3 (1991-3)	100	1537	1401	1015	1029	143	0	5225
	5 (1997-9)	0	9	783	964	614	653	180	3203
*Number of subsequent incident major CHD events**									
Phase	1 (1985-8)	6	4	9	25	5			49
	3 (1991-3)	1	21	12	31	36	6		107
	5 (1997-9)		0	4	9	14	21	4	52

WOMEN		Age group, years							
		35-39	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-68*	*All*
Number of participants									
Phase	1 (1985-8)	547	562	532	629	99	0	0	2369
	3 (1991-3)	45	549	582	487	575	76	0	2314
	5 (1997-9)	0	2	291	336	288	289	79	1285
*Number of subsequent incident major CHD events**									
Phase	1 (1985-8)	0	2	3	6	1			12
	3 (1991-3)	0	4	1	9	6	2		22
	5 (1997-9)		0	0	1	1	8	4	14

*Events occurring between phases 1 and 3 for participants at phase 1, between phases 3 and 5 for participants at phase 3 and between phase 5 and phase 7 (2002-4) for participants at phase 5.

Table 2. Age-adjusted population-averaged time-trends in coronary risk factors among men and women over 12 years from 1985-8 (baseline) to 1997-9 (phase 5)

	Men			Women		
Risk factor	Change in mean levels per annum (95% CI)	p-value	Change over 12 years (95% CI)	Change in mean levels per annum (95% CI)	p-value	Change over 12 years (95% CI)
BMI, kg/m^2	0.10 (0.08, 0.11)	<0.001	1.16 (0.99, 1.33)	0.07 (0.03, 0.10)	<0.001	0.78 (0.41, 1.15)
Systolic blood pressure, mmHg	-0.35 (-0.42, -0.28)	<0.001	-4.19 (-5.02, -3.35)	-0.52 (-0.63, -0.41)	<0.001	-6.21 (-7.52, -4.90)
Non-HDL cholesterol, mmol/L	-0.033 (-0.038, -0.028)	<0.001	-0.40 (-0.46, -0.33)	-0.047 (-0.054, -0.039)	<0.001	-0.56 (-0.65, -0.47)
HDL cholesterol, mmol/L	0.011 (0.009, 0.012)	<0.001	0.13 (0.11, 0.15)	0.006 (0.004, 0.009)	<0.001	0.08 (0.04, 0.11)
Risk factor	% change in prevalence per annum (95% CI)	p-value	% change over 12 years (95% CI)	% change in prevalence per annum (95% CI)	p-value	% change over 12 years (95% CI)
Current smoker	-0.80 (-1.89, 0.30)	0.2	-9.2 (-20.4, 3.6)	-3.78 (-4.94, -2.62)	<0.001	-37.1 (-45.5, -27.2)
At least moderate physical activity	-1.06 (-1.35, -0.76)	<0.001	-12.0 (-15.1, -8.8)	-0.48 (-1.16, 0.21)	0.2	-5.6 (-13.1, 2.5)
Consume alcohol over recommended limit	6.12 (5.15, 7.10)	<0.001	104 (82.8, 128)	7.96 (5.79, 10.17)	<0.001	151 (96.5, 220)
White bread as usual bread type	-0.26 (-0.53, 0.01)	0.06	-3.1 (-6.2, 0.1)	0.12 (-0.24, 0.47)	0.5	1.4 (-2.8, 5.8)
Consume fruit and vegetables ≥2 daily	7.99 (7.01, 8.98)	<0.001	151 (125, 180)	8.73 (7.56, 9.92)	<0.001	173 (140, 211)

Table 3. Fall in hazard of a first MI per annum among all participants and percentage of this fall explained by risk factor time-trends

Model	Risk factors adjusted for in addition to age and gender	Fall in hazard per annum, % (95% CI)	p-value	% of the observed decline in hazard explained by the risk factor(s), (95% CI)*
A	**No adjustment**	6.51 (3.22, 9.68)	<0.001	
	Effect of adjustment for individual risk factors in isolation			
B	Smoking (current/ex/never)	6.13 (2.82, 9.33)	<0.001	**5.9 (2.3, 13.6)**
C	Physical activity (low/medium/high)	6.51 (3.20, 9.70)	<0.001	**0.1 (-4.5, 5.3)**
D	Alcohol units per week (none/within limit/over limit/heavy)	6.44 (3.13, 9.65)	<0.001	**1.0 (-6.1, 8.3)**
E	Usual bread consumption (white/wholemeal/granary or wheatmeal/other brown bread/combination)	6.55 (3.26, 9.72)	<0.001	**-0.6 (-3.3, 0.3)**
F	Usual fruit and vegetable consumption (<3 per week/3-4 per week/5-6 per week/daily/>1 per day)	6.07 (2.72, 9.31)	<0.001	**6.8 (-1.1, 19.9)**
G	BMI, kg/m^2 (continuous)	7.18 (3.94, 10.32)	<0.001	**-10.8 (-23.2, -4.6)**
H	Systolic blood pressure, mmHg (continuous)	5.70 (2.41, 8.87)	0.001	**12.8 (7.4, 24.4)**
I	HDL cholesterol, mmol/L (continuous)	5.45 (2.13, 8.67)	0.001	**16.6 (9.9, 32.3)**
J	Non-HDL cholesterol, mmol/L (continuous)	4.32 (0.79, 7.72)	0.02	**34.4 (20.4, 75.7)**
	Effect of adjustment for combinations of risk factors			
K	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure	3.05 (-0.47, 6.44)	0.09	**54.4 (34.4, 105)**
L	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure, usual fruit and vegetable consumption	2.92 (-0.64, 6.36)	0.1	**55.9 (34.3, 112)**
M	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure, usual fruit and vegetable consumption, BMI	3.44 (-0.15, 6.91)	0.06	**47.9 (26.6, 95.5)**

*% of the observed fall in hazard rate explained by risk factor = $100\% \times (\beta_0 - \beta_1)/\beta_0$, where β_0 is the coefficient of calendar time in the Cox regression model which only included calendar time (Model A), and β_1 is the coefficient of calendar time in the Cox regression model adjusting additionally for the risk factor(s)

Table 4. Fall in hazard of a first MI per annum and percentage of this fall explained by risk factor time-trends among men and women

Model		Men			Women		
		Fall in hazard per annum, % (95% CI)	p-value	% of decline in hazard explained by risk factor(s), (95% CI)*	Fall in hazard per annum, % (95% CI)	p-value	% of decline in hazard explained by risk factor(s), (95% CI)*
A	No adjustment	6.26 (2.66, 9.73)	0.001		8.12 (-0.25, 15.80)	0.06	
	Effect of adjustment for individual risk factors in isolation						
B	Smoking (current/ex/never)	5.96 (2.34, 9.45)	0.001	**4.8 (1.4, 13)**	7.51 (-0.96, 15.27)	0.08	**7.9 (-3.3, 43.9)**
C	Physical activity (low/medium/high)	6.31 (2.70, 9.79)	0.001	**-0.9 (-6.9, 4.7)**	7.78 (-0.75, 15.58)	0.07	**4.5 (-3.1, 60.7)**
D	Alcohol units per week (none/within limit/over limit/heavy)	6.25 (2.62, 9.75)	0.001	**0.1 (-9.2, 9.3)**	7.84 (-0.64, 15.60)	0.07	**3.7 (-10.2, 32.6)**
E	Usual bread consumption (white/wholemeal/granary or wheatmeal/other brown bread/combination)	6.29 (2.69, 9.75)	0.001	**-0.5 (-3.8, 0.6)**	8.16 (-0.26, 15.86)	0.06	**-0.4 (-9.1, 6.4)**
F	Usual fruit and vegetable consumption (<3 per week/3-4 per week/5-6 per week/daily/>1 per day)	5.87 (2.20, 9.40)	0.002	**6.3 (-2.2, 23.1)**	7.29 (-1.32, 15.18)	0.1	**10.6 (-23.1, 57.3)**
G	BMI, kg/m^2 (continuous)	7.32 (3.73, 10.77)	<0.001	**-17.6 (-41.1, -8.2)**	8.22 (-0.06, 15.81)	0.05	**-1.2 (-28.0, 14.2)**
H	Systolic blood pressure, mmHg (continuous)	5.58 (1.98, 9.05)	0.003	**11.1 (5.7, 25.5)**	6.67 (-1.73, 14.37)	0.1	**18.5 (6.8, 69.8)**
I	HDL cholesterol, mmol/L (continuous)	5.10 (1.43, 8.62)	0.007	**19.1 (10.2, 39.0)**	7.48 (-0.91, 15.17)	0.08	**8.3 (1.0, 44.4)**
J	Non-HDL cholesterol, mmol/L (continuous)	4.19 (0.32, 7.91)	0.03	**33.8 (18.2, 87.4)**	5.52 (-3.47, 13.73)	0.2	**33.0 (10.8, 214)**
	Effect of adjustment for combinations of risk factors						
K	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure	2.99 (-0.88, 6.71)	0.1	**53.0 (30.7, 123)**	3.66 (-5.35, 11.89)	0.4	**56.0 (21.5, 269)**
L	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure, usual fruit and vegetable consumption	2.90 (-1.02, 6.67)	0.1	**54.4 (29.8, 126)**	3.38 (-5.66, 11.65)	0.5	**59.4 (19.2, 221)**
M	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure, usual fruit and vegetable consumption, BMI	3.48 (-0.49, 7.30)	0.09	**45.1 (21.7, 119)**	3.76 (-5.27, 12.02)	0.4	**54.7 (11.2, 210)**

* % of the observed fall in hazard rate explained by risk factor = 100% × (β_0- β_1)/ β_0, where β_0 is the coefficient of calendar time in the Cox regression model which only included calendar time (Model A), and β_1 is the coefficient of calendar time in the Cox regression model adjusting additionally for the risk factor(s)