Articles

Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations

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Summary

Background From the mid-1980s to mid-1990s, the WHO MONICA Project monitored coronary events and classic risk factors for coronary heart disease (CHD) in 38 populations from 21 countries. We assessed the extent to which changes in these risk factors explain the variation in the trends in coronary-event rates across the populations.

Methods In men and women aged 35–64 years, non-fatal myocardial infarction and coronary deaths were registered continuously to assess trends in rates of coronary events. We carried out population surveys to estimate trends in risk factors. Trends in event rates were regressed on trends in risk score and in individual risk factors.

Findings Smoking rates decreased in most male populations but trends were mixed in women; mean blood pressures and cholesterol concentrations decreased, body-mass index increased, and overall risk scores and coronary-event rates decreased. The model of trends in 10-year coronary-event rates against risk scores and single risk factors showed a poor fit, but this was improved with a 4-year time lag for coronary events. The explanatory power of the analyses was limited by imprecision of the estimates and homogeneity of trends in the study populations.

Interpretation Changes in the classic risk factors seem to partly explain the variation in population trends in CHD. Residual variance is attributable to difficulties in measurement and analysis, including time lag, and to factors that were not included, such as medical interventions. The results support prevention policies based on the classic risk factors but suggest potential for prevention beyond these.

Lancet 2000; **355:** 675–87
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Introduction

Routinely collected statistics on mortality rates from coronary heart disease (CHD) showed increases in the 1950s and early 1960s in most industrialised countries, but a decline started in the 1960s in the USA and Australia, followed by other countries.[1] Key questions were raised at a conference on this decline, convened by the National Institutes of Health in Bethesda, MD, USA, in 1978. Were the mortality changes real, and if so, how much was attributable to change in incidence of coronary events, and how much to change in case fatality? Could the changes in coronary-event rates be related to population trends in the known coronary risk factors of cigarette smoking, blood pressure, and serum cholesterol? Could the changes in case fatality be related to trends in coronary care? These questions could not be answered because of a lack of basic information.[2] Consequently, WHO invited investigators with an interest in what was happening to CHD in their own populations in many different countries, to collaborate in an epidemiological study that became the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project. Protocols, procedures, and quality-assurance methods were developed for collecting a standard set of data on trends in CHD mortality, non-fatal acute myocardial infarction, coronary care, and major coronary risk factors, in defined populations for men and women aged 35–64 years.[3] Apart from fulfilling local needs, the data from the different populations were to be put together centrally to address the unanswered questions from the Bethesda meeting. (For objectives and outline protocol of the WHO MONICA Project see URL: www.ktl.fi/publications/monica/manual/part1/i-1.htm URN: NBN:fi-fe19981147)

In a previous paper, we confirmed the validity of the mortality trends and showed that, in populations in which mortality declined, coronary-event rates contributed two-thirds of the decline and one-third came from change in case fatality.[4] The conclusion was that the main determinant of change in CHD mortality was whatever drives changes in rates of coronary events.

The two other questions from Bethesda are now addressed in separate papers. Here we address the first question, formulated for the 1983 protocol as a null hypothesis that for the population reporting units there is no relation between: 10-year trends in the major cardiovascular-disease risk factors of serum cholesterol, blood pressure, and cigarette consumption; and 10-year trends in incidence rate (fatal plus non-fatal attack rates) of CHD.

Relative bodyweight was not originally included in the study protocol for this analysis, but we have included it because of its perceived public-health importance.[5]

Country	Population (abbreviation)	Event registration periods (full/lagged)	Total numbers of events (M/F)	Survey periods			Totals of survey participants (M/F)	Overall quality score
				Initial	Middle	Final		
Australia	Newcastle (AUS-NEW)	85–93/87–93	3213/1071	5/83–12/83	6/88–11/89	6/94–12/94	2482/2507	1·5
	Perth (AUS-PER)	84–93/87–93	5195/1246	5/83–11/83	6/89–12/89	5/94–11/94	1214/1225	0·8
Belgium	Charleroi (BEL-CHA)	83–92/88–92	1996/556	3/85–7/87	9/87–6/90	7/90–2/93	747/642	1·2
	Ghent (BEL-GHE)	83–92/88–92	1546/398	2/85–6/87	6/88–3/90	4/90–4/92	1114/986	1·4
Canada	Halifax County (CAN-HAL)	84–93/89–93	2445/678	9/85–11/88	Not done	5/95–11/95	569/554	1·7
China	Beijing (CHN-BEI)	84–93/88–93	1167/475	9/84–11/85	9/88–10/89	9/93–10/93	1616/1958	1·4
Czech Republic	Czech Republic (CZE-CZE)	84–93/88–93	5947/1335	3/85–11/85	3/88–11/88	3/92–12/92	2858/2988	1·3
Denmark	Glostrup (DEN-GLO)	82–91/86–91	3261/909	11/82–1/84	8/86–4/87	2/91–3/92	2629/2535	1·4
Finland	Kuopio Province (FIN-KUO)	83–92/86–92	3397/660	1/82–4/82	1/87–4/87	1/92–3/92	2109/2205	1·9
	North Karelia (FIN-NKA)	83–92/86–92	2728/529	1/82–4/82	1/87–4/87	1/92–3/92	2723/2982	1·9
	Turku/Loimaa (FIN-TUL)	83–92/86–92	2028/433	1/82–4/82	1/87–4/87	1/92–3/92	2303/2471	1·8
France	Lille (FRA-LIL)	85–94/90–94	4823/1177	6/86–2/89	Not done	6/95–11/96	1126/993	1·2
	Strasbourg (FRA-STR)	85–93/89–93	4306/1029	1/85–8/87	Not done	3/95–4/97	1144/1169	1·4
	Toulouse (FRA-TOU)	85–93/89–93	3277/561	5/85–2/87	10/88–5/91*	12/94–7/96	1848/1171	1·1
Germany	Augsburg Rural (GER-AUR)	85–94/88–94	1523/323	10/84–5/85	10/89–6/90	10/94–6/95	2420/2485	1·8
	Augsburg Urban (GER-AUU)	85–94/88–94	1636/441	10/84–5/85	10/89–6/90	10/94–7/95	1950/1908	1·7
	Bremen (GER-BRE)	85–92/87–92	1216/329	5/84–11/84	5/88–11/88	5/91–6/92	1418/1450	0·7
	East Germany (GER-EGE)	85–93/87–93	2736/643	11/82–8/84	1/88–11/88	9/93–12/94	1115/1322	0·4
Iceland	Reykjavik (ICE-ICE)	81–94/87–94	978/203	6/83–11/83	9/88–3/89	6/93–4/94	1025/1023	1·9
Italy	Area Brianza (ITA-BRI)	85–94/89–94	4850/806	4/86–3/87	5/89–7/90	9/93–11/94	1839/1889	1·6
	Friuli (ITA-FRI)	84–93/89–93	4969/1054	1/86–9/86	3/89–12/89	3/94–10/94	2070/2100	1·7
Lithuania	Kaunas (LTU-KAU)	83–92/87–92	3117/669	2/83–1/85	12/86–6/87	2/92–5/93	2170/2180	1·2
New Zealand	Auckland (NEZ-AUC)	83–91/86–91	5389/1444	2/82–7/82	Not done	1/93–3/94	1727/1227	1·6
Poland	Tarnobrzeg Voivodship (POL-TAR)	84–93/87–93	4510/1225	6/83–11/84	5/87–11/88	6/92–7/93	2452/2789	0·8
	Warsaw (POL-WAR)	84–94/88–94	5887/1804	12/83–1/85	1/88–1/89	1/93–12/93	2730/2759	1·8
Russia	Moscow-Control (RUS-MOC)	85–93/88–93	1668/517	2/84–2/86	3/88–10/89	3/92–3/95	1873/1648	1·0
	Moscow-Intervention (RUS-MOI)	85–93/88–93	615/214	2/84–12/85	2/88–1/89	1/92–3/95	1583/1990	0·8
	Novosibirsk-Control (RUS-NOC)	84–92/87–92	1228/453	11/85–1/86	Not used†	1/95–6/95	1088/1089	1·0
	Novosibirsk-Intervention (RUS-NOI)	84–93/88–93	1104/426	5/85–12/85	Not used†	5/94–2/95	1134/1212	1·1
Spain	Catalonia (SPA-CAT)	85–94/90–94	4155/732	4/86–7/88	10/90–5/92	6/94–5/96	3613/2914	1·8
Sweden	Gothenburg (SWE-GOT)	84–94/89–94	3133/770	2/85–11/86	2/90–5/91	9/94–2/96	1678/1831	1·3
	Northern Sweden (SWE-NSW)	85–95/90–95	5695/1330	1/86–4/86	1/90–4/90	1/94–4/94	1805/1805	1·4
Switzerland	Ticino (SWI-TIC)	85–93/89–93*	1461/0	11/85–5/86	10/88–4/89	10/92–5/93	2162/2158	1·3
	Vaud/Fribourg (SWI-VAF)	85–93/88–93*	2922/0	10/84–6/85	11/88–6/89	11/92–6/93	1809/1695	1·0
UK	Belfast (UNK-BEL)	83–93/87–93	6070/1959	10/83–9/84	9/86–12/87	10/91–12/92	2594/2515	1·6
	Glasgow (UNK-GLA)	85–94/89–94	5450/2143	2/86–7/86	1/92–9/92	2/95–10/95	1612/1642	1·7
USA	Stanford (USA-STA)	80–92/83–92	2515/905	5/79–4/80	5/85–6/86	6/89–6/90	1245/1486	1·5
Yugoslavia	Novi Sad (YUG-NOS)	84–95/88–95	2789/757	9/84–12/84	9/88–4/89	9/94–2/95	1657/1684	1·3

*Men only. †Not used for analysis.

Table 1: **Event-registration, survey, and quality-score data by population**

We address the second question, which relates changes in case fatality and other coronary endpoints to changes in coronary care, in another paper in this issue of *The Lancet*.[6] Differences in definitions of populations and in timing of data on risk factors and coronary care inhibit an all-inclusive first analysis of the two questions.

Accumulated evidence of causality through the consistency, strength and reversibility of the classic coronary risk factors in individuals has increased substantially since 1983. The null hypothesis is, therefore, of less importance than estimating the size of the effect. We attempted to estimate the extent to which trends in classic risk factors are driving the change in coronary-event rates at population level. Since the units in this paper are populations, the analysis was ecological.[7,8]

Methods

Study populations

Study populations consisted of residents of geographically defined areas aged 35–64 years. There was no follow-up of individuals beyond the 28-day duration of a coronary event. The 38 populations in 21 countries were mostly in Europe, but three were in Asia, three in Australasia, and two in North America (table 1). Short descriptions of the populations have been published elsewhere.[9] The populations are almost the same as in our previous paper on coronary events,[4] except for six that cover smaller areas, in which we collected data on coronary events and risk factors (Perth, Bremen, East Germany, Iceland, Moscow Intervention, and Novosibirsk Control). One population was separated into two groups because complete risk-factor surveys were done in two subareas (Augsburg Rural and Urban).

Data collection

Coronary events were registered continuously for a mean of 10 years. Suspected myocardial infarction and coronary deaths were validated and allocated to standard diagnostic categories. The numerators for calculation of coronary-event rates were non-fatal definite myocardial infarction, and definite, possible, or unclassifiable coronary deaths. The denominators came from the official sources of demographic data and were numbers of men and women in different age-groups for each year of the study. Registration methods have been described previously[4,9] (URL: www.ktl.fi/publications/monica/manual/part4/iv-1.htm URN: NBN:fi-fe19981154).

To measure the risk factors, we carried out two surveys based on independent probability samples of the populations at the beginning and the end of the 10-year period, generally with a third survey in the middle. The best available sampling frames were used, and the samples were most frequently stratified by sex and age, with equal numbers in each 10-year age-group for the two sexes. Survey periods and numbers of respondents are

Population	Coronary-event rate over last 5 years (average annual % change during full/lagged period)	Mean for final survey (average annual change)				
		Daily smoking (%)	Systolic blood pressure (mm Hg)	Total cholesterol (mmol/L)	Body-mass index (kg/m²)	Risk score
AUS-NEW	430 (−5·1/−5·6)	22 (−1·35)	131 (−0·28)	5·8 (−0·016)	27·9 (0·12)	7·0 (−1·74)
AUS-PER	366 (−3·0/−3·1)	24 (−0·87)	134 (0·04)	5·5 (−0·033)	26·4 (0·07)	6·9 (−1·65)
BEL-CHA	485 (0·3/0·3)	48 (−0·30)	131 (0·19)	6·2 (−0·011)	27·1 (0·09)	7·3 (−0·83)
BEL-GHE	314 (−3·2/−1·9)	43 (−0·34)	129 (0·37)	6·0 (−0·026)	26·4 (0·14)	7·2 (0·37)
CAN-HAL	456 (−4·7/−1·6)	32 (0·17)	130 (0·85)	5·6 (−0·036)	27·5 (0·10)	6·9 (0·46)
CHN-BEI	86 (2·3/2·0)	64 (1·65)	131 (−0·13)	4·5 (0·033)	24·1 (0·07)	6·6 (2·78)
CZE-CZE	508 (−0·4/−0·9)	39 (−0·75)	137 (−0·12)	6·2 (−0·022)	27·6 (0·05)	7·4 (−1·70)
DEN-GLO	469 (−4·2/−3·1)	43 (−0·29)	126 (−0·08)	6·0 (0·001)	26·0 (0·05)	7·1 (−0·16)
FIN-KUO	603 (−6·0/−7·4)	30 (−0·70)	140 (−0·58)	6·0 (−0·048)	27·3 (0·09)	7·4 (−3·60)
FIN-NKA	697 (−6·5/−7·2)	27 (−0·47)	142 (−0·06)	6·0 (−0·034)	27·5 (0·06)	7·4 (−1·63)
FIN-TUL	483 (−4·2/−4·6)	29 (−0·62)	139 (−0·52)	5·9 (−0·045)	27·1 (0·09)	7·3 (−3·14)
FRA-LIL	290 (−1·1/1·2)	33 (−0·82)	135 (−0·60)	5·8 (−0·082)	26·4 (0·07)	7·1 (−5·18)
FRA-STR	270 (−3·9/−2·3)	23 (−1·06)	135 (−0·72)	6·0 (0·036)	27·3 (0·03)	7·2 (−0·97)
FRA-TOU	226 (−2·1/−3·5)	24 (−1·57)	125 (−0·69)	5·8 (−0·009)	26·1 (0·06)	6·8 (−2·95)
GER-AUR	230 (−4·4/−4·9)	24 (−0·82)	136 (0·04)	6·1 (−0·010)	27·8 (0·05)	7·3 (−0·75)
GER-AUU	309 (−1·9/−1·6)	35 (−0·31)	137 (0·24)	6·2 (−0·013)	27·1 (0·03)	7·4 (−0·04)
GER-BRE	365 (−2·6/−3·5)	45 (−0·51)	132 (−0·82)	6·2 (0·017)	26·8 (0·08)	7·3 (−1·04)
GER-EGE	376 (−0·4/−0·8)	26 (−1·45)	141 (−0·04)	5·8 (−0·009)	26·9 (0·10)	7·2 (−1·31)
ICE-ICE	370 (−5·4/−4·1)	23 (−0·17)	125 (0·08)	6·2 (0·015)	26·8 (0·09)	7·0 (1·16)
ITA-BRI	265 (−2·3/−2·2)	34 (−0·89)	131 (−0·71)	5·9 (0·037)	26·4 (0·10)	7·1 (−0·31)
ITA-FRI	248 (−0·9/0·9)	29 (−0·96)	140 (−0·19)	5·9 (−0·042)	26·9 (0·06)	7·2 (−2·82)
LTU-KAU	509 (1·2/1·8)	35 (−0·91)	137 (0·16)	6·0 (−0·016)	27·1 (−0·07)	7·3 (−1·46)
NEZ-AUC	393 (−5·1/−6·7)	17 (−0·99)	126 (−0·44)	5·7 (0·000)	26·7 (0·09)	6·8 (−1·40)
POL-TAR	466 (1·1/−1·0)	54 (−0·44)	134 (−0·08)	5·6 (0·021)	25·9 (0·04)	7·1 (0·46)
POL-WAR	605 (0·8/−2·3)	52 (−0·93)	132 (−1·35)	5·7 (0·020)	27·1 (0·03)	7·2 (−2·63)
RUS-MOC	466 (−1·0/0·6)	47 (−0·19)	130 (−0·39)	5·3 (−0·021)	25·2 (−0·07)	6·8 (−2·15)
RUS-MOI	371 (−3·0/−1·8)	42 (−0·23)	133 (−1·37)	5·4 (−0·053)	25·6 (−0·15)	6·9 (−6·35)
RUS-NOC	498 (−0·5/0·8)	60 (−0·56)	132 (−0·17)	5·0 (−0·064)	25·9 (−0·02)	6·9 (−3·73)
RUS-NOI	492 (2·8/2·2)	58 (0·28)	135 (0·52)	5·4 (−0·001)	26·1 (0·02)	7·1 (1·49)
SPA-CAT	218 (1·8/−1·3)	41 (−1·10)	121 (−0·50)	5·6 (−0·023)	26·7 (0·09)	6·8 (−2·57)
SWE-GOT	312 (−4·2/−4·9)	25 (−0·47)	134 (0·17)	5·6 (−0·063)	26·2 (0·10)	6·9 (−2·20)
SWE-NSW	439 (−5·1/−5·4)	21 (−0·41)	130 (−0·21)	6·3 (−0·005)	26·4 (0·06)	7·1 (−0·73)
SWI-TIC	270 (−2·6/0·7)	36 (−0·22)	132 (−0·53)	6·5 (0·140)	26·5 (−0·10)	7·4 (4·49)
SWI-VAF	215 (−3·6/−2·9)	27 (−0·79)	132 (0·06)	6·3 (−0·002)	26·5 (0·00)	7·2 (−0·54)
UNK-BEL	593 (−4·6/−6·1)	29 (−0·82)	135 (0·12)	5·9 (−0·012)	26·3 (0·06)	7·1 (−0·53)
UNK-GLA	744 (−1·4/−0·6)	41 (−1·17)	133 (−0·70)	6·1 (−0·011)	26·8 (0·12)	7·3 (−2·34)
USA-STA	349 (−4·2/−5·9)	23 (−0·94)	129 (−0·11)	5·4 (−0·008)	26·9 (0·08)	6·8 (−0·92)
YUG-NOS	440 (0·4/2·3)	49 (−0·07)	136 (0·48)	6·4 (0·089)	27·3 (0·07)	7·5 (5·10)
Mean	401 (−2·3/−2·2)	36 (−0·59)	133 (−0·21)	5·8 (−0·008)	26·6 (0·05)	7·1 (−1·08)
SD	142 (2·5/2·8)	12 (0·56)	5 (0·47)	0·4 (0·041)	0·7 (0·06)	0·2 (2·24)

Table 2: **Age-standardised levels and trends of coronary-event rates and risk factors in men aged 35–64 years**

shown in table 1. Response rates varied from less than 50% to 90%. (URL: www.ktl.fi/publications/monica/nonres/nonres.htm URN: NBN:fi-fe19991076).

Risk factors were measured with standard procedures. Status of current cigarette smoking was classified as daily (code 1) or not (code 0) to conform with the risk score that was used. Systolic blood pressure was the mean of two consecutive measurements. Relative bodyweight was expressed as body-mass index. Full details of the survey methods are given in the MONICA manual, quality-control reports, and other MONICA publications.[10] (URL: www.ktl.fi/publications/monica/manual/part3/iii-1.htm URN: NBN:fi-fe19981151). Smoking[11] (URL: www.ktl.fi/publications/monica/smoking/qa30.htm URN: NBN: fi-fe19991077), blood pressure[12,13] (URL: www.ktl.fi/publications/monica/bp/bpqa.htm URN: NBN: fi-fe19991082), blood cholesterol[14] (URL: www.ktl.fi/publications/monica/tchol/tcholqa.htm URN: NBN:fi-fe19991083), weight and height[15] (URL: www.ktl.fi/publications/monica/bmi/bmiqa20.htm URN: NBN:fi-fe19991079).

To assess an individual's relative hazard of a coronary event, we summarised the degree of risk in a risk score, defined as a linear combination of the risk-factor levels. The coefficients were obtained from the Nordic Risk Assessment study (NORA),[16] which used a Cox's proportional-hazards model with CHD death as the outcome variable. During follow-up of the NORA study, there were 1422 CHD deaths among men and 228 among women. For risk factors for which the within-person variation is large compared with the between-person variation, the regression coefficients underestimate the true effects.[17] To compensate for this regression dilution, the NORA coefficients for systolic blood pressure and total cholesterol were multiplied by 1·5.[17–19] Coefficients for cigarette smoking and body-mass index were uncorrected. Consequently, the NORA coefficients used were, for men, 0·807 for cigarette smoking (0/1), 0·021 for systolic blood pressure (mm Hg), 0·435 for total cholesterol (mmol/L), and 0·049 for body-mass index (kg/m²). For women the coefficients were 0·851 for smoking, 0·030 for systolic blood pressure, 0·375 for cholesterol, and 0·007 for body-mass index.

We prepared retrospective quality-assessment reports on all major data items to document and score the quality of the data obtained for each population (URL: www.ktl.fi/publications/monica/index.html). An overall quality score (perfect score 2·0) was calculated to summarise the quality of demographic data, response rates, and trends in coronary events, cigarette smoking, systolic blood pressure, total cholesterol, and body-mass index (table 1, URL: www.ktl.fi/publications/monica/earwig/appendix.htm URN: NBN:fi-fe19991356).

Statistical analysis

We analysed data for men and women separately. Unless otherwise specified, the full age range of 35–64 years was used. Annual rates of coronary events were standardised to the world standard population, with weights 6, 6, 6, 5, 4, and 4, respectively, for the six 5-year age-groups—35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, and 60–64 years.[20] To describe the risk factors for each population, for which the samples were stratified by the three 10-year age-groups in most populations, we standardised the sample means with weights 12, 11, and 8, respectively.

Trends in event rates were calculated from the age-standardised annual rates (r_t) by the model:

$$\log r_t = a + bt + e_t,$$

where log denotes the natural logarithm, t the year, and e_t the error term, with allowance for extra-Poisson variation. (URL: www.ktl.fi/publications/monica/is97/isi97.htm).[21,22] The parameter b, which is the rate of change of the event rate, will be called the trend in the event rate.[4]

Population	Coronary-event rate over last 5 years (average annual % change during full/lagged period)	Mean for final survey (average annual change)				
		Daily smoking (%)	Systolic blood pressure (mm Hg)	Total cholesterol (mmol/L)	Body-mass index (kg/m^2)	Risk score
AUS-NEW	137 (−5·6/−5·8)	17 (−0·71)	127 (−0·33)	5·6 (−0·024)	27·3 (0·14)	6·1 (−2·49)
AUS-PER	88 (−2·2/−4·3)	13 (−0·76)	125 (−0·32)	5·4 (−0·042)	26·1 (0·14)	5·9 (−3·21)
BEL-CHA	122 (1·1/−4·7)	29 (0·09)	125 (0·05)	6·1 (0·042)	26·8 (−0·14)	6·2 (1·08)
BEL-GHE	73 (−3·0/−0·4)	27 (0·21)	122 (−0·07)	6·0 (−0·005)	26·1 (−0·12)	6·1 (0·34)
CAN-HAL	137 (0·5/4·0)	25 (−0·74)	126 (1·04)	5·8 (−0·030)	27·6 (0·21)	6·1 (1·23)
CHN-BEI	33 (−0·5/−2·9)	9 (−1·00)	130 (0·15)	4·5 (0·025)	24·5 (0·05)	5·7 (0·30)
CZE-CZE	102 (2·1/4·9)	23 (0·32)	134 (−0·13)	6·1 (−0·004)	27·8 (−0·07)	6·5 (−0·23)
DEN-GLO	134 (−2·5/−0·9)	45 (0·72)	121 (−0·47)	5·8 (−0·019)	24·7 (0·01)	6·2 (−1·49)
FIN-KUO	110 (−4·5/−5·4)	13 (0·02)	139 (−0·61)	5·8 (−0·059)	27·1 (0·04)	6·4 (−3·81)
FIN-NKA	125 (−5·1/−8·7)	11 (0·17)	137 (−0·49)	5·7 (−0·064)	27·1 (0·00)	6·4 (−3·57)
FIN-TUL	87 (−4·5/−1·6)	19 (0·23)	135 (−0·38)	5·7 (−0·045)	26·2 (0·02)	6·4 (−2·51)
FRA-LIL	63 (−1·6/−5·9)	17 (0·44)	129 (−0·73)	5·8 (−0·087)	26·4 (0·07)	6·2 (−4·65)
FRA-STR	54 (−6·6/−3·9)	15 (−0·14)	127 (−0·85)	5·9 (0·036)	26·2 (−0·07)	6·1 (−1·63)
FRA-TOU	35 (−1·7/−7·0)	22 (−0·02)	117 (−0·88)	5·6 (−0·024)	24·5 (0·03)	5·8 (−3·56)
GER-AUR	57 (3·1/−0·1)	16 (0·24)	129 (−0·40)	5·9 (−0·017)	26·8 (0·01)	6·2 (−1·53)
GER-AUU	72 (−0·5/−5·9)	25 (0·43)	131 (0·21)	5·9 (−0·034)	26·5 (0·02)	6·4 (0·17)
GER-BRE	92 (−0·4/−0·3)	30 (−0·40)	128 (−1·59)	6·2 (0·002)	26·3 (−0·02)	6·4 (−5·55)
GER-EGE	77 (1·7/2·4)	11 (−0·78)	137 (−0·27)	5·8 (−0·017)	26·4 (0·05)	6·4 (−2·31)
ICE-ICE	83 (−3·9/1·4)	31 (−0·38)	121 (0·29)	6·0 (−0·031)	26·3 (0·16)	6·2 (−0·45)
ITA-BRI	39 (−3·5/−5·1)	23 (−0·06)	127 (−0·91)	5·9 (0·062)	25·5 (0·00)	6·2 (−0·65)
ITA-FRI	45 (−0·8/8·4)	22 (−0·46)	134 (−0·36)	5·7 (−0·064)	25·8 (−0·06)	6·4 (−3·75)
LTU-KAU	85 (2·7/4·8)	4 (−0·16)	134 (−0·28)	6·2 (0·035)	28·0 (−0·16)	6·4 (0·19)
NEZ-AUC	105 (−3·5/−6·1)	14 (−0·89)	122 (−0·19)	5·6 (−0·025)	25·6 (0·08)	5·9 (−2·31)
POL-TAR	109 (−0·1/−1·1)	21 (0·50)	134 (−0·22)	5·5 (0·000)	28·5 (0·12)	6·3 (−0·16)
POL-WAR	158 (1·0/0·0)	34 (−0·69)	128 (−1·52)	5·6 (0·013)	27·5 (0·02)	6·3 (−4·96)
RUS-MOC	78 (−6·7/−8·5)	14 (−0·11)	133 (−0·89)	5·6 (0·000)	26·5 (−0·26)	6·2 (−2·99)
RUS-MOI	83 (−1·6/−1·7)	14 (−0·13)	133 (−1·40)	5·5 (−0·045)	26·3 (−0·24)	6·2 (−6·05)
RUS-NOC	127 (1·2/7·5)	6 (−0·11)	131 (−0·16)	5·3 (−0·072)	28·5 (−0·08)	6·0 (−2·84)
RUS-NOI	130 (1·4/0·5)	8 (0·08)	137 (−0·07)	5·4 (−0·060)	29·3 (−0·01)	6·2 (−2·55)
SPA-CAT	36 (2·0/−0·1)	15 (0·50)	118 (−0·48)	5·5 (−0·024)	27·4 (0·08)	5·8 (−1·78)
SWE-GOT	73 (−3·7/0·4)	29 (−0·50)	130 (0·20)	5·4 (−0·085)	24·9 (0·06)	6·2 (−2·80)
SWE-NSW	112 (−2·4/−5·4)	28 (0·50)	126 (−0·25)	6·1 (−0·009)	25·7 (−0·01)	6·3 (−0·65)
SWI-TIC	..	26 (0·51)	124 (−0·93)	6·2 (0·123)	25·3 (0·03)	6·3 (1·81)
SWI-VAF	..	25 (0·58)	124 (−0·20)	6·1 (0·001)	24·7 (0·04)	6·2 (−0·11)
UNK-BEL	174 (−2·4/−4·0)	25 (−1·28)	129 (−0·41)	5·9 (−0·024)	25·6 (0·01)	6·3 (−3·43)
UNK-GLA	269 (0·2/−3·3)	41 (−0·68)	126 (−0·93)	6·1 (−0·047)	26·9 (0·11)	6·4 (−4·99)
USA-STA	116 (−2·4/−1·8)	19 (−1·20)	119 (−0·34)	5·3 (−0·009)	26·6 (0·14)	5·8 (−2·69)
YUG-NOS	116 (2·8/4·3)	30 (0·25)	137 (0·47)	6·2 (0·059)	27·8 (−0·04)	6·7 (3·54)
Mean	98 (−1·4/−1·5)	21 (−0·14)	129 (−0·38)	5·8 (−0·015)	26·5 (0·01)	6·2 (−1·87)
SD	46 (2·7/4·3)	9 (0·54)	6 (0·53)	0·3 (0·043)	1·2 (0·10)	0·2 (2·17)

Table 3: **Age-standardised levels and trends of coronary-event rates and risk factors in women aged 35–64 years**

Trends in risk factors for each 10-year age-group in each population were calculated by simple regression of the individual observations on the date of examination. If data were available for the optional middle survey, they were incorporated, except for two populations (Novosibirsk Control and Intervention), for which the data quality was lower than in the initial and final surveys. Trends in the risk score were calculated as for the risk factors after we had derived individual values. If we assumed that the proportional-hazards model, from which the risk-score coefficients were derived, accurately reflected an individual's relative risk soon after measurement of the risk factors, the trend in risk scores from individuals sampled over time would be related to expected change in CHD mortality due to changes in the risk factors. The contribution of an individual risk factor to the risk-score trend can be derived by multiplying the risk-factor trend by the NORA coefficient.

We standardised the trends in risk factors taking the weighted mean of the trends for age-groups 35–44 years, 45–54 years, and 55–64 years and using weights 1, 3, and 7, respectively. Such weighting makes the risk-factor trends comparable with the event trends and reflects the greater contribution to coronary events of the older age-groups (URL: www.ktl.fi/publications/monica/earwig/appendix.htm. URN: NBN:fi-fe19991356). The weights used for the analyses of trends in risk factors are, therefore, different from the weights used simply to describe the population means of the risk factors in tables 2 and 3.

To estimate the degree of linear association across populations, we constructed a correlation matrix for trends in risk factors, risk score, and coronary-event rates.

The association between the trends in coronary-event rates and the risk scores was estimated by a simple linear-regression model, with the population as the unit of analysis, the trend in event rate as the dependent variable, and the trend in risk scores as the explanatory variable. For proper weighting of the populations, the error term of the regression model was defined as the sum of two components: one attributable to the known SE of the estimates of trends, and the other representing variation not explained by the model. For some analyses, the data were further weighted with quality scores (URL: www.ktl.fi/publications/monica/isi97/isi97.htm).[21,23] For the percentage of variation explained by the trends in risk factors, we report the variation of the fitted values divided by this variation, plus the variation of the weighted residuals, but omitting variation attributable to the known SE of the trend estimates, then multiplied by 100.[22] (URL: www.ktl.fi/publications/monica/earwig/appendix.htm. URN: NBN:fi-fe19991356). The analysis was repeated for the trends in the individual risk factors instead of the risk score, singly, and together by multiple linear regression.

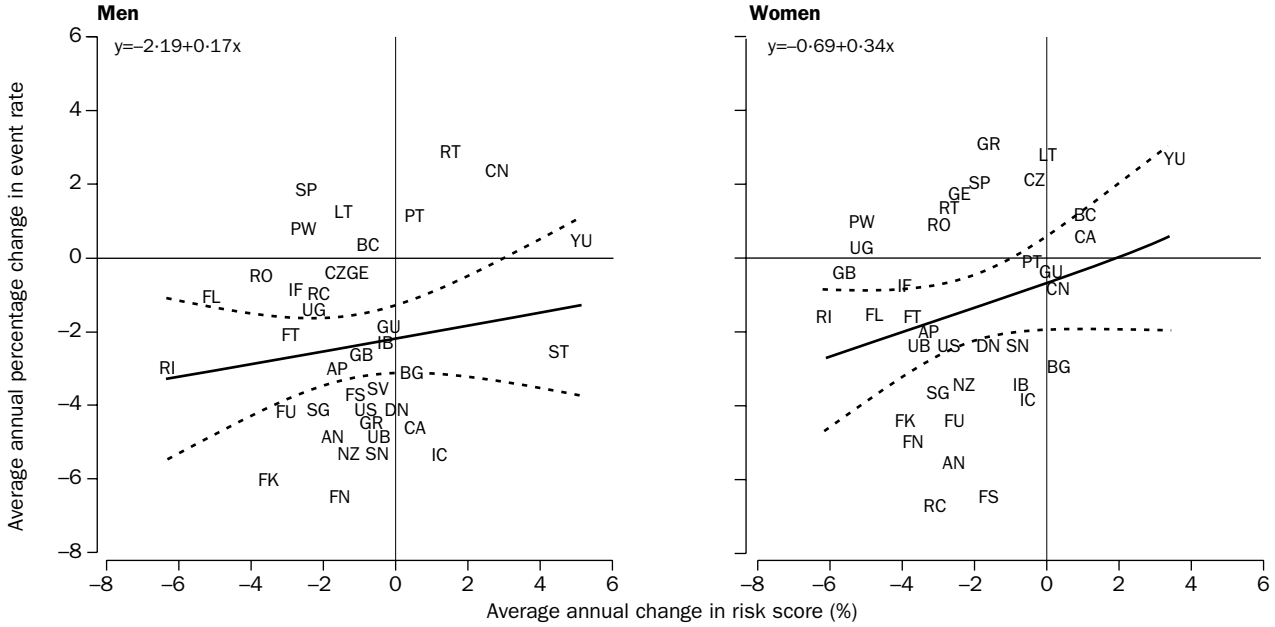
The association between trends in event rates and trends in risk factors was first assessed for the full period of coronary-event registration (table 1). To allow for a time lag between the risk-factor changes and event-rate changes, the analysis was repeated for a coronary-event period that started 4 years after the middle of the initial risk-factor survey. For the populations in which this period would have been less than 6 years of trends in events, the event period was started 3 years after the initial survey (table 1).

Different analyses were done to assess the robustness of the study findings, by varying the endpoints, coefficients of risk score, weighting for quality scores, age-groups, and risk-factor trend periods.

Results

Trends in coronary-event rates and risk factors

The average annual coronary-event rates in the last 5 years of event registration, the means of the risk factors,



AN=AUS-NEW; AP=AUS-PER; BC=BEL-CHA; BG=BEL-GHE; CA=CAN-HAL; CN=CHN-BEI; CZ=CZE-CZE; DN=DEN-GLO; FK=FIN-KUO; FN=FIN-NKA; FL=FRA-LIL; FS=FRA–STR; FT=FRA-TOU; FU=FIN-TUL; GB=GER-BRE; GE=GER-EGE; GR=GER-AUR; GU=GER-AUI; IC=ICE-ICE; IB-ITA-BRI; IF=ITA-FRI; LT=LTU-KAU; NZ=NEZ-AUC; PT=POL-TAR; PW=POL-WAR; RC=RUS-MOC; RI=RUS-MOI; RO=RUS-NOC; RT=RUS-NOI; SP=SPA-CAT; SG=SWE-GOT; SN=SWE-NSW; ST=SWI-TIC; SV=SWI-VAF; UB=UNK-BEL; UG=UNK-GLA; US=USA-STA; YU=YUG-NOS.
Dashed lines show 95% CI of regression line.

Figure 1: **Regression of change in coronary-event rate on change in risk score for full registration period**

the risk score in the final survey, and the trends in these are shown in tables 2 and 3. An average annual change in daily cigarette smoking of 0·5% means that over 10 years, the prevalence of smoking increased by 5 percentage points; likewise an average annual change of systolic blood pressure of –0·69 mm Hg means that, over 10 years, the mean systolic blood pressure of a given population fell by almost 7·0 mm Hg. The average annual change of risk score of –1·7% means that the coronary-event rate in the population was expected to decline by 17·0% because of the observed changes in the risk factors over 10 years. There was substantial heterogeneity in the trends in event rates, ranging from less than –6·0% to more than 3·0% per year in men and women (figure 1). The event rates declined in most populations.

For men and women, the overall range of the trends in risk scores was similar to the event rates (figures 1 and 2). For men, however, the trend in risk scores was mostly concentrated from –3·0% to 0%. The horizontal axes of figure 3 show the distribution of the trends in the individual risk factors. The populations were heterogeneous for trends in cigarette smoking, ranging in most of the male populations from –1·2% to 0% and in most of the female populations from –1·0% to 0·5% per year. The changes in systolic blood pressure in men and women mostly ranged from –1·0 mm Hg to 0·5 mm Hg

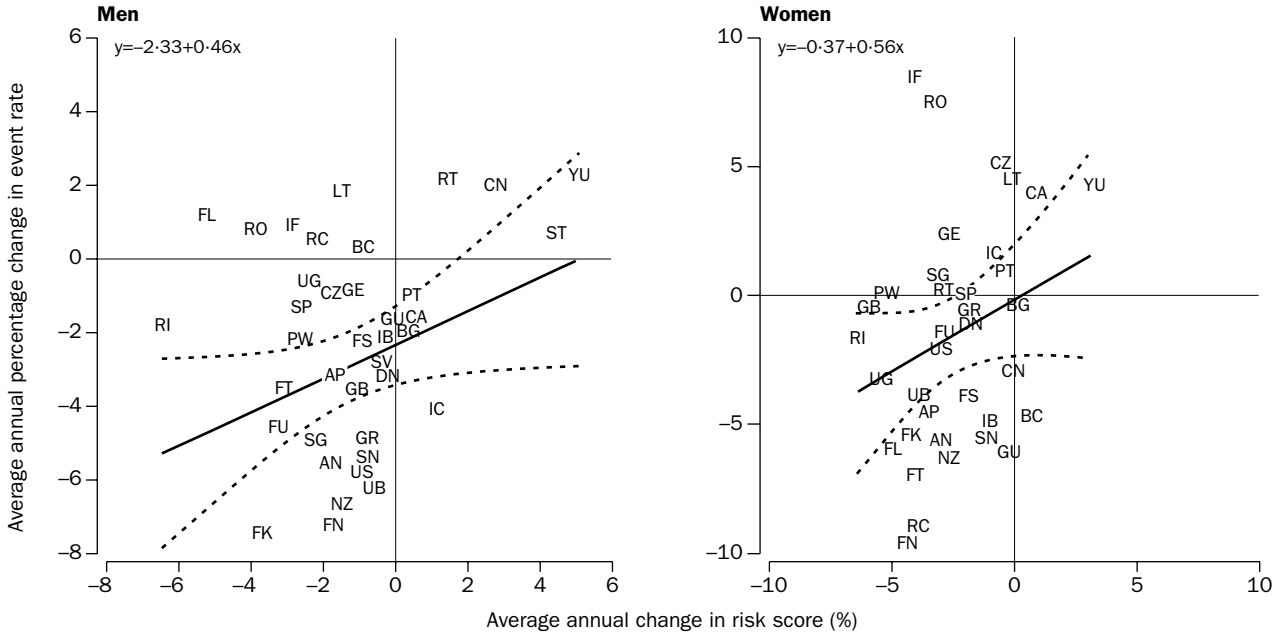


Figure 2: **Regression of change in coronary-event rate on change in risk score for lagged registration period**
Abbreviations as in figure 1. Dashed lines show 95% CI of regression line.

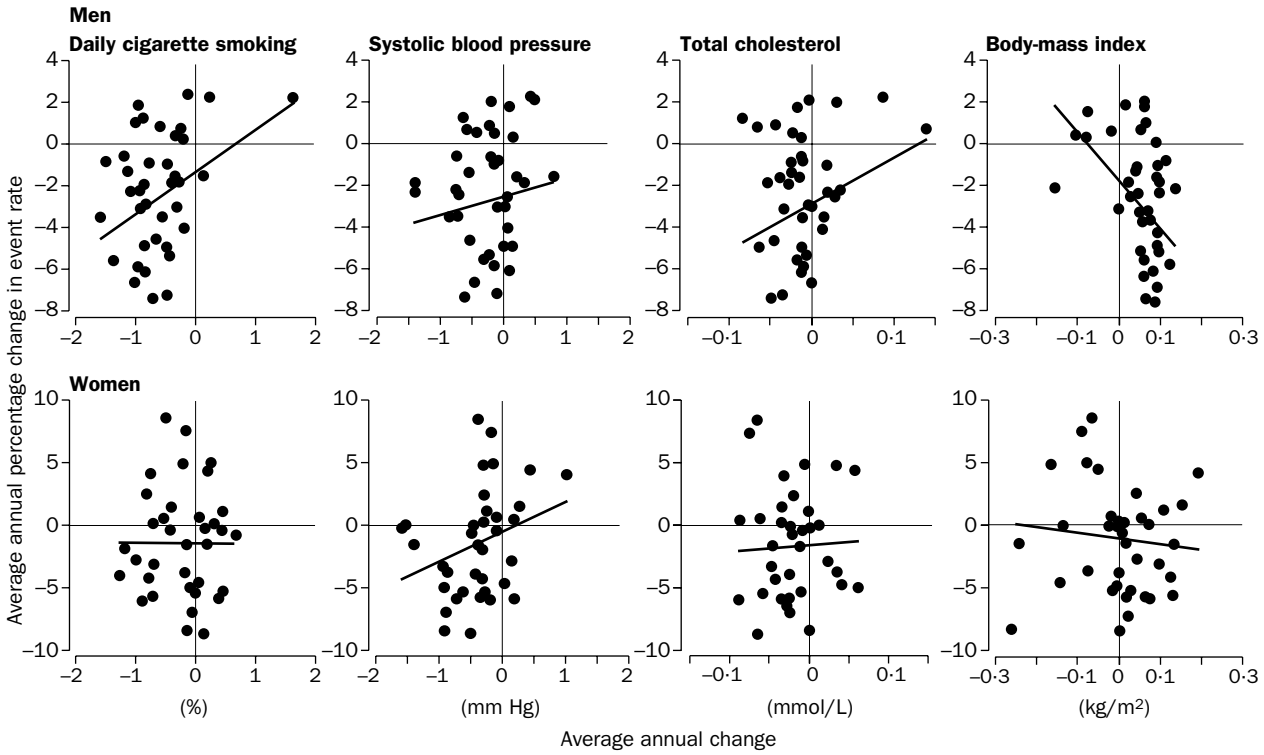


Figure 3: **Regressions of change in coronary-event rate on changes in individual risk factors for lagged registration period**

per year, declining in most but showing moderate heterogeneity between populations. The trends in total cholesterol ranged mostly from –0·06 mmol/L to 0·04 mmol/L per year in men, with a slightly wider range in women, and a decline in most populations. There was little heterogeneity, since in half the populations the trends ranged from –0·02 mmol/L to 0 mmol/L per year. Body-mass index increased in nearly all male populations, within a range per year of 0–0·10 kg/m^2; there was more variation in the trends in women, with changes in most populations ranging from –0·15 kg/m^2 to 0·15 kg/m^2 per year. Correlations between the trends in risk factors were generally small (table 4).

The contribution of cigarette smoking to the trend in risk score (ie, the trend in cigarette smoking multiplied by the coefficient of the risk score) was between –1 and 0 percentage points in men for most populations. The contribution was between –1·0 and 0·5 percentage points for systolic blood pressure, between –1·5 and 1·0 for total cholesterol, and between 0 and 0·5 for body-mass index. For women, the ranges were a little wider. Since the trend in risk scores for an individual population is roughly the sum of the contributions of the individual risk factors, we can conclude from these ranges that total cholesterol was the biggest contributor to heterogeneity in trends in the risk score; systolic blood pressure was next, cigarette smoking was about half that of cholesterol, and the contribution of body-mass index was very small. In women, the contribution of body-mass index was negligible because its NORA coefficient is very small.

Association between trends in coronary-event rates and in risk factors

Figure 1 shows the contemporaneous changes in coronary-event rates against the changes in risk score. In 68% of the male populations and 58% of the female populations, the event rates and the risk scores were declining. The remaining male populations were scattered evenly across the other three quadrants and the female populations were distributed mostly in the two upper quadrants. For these 10-year trend estimates, there was a weak association for men (regression coefficient 0·17 [95% CI –0·21 to 0·55], table 5). For women, the association was stronger (0·34 [–0·09 to 0·77], table 5).

The results shown in figure 1 did not take into account the possible time lag between changes in risk score and in event rates. After the 3-year or 4-year time lags were introduced, the association was stronger (0·43 [–0·01 to 0·87] for men, 0·57 [–0·10 to 1·24] for women, table 5). When differences in data quality were taken into account and the quality scores were used as weights in the analysis, the results remained similar (table 5). Despite the stronger association, when the time lag was taken into account, the scatter of trends remained substantial in coronary-event rates for any given change in the risk scores (figure 2). This finding was reflected in the wide CI and, therefore, low precision of the regression coefficients. The variation explained by the trends in risk score was 22% for men and 10% for women. About half of the residual variation came from the known SE of the trend estimates (data not shown).

In the multiple-regression analysis, done with the individual risk-factor changes instead of the risk score as the explanatory variables (table 5), the lagged coronary-event period and weighting by the quality scores were used. As for the analysis with the risk scores, the regression coefficients are imprecise. They are, however, in line with the NORA coefficients, except for smoking in women and body-mass index in both sexes, which have negative coefficients. The percentage of variation explained by the risk factors was 46% for men and 19% for women.

Trend	Trend						
	Smoking	Systolic blood pressure	Cholesterol	Body-mass index	Risk score	Event rate	Lagged event rate
Smoking	. .	0·34	0·21	−0·18	0·50	0·22	0·35
Systolic blood pressure	0·00	. .	−0·03	0·26	0·53	0·02	0·14
Cholesterol	0·01	−0·03	. .	−0·16	0·80	0·17	0·22
Body-mass index	−0·31	0·32	−0·25	. .	0·08	−0·23	−0·37
Risk score	0·26	0·76	0·56	0·03	. .	0·14	0·25
Event rate	0·12	0·20	0·16	−0·02	0·27	. .	0·84
Lagged event rate	−0·01	0·32	0·00	−0·04	0·25	0·61	. .

Men are in the upper right triangle and women in the lower left. SE and quality scores have not been taken into account.

Table 4: **Correlations between trends in risk factors, risk score, and coronary-event rates**

The negative coefficient for body-mass index for men was especially large compared with its CI. Since the negative coefficient is inconsistent with our knowledge of body-mass index as a risk factor in individuals, we investigated this result further. In a univariate analysis in men, a negative slope for body-mass index was determined by the five populations that had a decline in body-mass index (figure 3). Four of these populations were from the former Union of Soviet Socialist Republics (USSR). When all five populations from the former USSR were excluded from the simple regression analysis on risk score, the percentage of variation explained increased from 22% to 31% in men and remained at 10% in women (table 5). Exclusion of these populations from the multiple-regression analysis led to 38% of the variation being explained by the trends in risk factors, irrespective of whether body-mass index was included or not. For women, the percentage was 18% with body-mass index included and 15% without. The results show that the strong negative association between the trends in coronary events and body-mass index in men can be attributed to the populations of the former USSR, which did not fit the model well when body-mass index was not included.

Scatterplots of the trends in coronary-event rates over the lagged event registration periods against trends in individual risk factors are shown in figure 3. Most of the populations were in the lower left quadrant of the scatter plots, which showed that, in these populations, the event rate and the risk factors were declining, with the exception of body-mass index and smoking in women. The coefficients obtained from regression analyses between trends in event rates and trends in the individual risk factors were similar to those obtained from the multiple-regression analysis (table 5).

Sensitivity analyses

The scaling of quality scores is arbitrary. Regression analysis without weighting by quality scores gave similar results to the weighted analysis (table 5). Squaring of the quality scores given in table 1 increased the regression coefficients for men and decreased them for women, but only slightly. Exclusion of populations with quality scores lower than 1·0, without weighting the other populations for data quality, increased the coefficients a little for both sexes. Results were, therefore, insensitive to quality scoring.

When the original NORA score was used, without correction for regression dilution, the percentage of variation explained by the model remained relatively unchanged.

If the trends in the rates of MONICA fatal events was used as the dependent variable, the regression coefficient for men decreased by about a third, but for women it increased by nearly half (table 5). For non-fatal events, the regression coefficient was more similar to the

	Explanatory variable	Men		Women	
		Coefficient (95% CI)	Percentage of variation explained	Coefficient (95% CI)	Percentage of variation explained
Fatal and non-fatal coronary events					
Full registration period					
Simple regression*	Risk score	0·17 (−0·21 to 0·55)	3	0·34 (−0·09 to 0·77)	10
Lagged registration period					
Simple regression*	Risk score	0·43 (−0·01 to 0·87)	19	0·57 (−0·10 to 1·24)	12
Simple regression†	Risk score	0·46 (0·01 to 0·91)	22	0·56 (−0·12 to 1·24)	10
	Smoking (%)	0·019 (0·00 to 0·04)	20	−0·001 (−0·03 to 0·03)	0
	Systolic blood pressure (mm Hg)	0·008 (−0·01 to 0·03)	6	0·024 (0·00 to 0·05)	11
	Total cholesterol (mmol/L)	0·22 (−0·04 to 0·48)	19	0·04 (−0·39 to 0·47)	0
	Body-mass index (kg/m^2)	−0·23 (−0·39 to −0·07)	36	−0·05 (−0·21 to 0·11)	2
Multiple regression†	Smoking (%)	0·009 (−0·01 to 0·03)	46	−0·012 (−0·04 to 0·02)	19
	Systolic blood pressure (mm Hg)	0·007 (−0·02 to 0·03)		0·030 (0·00 to 0·06)	
	Total cholesterol (mmol/L)	0·19 (−0·05 to 0·42)		0·04 (−0·38 to 0·46)	
	Body-bass index (kg/m^2)	−0·19 (−0·35 to −0·02)		−0·10 (−0·29 to 0·08)	
Simple omitting former USSR†	Risk score	0·59 (0·14 to 1·04)	31	0·52 (−0·17 to 1·21)	10
Multiple omitting former USSR†	Smoking (%)	0·011 (−0·01 to 0·03)	38	−0·012 (−0·04 to 0·02)	18
	Systolic blood pressure (mm Hg)	0·001 (−0·02 to 0·03)		0·026 (0·00 to 0·05)	
	Total cholesterol (mmol/L)	0·26 (−0·02 to 0·54)		0·08 (−0·37 to 0·53)	
	Body mass index (kg/m^2)	−0·03 (−0·31 to 0·24)		−0·10 (−0·34 to 0·14)	
Fatal coronary events					
Lagged registration period					
Simple regression†	Risk score	0·29 (−0·28 to 0·86)	6	0·81 (−0·12 to 1·74)	13
Non-fatal coronary events					
Lagged registration period					
Simple regression†	Risk score	0·53 (−0·04 to 1·09)	17	0·50 (−0·40 to 1·40)	6

*Not weighted with quality score. †Weighted with quality score.

Table 5: **Regression of trends in coronary-event rates on trends in risk scores and individual risk factors in people aged 35–64 years**

	Explanatory variable	Men		Women	
		Coefficient (95% CI)	Percentage of variation explained	Coefficient (95% CI)	Percentage of variation explained
Fatal and non-fatal coronary events					
Full registration period					
Simple regression*	Risk score	0·20 (−0·12 to 0·53)	5	0·29 (−0·10 to 0·67)	11
Lagged registration period					
Simple regression*	Risk score	0·50 (0·13 to 0·87)	35	0·55 (−0·15 to 1·26)	12
Simple regression†	Risk score	0·51 (0·13 to 0·89)	35	0·55 (−0·18 to 1·28)	10
	Smoking (%)	0·016 (0·00 to 0·03)	21	0·004 (−0·02 to 0·03)	1
	Systolic blood pressure (mm Hg)	0·009 (−0·01 to 0·03)	9	0·031 (0·00 to 0·06)	18
	Total cholesterol (mmol/L)	0·30 (0·05 to 0·55)	35	−0·10 (−0·54 to 0·33)	1
	Body-mass index (kg/m^2)	−0·14 (−0·30 to 0·02)	22	0·04 (−0·15 to 0·23)	2
Multiple regression†	Smoking (%)	0·005 (−0·01 to 0·02)	50	0·000 (−0·03 to 0·03)	19
	Systolic blood pressure (mm Hg)	0·006 (−0·01 to 0·02)		0·031 (0·00 to 0·06)	
	Total cholesterol (mmol/L)	0·28 (0·03 to 0·54)		−0·06 (−0·49 to 0·38)	
	Body-bass index (kg/m^2)	−0·10 (−0·25 to 0·04)		0·01 (−0·20 to 0·22)	
Simple omitting former USSR†	Risk score	0·68 (0·28 to 1·08)	45	0·60 (−0·15 to 1·34)	12
Multiple omitting former USSR†	Smoking (%)	0·011 (−0·01 to 0·03)	57	0·002 (−0·03 to 0·03)	16
	Systolic blood pressure (mm Hg)	0·001 (−0·02 to 0·02)		0·027 (0·00 to 0·06)	
	Total cholesterol (mmol/L)	0·39 (0·12 to 0·67)		0·05 (−0·45 to 0·55)	
	Body mass index (kg/m^2)	0·08 (−0·15 to 0·31)		0·03 (−0·22 to 0·29)	
Fatal coronary events					
Lagged registration period					
Simple regression†	Risk score	0·45 (−0·03 to 0·92)	20	0·89 (0·08 to 1·69)	24
Non-fatal coronary events					
Lagged registration period					
Simple regression†	Risk score	0·31 (−0·31 to 0·93)	7	0·21 (−0·87 to 1·28)	1

*Not weighted with quality score. †Weighted with quality score.

Table 6: **Regression of coronary-event rates on trends in risk scores and individual risk factors in people aged 55–64 years**

coefficient for fatal and non-fatal events combined, but for the analyses of only fatal or only non-fatal events, the numbers and precision were low (table 5).

Use of data for the age-group 55–64 years increased the regression coefficient of the risk score and narrowed the CI for men, but for women the results were similar to those for the whole age range (table 6). Restriction of the analysis to the age-group 45–54 years decreased precision through the smaller number of events.

Restriction of the risk-factor changes to the period between the initial and middle survey decreased the strength of the association shown previously with the 10-year data, which suggests that the precision of the estimates of trends between these surveys done 5 years apart was too small for an adequate investigation of the effects of possible non-linearity in the trends.

Discussion

Rationale for the study

From the 1950s onwards, epidemiological studies, led by Framingham in the USA,[24] identified personal characteristics as risk factors for the development of premature CHD in previously healthy people. Of these modifiable factors, distinct from age and sex, cigarette smoking, blood pressure, and total blood cholesterol were most consistently and powerfully implicated.[25–27] In the Seven Countries study,[28] investigators showed these risk factors to be important within populations in different countries, but claimed that the key determinant of population differences in risk was the mean concentration of blood cholesterol, which was in turn related to dietary saturated fat. Later cross-sectional studies across geographically diverse populations have been less successful in explaining differences in CHD mortality,[29,30] which had led to the idea of a French, southern European, or Mediterranean paradox.[31,32] Other psychosocial, lifestyle, dietary, and metabolic factors have therefore been nominated, but few of these have approached the power, consistency or prevalence of the original three. When the countries that pioneered CHD epidemiology saw a rapid decline in CHD mortality from the 1960s onwards, the obvious question was how much of this decline was attributable to the major known risk factors.[2] Since this question was asked in the late 1970s, the answer has ceased to be academic. Control of known risk factors has been widely promoted in the expectation of diminishing the burden of CHD and of the rising medical costs of its treatment.

Strengths and limitations of the study design

Studies in single populations have assessed whether the decline in CHD is commensurate with that expected from the change in risk factors.[33–35] We combined data, collected from many populations, in the same analysis. We were able to investigate the extent to which CHD trends within each population are explained by trends in risk factors and to which the variation in the trends in CHD between the populations can be explained by the variation of the trends in risk factors. The variation that remained unexplained was attributed to the imprecision of measurements, complexities in the relation between the changes in risk factors and event rates, and to other possible factors driving changes in event rates. We are unable to separate the contribution of other possible factors from the unexplained variation. The value of regression modelling is dependent on the extent of heterogeneity in trends across the populations.

To have a wide range of contrasting trends, the populations need to be geographically, culturally, and economically diverse. This requirement was, however, constrained in MONICA by the need for participating populations to have routine death certification, an efficient system of population enumeration, and availability of hospitals with diagnostic services. Most less-developed countries, therefore, had to be excluded. The WHO MONICA Project consisted of a consortium of quasi-autonomous and independently funded investigators who produced data for local use, but also

collaborated in producing standard data to answer the Bethesda conference questions.[2] Accurate measurements of coronary events, population denominators, and population levels of smoking and mean blood pressure and mean concentrations of cholesterol were needed over many years. Substantial effort was expended on the standardisation of procedures and monitoring of data quality. The study was at the limits of what was feasible, and what might be funded locally or collaboratively. In an observational study such as MONICA, investigators cannot anticipate the magnitude of changes in risk factors that may occur over a decade, nor control the availability of diagnostic data or the social and political conditions that make the study feasible. Our analyses were clearly made difficult by restricted heterogeneity in some of the risk-factor trends, compared with the precision with which the trends could be measured.

Choice of age-groups, coronary-disease endpoints, and risk factors

The WHO MONICA Project has been questioned for studying people aged 35–64 years and for measuring so few risk factors. At its inception, the focus was on premature CHD. The greatest relative risks from risk factors and greatest relative changes in mortality rates were seen in people younger than 65 years. This age-group is also that in which coronary diagnoses in fatal and non-fatal cases were most likely to be supported by diagnostic evidence and in which suspected cases were most likely to be sent to hospital.[36] Ageing populations and the decline of premature CHD in many countries have since led to increasing interest in older age-groups, in which most of the deaths occur.

For trends in event rates we counted attack rates for first and recurrent coronary events. There are theoretical reasons why use of incidence rates for coronary events would be preferable, although even they may be complicated by previous CHD in the form of angina. In practice, however, attack rates are easier to measure because in many populations first and recurrent events could not be separated when deaths occurred out of hospital. For other populations, we found that trends in incidence rates and attack rates were similar.[4] An alternative outcome variable would be CHD mortality, which first aroused epidemiological interest. We included this outcome in the sensitivity analyses, but the estimates were imprecise compared with attack rates because of the smaller numbers of events.

Smoking, blood pressure, and blood cholesterol were included as major risk factors prevalent in a large proportion of the population. Body-mass index was added to the analysis because of its public-health interest and ease of measurement, although its contribution to risk of CHD was more debatable.[5] All of these had standard internationally accepted protocols for survey measurement. The Framingham study's current coronary risk score incorporates three factors not included in the MONICA core study, HDL cholesterol, diabetes, and electrocardiographic left-ventricular hypertrophy.[37] Measurement of HDL cholesterol was widespread, although optional, in MONICA but standardisation of participating laboratories for the first population surveys was judged inadequate for subsequent assessment of longitudinal trends (URL: www.ktl.fi/publications/monica/hdl/hdlqa.htm URN: NBN:fi-fe19991137). HDL cholesterol is a major predictor for individuals, but its role in determining risk differences between populations seems to be much less than that for total cholesterol or LDL cholesterol.[38] Diabetes and left-ventricular hypertrophy are powerful risk predictors in individuals, but did not seem to be sufficiently prevalent to contribute significantly to the trends in CHD in the countries whose experience provoked the study. There were also potential difficulties with definition of diabetes[39] and of sensitivity of electrocardiography for left-ventricular hypertrophy. For simplicity, risk-factor surveys were generally carried out throughout the day on non-fasting participants. A requirement to study blood glucose, a doubtful coronary risk factor in the early 1980s, in depth with oral glucose tolerance tests would have added difficulty and expense.[40] The same difficulties applied to fasting blood triglycerides and to measurement of apolipoproteins. These factors were not incorporated into the core study, although they were added to many MONICA surveys as a local option.

Social status was widely recognised as a risk factor when MONICA was launched but, as for other psychosocial factors, was difficult to standardise across different cultures. The same applied to physical activity and to the recording of diet, although all of these figured in optional MONICA studies, which also included antioxidant vitamins.[41] Haemostatic factors were measured in some MONICA populations but fibrinogen measurement has had an international standard defined only in the 1990s,[42] as has homocysteine. Interest in inflammatory proteins is also recent. Much interest has centred on the Barker hypothesis that future coronary risk is affected by foetal and early-life factors, some of which might be determined before conception.[43] Height is a factor determined in early life, which was measured in MONICA, but it contributed nothing when introduced into the regression analyses. A study of the comparative impact of 27 old and new putative coronary risk factors in a coronary prone population, included many of the above factors but showed the classic three to be the most powerful, along with HDL cholesterol and fibrinogen.[44]

To incorporate the existing knowledge of risk prediction through the classic risk factors, we adopted a risk score derived from the NORA study. This risk score was chosen over others because it was based on large cohorts for men and women, with many deaths; therefore, SE of its coefficients were small and, in women, estimated more precisely than in any previous study. In a comparison, risk scores from other studies either had similar coefficients or the SE of their coefficients were large.[16] Sensitivity analyses that used coefficients of the NORA score uncorrected for regression-dilution bias did not change the fit of our regression model, although the relative contribution of the risk factors in the risk score were changed substantially. The results are, therefore, probably not sensitive to the specific risk score chosen.

Results of regression analyses

If the wide CI are taken into account, the coefficients from the multiple-regression analyses were in line with the coefficients of the risk score, with the exception of body-mass index in men. Exclusion of the five populations from the former USSR removed the strong negative coefficient for body-mass index in the multiple-regression analysis and increased the percentage of variation explained by the trends in risk score. A plausible

explanation for the discrepant results from the former USSR is that the increase in coronary-event rates was driven by factors other than the classic risk factors, such as the vast increase in alcohol consumption or deaths from other causes being attributed to CHD in the steeply increasing total mortality.[45,46]

Even after exclusion of the former USSR populations, the risk factors explained more of the variation through the multiple-regression analysis than through the risk score. However, at least a part of the difference may be because of overfitting, when there are four explanatory variables for 33 observations.

Diverging trends between different age-groups may have a confounding effect in the results. Indeed, when the analysis was restricted to the upper age-group, in which most of the coronary events occur, and the populations of the former USSR were excluded, the percentage of variation between the populations explained by the trends in the risk factors increased for men—to 45% when the risk score was used and to 57% for multiple-regression analysis (12% and 16% in women). Although this increase in the percentage has a plausible explanation, it may also have some overfitting because it is the result of one of several sensitivity analyses.

If an individual's short-term relative risk were fully determined by his or her risk-factor values, combined according to the risk score used, the expected slope in the regression analysis of change in event rates on change in risk scores would be 1. The coefficients of about 0·5 from our analysis, however, suggest that a 2% change in the predicted risk in the population corresponds to only a 1% change in the trend in coronary-event rates. The precision of the estimates is low, as can be seen from the wide CI. Since our regression analysis was not corrected for the regression dilution caused by the SE of the trends in risk scores, the coefficients were probably underestimated.[47]

Time lag

Clinical trials and other studies have shown that stopping smoking, lowering blood pressure, and lowering serum cholesterol decrease the individual's risk of CHD within a few years, and for smoking and cholesterol, most of the benefit may occur within 5 years.[48,49] Much less is known about the long-term effects of increases in the risk factors, but the incubation period is suggested to be at least 10 years, even up to 25–35 years for cholesterol.[50,51] Our results agree with the existence of a time-lag. The study was, however, originally designed as a contemporaneous 10-year study, which placed constraints on what time lags could be introduced. For example, even the lagged event-registration periods, which started 3 years or 4 years after the initial risk-factor survey, ended in most populations before or at the time of the final risk-factor survey. The time lag between the risk-factor change and the change in the individual's risk is not a fixed period, but is distributed in time, and the distribution differs for the various risk factors. Lack of accurate knowledge about the time lags and our inability to take these fully into account may have diluted our estimates of the association between the risk-factor changes and event-rate changes. The best source of data for assessing time lags are long-term cohort studies that follow up participants from a young age and measure their risk-factor values regularly. Insight into the nature of the time lags could be obtained from population monitoring studies, such as MONICA, but a monitoring period of 20–30 years would be needed.

The possible time lag relates to the changes in an individual's risk factors. In addition, the trend in the population is affected by the loss of older age-groups over time and their replacement with later birth cohorts with potentially different characteristics, and by migration into and out of the area. The relative magnitude of these components may vary from population to population, although net migration in MONICA populations was limited.

We ignored non-linearity in the trends. For most of the populations the trends were almost linear and any estimates of non-linearity would be imprecise during such a short period. In the sensitivity analyses, we looked at risk-factor changes between the initial and middle surveys, which were about 5 years apart, but the imprecision of 5-year-trend estimates was too large for any useful inference. The issue of non-linearity is also closely related to the issue of time lags. Even the time lag that we studied decreased the importance of any short-term non-linearity in the study period.

Influence of other factors on CHD trends

Our results do not exclude the possibility of other factors influencing the population trends. Indeed, the intercept of the regression line for men in figure 2 at well below zero suggests that other factors are in operation. We have discussed risk factors not measured in MONICA. Increases in use of antihypertensive and lipid-lowering medication may also decrease event rates, but this effect is taken into account to the extent that they influence the population distributions of blood pressure and total cholesterol. Unmeasured population-level factors, even those not generally thought to be related to risk of cardiovascular disease, could modify the relation between the trends in classic risk factors and event rates.[7,52]

Major changes in the treatment of CHD took place in the populations during the study period. Our accompanying paper[6] shows that trends in CHD rates are strongly related to the introduction of new treatments. We have been cautious in accepting that the effect is entirely specific and suggest that there may be other factors that are exaggerating the effect. This analysis of classic risk factors has not identified what these might be. The two analyses need to be integrated in the future. There is a paradox if these analyses are interpreted as showing that the effects on CHD trends of treatments are large, and those of risk factors are small. The WHO MONICA Project was started to explain why the USA and Australia, followed by other countries, had seen a decline in CHD mortality starting in the 1960s. When the decline began in the USA, the revolution in coronary care had not started and the current powerful drugs were not available. Countries with rising or stable rates were using and adopting treatments at the same time as the USA. If new drugs and treatments are the main contributor to the decline in coronary-event rates between the mid-1980s and mid-1990s, this finding cannot be extrapolated back to the 1960s and 1970s or, necessarily, into the future, since the population impact of affordable innovations may not be sustained. Similarly, the smaller apparent overall contribution of change in risk factors than that of treatments in the WHO MONICA Project does not preclude larger contributions in individual populations, or in the future.

Monitoring cardiovascular disease and risk factors

The WHO MONICA Project has shown the usefulness and difficulties of monitoring population trends in cardiovascular disease morbidity and risk factors. Standard measurements additional to those of mortality are important for planning and monitoring the effectiveness of public-health policies. Greater attention to monitoring would be warranted in many countries. Trends in the prevalence of obesity and the global spread of tobacco use are reasons to expect that the past will not predict the future.

Conclusion

The apparent contribution of the classic risk factors to the trends in CHD over 10 years across the WHO MONICA Project populations has been less precisely estimated than had been hoped. Estimates for women were less reliable than those for men because of greater imprecision in the estimation of trends in event rates. Estimates are low, with perhaps 15% in women and 40% in men of the variability of trends in coronary-event rates being "explained" by trends in the major risk factors. How much of the remaining variance is attributable to other factors, and how much to complexities of measurement, the time delay between risk-factor change, and changes in incidence cannot be estimated. The negative intercepts of the regression models suggest that a decline in CHD is occurring independent of the classic risk factors, which is supported by our accompanying paper on the effects of coronary care.[6]

The separation of risk factors and coronary care into the two MONICA hypotheses, which dates back to the early 1980s, is now outmoded.[3] Before the longer-term effects of treatments were known, the simple assumption was that coronary care affected survival or case fatality in the event, and that risk factors (whether or not they were affected by medication) determined event rates. Our previous paper showed that change in CHD mortality was two-thirds determined by change in event rates and one-third by case fatality. The current analyses raise the question of the specificity of the different factors on the different endpoints.

Measurement of coronary care has been easier, and the size of changes greater than those for the standard risk factors in the MONICA populations. Our results do not therefore set limits to the amount of potential benefit from future risk-factor changes. The findings in men generally endorse current public-health policies on the classic risk factors. However, the larger changes in the incidence of CHD in many populations than expected from the risk-factor changes suggest that there is a broader range of interventions potentially available that may or may not be already identified.

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Acknowledgments

We thank a *Lancet* reviewer whose critical comments led to substantial improvement of the previous draft of the paper, the MONICA internal reviewers, Philippe Amouyel and Lloyd Chambless, Esa Ruokokoski, and Vladislav Moltchanov, for contribution to the statistical programming, and the people who prepared the quality-assessment reports that we referred to in the text and published in the internet. The MONICA Centres are funded mainly by regional and national governments, research councils, and research charities. Coordination is the responsibility of WHO, assisted by local fund raising for congresses and workshops. WHO also supports the MONICA Data Centre in Helsinki. We thank the National Public Health Institute of Finland for their continuing support of the MONICA Data Centre, and National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA, for a contribution to WHO to support of the MONICA Data Centre and Quality Control Centre for Event Registration in Dundee, UK. The completion of the MONICA Project is supported through a Concerted Action Grant from the European Community, and we thank also ASTRA Hässle AB, Sweden, Hoechst AG, Germany, Hoffmann-La Roche AG, Switzerland, the Institut de Recherches Internationales Servier (IRIS), France, and Merck and Co Inc, NJ, USA, for grants to support data analysis and preparation of publications.

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