Do Trends in Population Levels of Blood Pressure and Other Cardiovascular Risk Factors Explain Trends in Stroke Event Rates?

Comparisons of 15 Populations in 9 Countries Within the WHO MONICA Stroke Project

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Background and Purpose—Previous studies have indicated a reasonably strong relationship between secular trends in classic cardiovascular risk factors and stroke incidence within single populations. To what extent variations in stroke trends between populations can be attributed to differences in classic cardiovascular risk factor trends is unknown.

Methods—In the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (WHO MONICA) Project, repeated population surveys of cardiovascular risk factors and continuous monitoring of stroke events have been conducted in 35- to 64-year-old people over a 7- to 13-year period in 15 populations in 9 countries. Stroke trends were compared with trends in individual risk factors and their combinations. A 3- to 4-year time lag between changes in risk factors and change in stroke rates was considered.

Results—Population-level trends in systolic blood pressure showed a strong association with stroke event trends in women, but there was no association in men. In women, 38% of the variation in stroke event trends was explained by changes in systolic blood pressure when the 3- to 4-year time lag was taken into account. Combining trends in systolic blood pressure, daily cigarette smoking, serum cholesterol, and body mass index into a risk score explained only a small fraction of the variation in stroke event trends.

Conclusions—In this study, it appears that variations in stroke trends between populations can be explained only in part by changes in classic cardiovascular risk factors. The associations between risk factor trends and stroke trends are stronger for women than for men. **(*Stroke*. 2002;33:2367-2375.)**

Key Words: blood pressure ■ epidemiology ■ incidence ■ mortality ■ risk factors ■ stroke

Routinely collected statistics on stroke mortality have shown declining rates since at least the 1960s in most countries in Western Europe, North America, Australasia, and Japan, whereas the rates have been stable or even increasing in East and Central Europe.[1,2] The reasons behind these changes have remained ill defined.

In the search for explanations for the diverging trends in mortality, the first crucial question is this: Are the changes reported in official statistics real; ie, are routine mortality statistics valid? If so, are the time trends due to changes in stroke event rates (reflecting changes in incidence) or due to changes in case fatality? If event rates are changing, to what extent can this be attributed to changes in the levels of classic cardiovascular risk factors—blood pressure, smoking status, serum cholesterol, and relative body weight—in the population?

Long-term changes in mortality from coronary heart disease have been similar to those for stroke, and the search for the driving forces behind the secular trends has also been similar. Because reliable basic information on long-term trends in risk factors and cardiovascular event rates was scanty,[3] the World Health Organization (WHO) initiated the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project.[4] This multinational collaboration was started in the early 1980s. Ten-year trend data were collected from 38 populations in 21 countries on 4 continents. In addition to acute coronary heart disease events, about half of the MONICA centers also recorded data on stroke. Protocols, procedures, and quality assurance methods were developed for collecting a standard set of data on both fatal and nonfatal stroke events and on major cardiovascular risk factors within defined populations in men and women 35 to 64 years of age.[5,6]

Received May 3, 2002; final revision received June 5, 2002; accepted June 6, 2002.

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Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000033131.27936.7F**

TABLE 1. Years for Risk Factor Surveys and Age-Standardized Trends in Risk Factor Levels for the 35- to 64-Year-Old Group, Age Standardized

	Years for Risk Factor Surveys			Average Annual Trend					
				Systolic Blood Pressure Trend (mm Hg, SE)		Total Cholesterol Trend (mmol/L, SE)		Daily Smoking Trend (%, SE)	
Population	Initial	Middle	Final	Men	Women	Men	Women	Men	Women
Beijing, China (CN)	84–85	88–89	93	−0.13 (0.22)	0.15 (0.20)	0.033 (0.008)	0.025 (0.007)	1.65 (0.43)	−1.00 (0.30)
Glostrup, Denmark (DN)	82–84	86–87	91–92	−0.08 (0.13)	−0.47 (0.13)	0.001 (0.008)	−0.019 (0.008)	−0.29 (0.35)	0.72 (0.35)
Kuopio Province, Finland (FK)	82	87	92	−0.58 (0.14)	−0.61 (0.13)	−0.048 (0.008)	−0.059 (0.007)	−0.70 (0.30)	0.02 (0.14)
North Karelia, Finland (FN)	82	87	92	−0.06 (0.13)	−0.49 (0.13)	−0.034 (0.007)	−0.064 (0.007)	−0.47 (0.27)	0.17 (0.14)
Turku/Loimaa, Finland (FU)	82	87	92	−0.52 (0.11)	−0.38 (0.13)	−0.045 (0.007)	−0.045 (0.007)	−0.62 (0.26)	0.23 (0.20)
Friuli, Italy (IF)	86	89	94	−0.19 (0.17)	−0.36 (0.17)	−0.042 (0.010)	−0.064 (0.009)	−0.96 (0.37)	−0.46 (0.31)
Kaunas, Lithuania (LT)	83–85	86–87	92–93	0.16 (0.16)	−0.28 (0.17)	−0.016 (0.008)	0.035 (0.009)	−0.91 (0.33)	−0.16 (0.12)
Warsaw, Poland (PW)	83–85	88–89	93	−1.35 (0.15)	−1.52 (0.16)	0.020 (0.006)	0.013 (0.006)	−0.93 (0.30)	−0.69 (0.27)
Moscow, Russia (control; RC)	84–86	88–89	92–95	−0.39 (0.19)	−0.89 (0.26)	−0.021 (0.010)	0.000 (0.011)	−0.19 (0.39)	−0.11 (0.23)
Moscow, Russia (intervention; RI)	84–85	88–89	92–95	−1.37 (0.20)	−1.4 (0.18)	−0.053 (0.009)	−0.045 (0.009)	−0.23 (0.42)	−0.13 (0.18)
Novosibirsk, Russia (control; RO)	85–86	Not used*	95	−0.17 (0.16)	−0.16 (0.18)	−0.064 (0.009)	−0.072 (0.010)	−0.56 (0.37)	−0.11 (0.11)
Novosibirsk, Russia (intervention; RT)	85	Not used*	94–95	0.52 (0.18)	−0.07 (0.17)	−0.001 (0.009)	−0.060 (0.010)	0.28 (0.38)	0.08 (0.10)
Gothenburg, Sweden (SG)	85–86	90–91	94–96	0.17 (0.16)	0.20 (0.14)	−0.063 (0.009)	−0.085 (0.008)	−0.47 (0.35)	−0.50 (0.31)
Northern Sweden (SN)	86	90	94	−0.21 (0.16)	−0.25 (0.18)	−0.005 (0.011)	−0.009 (0.011)	−0.41 (0.36)	0.50 (0.36)
Novi Sad, Yugoslavia (YU)	84	88–89	94–5	0.48 (0.15)	0.47 (0.15)	0.089 (0.009)	0.059 (0.010)	−0.07 (0.34)	0.25 (0.26)

*Not used for analysis.

Studies on 10-year trends in stroke events in the WHO MONICA populations confirmed in most populations the mortality trends observed in routine mortality statistics (C. Sarti, MD, PhD, et al, unpublished data, 2002). On average, two thirds of the decline in stroke mortality was due to changes in case fatality and one third to changes in stroke event rates.

This article addresses the question of what drives the secular trends in stroke event rates. The initial MONICA main null hypothesis for stroke was formulated in the early 1980s as follows: "For the population reporting units there is no relationship between 10-year trends in the major cardiovascular risk factors of serum cholesterol, blood pressure and cigarette consumption; and 10-year trends in incidence rate of stroke."[8] Body mass index (BMI) was not originally in the study protocol for this analysis, but it was included because of its perceived public health importance.[9] Because it was realized that differentiating between first and recurrent events was not possible in many situations, trends in all event rates (first and recurrent together) were accepted to be used as proxies for trends in incidence rates.

Accumulated evidence of causality of the classic cardiovascular risk factors in individuals has increased substantially since the main MONICA stroke hypothesis was formulated in the early 1980s. However, whether changes in the population load of classic risk factors are the main determinants of changing stroke rates has not yet been settled. In this article, the extent to which trends in classic risk factors contribute to changes in stroke event rates at the population level is estimated. Because the question is about populations rather than individuals, the units of the analysis also are populations. Thus, this is an ecological analysis of secular trends.[10,11]

Methods

Full details of the methods used in the WHO MONICA Project are given in the MONICA manual, which is provided in the World Wide Web (http://www.ktl.fi/publications/monica/). Extensive quality assessment reports and data books are also available at this Web site.

Study Populations

Study populations were residents of geographically defined areas in the 35- to 64-year-old age group. The MONICA populations have been described elsewhere.[12] Fifteen populations in 9 countries were included in the present analyses (Table 1). All but 2 populations were European.

Demographic data of each population were obtained from population registers, census results, or intercensal estimates.[13] The total study population was ≈2.1 million people. The total number of stroke events included in the analysis was 34 544.

Population Levels of Risk Factors

For each MONICA population, levels and prevalence of risk factors were measured at surveys based on independent probability samples of the populations. Three surveys were carried out: 1 at the beginning, 1 in the middle, and 1 at the end of the 10-year period. The samples were mostly stratified by sex and age, with equal numbers in each 10-year age-sex group. Survey periods are shown in Table 1. Participation rates varied from <50% to 90%.[14] Risk factors were measured by use of standardized MONICA procedures.[15,16]

A stroke risk score was used to summarize the effect of all 4 risk factors. The coefficients of the stroke risk score were derived from Finnish data on 14 902 subjects having 553 stroke events during 8 to 13 years of follow-up. The coefficients used were as follows: for men, 0.011 for systolic blood pressure (mm Hg), 0.607 for daily smoking (0/1), 0.055 for serum cholesterol (mmol/L), and 0.054 for BMI; and for women, 0.010 for systolic blood pressure (mm Hg), 0.409 for daily smoking (0/1), −0.004 for serum cholesterol (mmol/L), and 0.043 for BMI.[17]

For the analyses, the risk score was adjusted for regression dilution by multiplying the above coefficients for systolic blood pressure and cholesterol by 1.5.[18,19]

TABLE 1. Continued

BMI Trend (kg/m^2, SE)		Risk Score Trend (%, SE)	
Men	Women	Men	Women
0.07 (0.03)	0.05 (0.03)	1.38 (0.52)	0.03 (0.37)
0.05 (0.03)	0.01 (0.03)	−0.06 (0.35)	−0.38 (0.28)
0.09 (0.03)	0.04 (0.03)	−1.35 (0.35)	−0.71 (0.25)
0.06 (0.02)	0.00 (0.03)	−0.28 (0.32)	−0.69 (0.25)
0.09 (0.02)	0.02 (0.03)	−1.08 (0.29)	−0.40 (0.25)
0.06 (0.03)	−0.06 (0.04)	−0.98 (0.41)	−0.96 (0.34)
−0.07 (0.03)	−0.16 (0.04)	−0.84 (0.36)	−1.22 (0.34)
0.03 (0.02)	0.02 (0.03)	−2.36 (0.34)	−2.43 (0.30)
−0.07 (0.03)	−0.26 (0.05)	−1.22 (0.45)	−2.49 (0.53)
−0.15 (0.03)	−0.24 (0.04)	−3.66 (0.49)	−3.21 (0.36)
−0.02 (0.03)	−0.08 (0.04)	−1.26 (0.41)	−0.51 (0.39)
0.02 (0.03)	−0.01 (0.04)	1.15 (0.43)	−0.46 (0.34)
0.10 (0.03)	0.06 (0.03)	0.08 (0.38)	0.38 (0.28)
0.06 (0.03)	−0.01 (0.04)	−0.31 (0.41)	−0.23 (0.37)
0.07 (0.03)	−0.04 (0.04)	1.76 (0.36)	0.55 (0.30)

Case Ascertainment

The MONICA stroke study was community based. Details of case ascertainment have been given elsewhere.[6,20,21]

The major source of information on fatal events was death certificates. All deaths with a stroke diagnosis in the death certificate or that otherwise could have been caused by stroke were registered,[22] and the cause was validated according to the MONICA criteria (see below). Hospitalized cases were identified from hospital admission lists (hot pursuit) or discharge diagnoses (cold pursuit). All suspected stroke cases were retrieved and validated.

A variety of procedures, which were adjusted to conform with local conditions, were used to identify nonfatal cases that occurred and were treated outside the hospitals.

Validation and Classification of Stroke Events

All suspected stroke events were validated and registered in a standardized way.[22,23] Coding procedures have been described in detail elsewhere.[22–24]

WHO criteria for stroke, in which stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than a vascular origin," were used.[22] The definition included patients presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. Subdural hemorrhage, transient ischemic attacks, traumatic intracerebral hemorrhage, and lesions caused by a brain tumor were excluded. Vascular brain lesions detected solely via brain CT scan in the absence of acute focal symptoms and signs were not included because, in the MONICA Project, the stroke diagnosis was based only on clinical presentation to avoid bias caused by the increasing availability of imaging techniques over time.

On the basis of the background information, each event was classified into 1 of 3 categories: definite stroke, unclassifiable stroke, or not stroke.[22,23] The unclassifiable stroke category was used when no diagnosis other than stroke was present to explain the event but the available information was insufficient for determining whether symptoms and duration fully met the criteria for definite stroke. The unclassifiable category was used mainly in fatal events. Nonfatal events were placed in this category if there were insufficient data on the duration of symptoms but symptoms were typical and no other diagnosis could explain them. In fatal events, the proportion of unclassified events varied from 0% to 25%; in nonfatal events, from 0% to 1%. MONICA definition I was used,[25] which includes fatal and nonfatal definite and unclassifiable strokes.

Stroke events were subdivided into first, recurrent, or indeterminate (order not known) events and into fatal or nonfatal. A period of 28 days was used to define case fatality and to distinguish one event from another. Therefore, multiple strokes occurring within 28 days from the onset of the first event were considered to be the same event. In some populations, there was a substantial proportion of indeterminate stroke events; ie, it was unknown if the event was first or recurrent. Therefore, all stroke events, whether first, recurrent, or indeterminate, are reported together as event rates.[26]

Quality Assurance of Event Registration

To ensure uniformity in the coding of stroke events between the MONICA centers, series of test cases were distributed to all participating centers, and the results were evaluated by the MONICA Quality Control Center for Event Registration. All data submitted to the MONICA Data Center were checked for completeness, for logical consistency, and for possible duplicate registrations of the same event before they were entered into the stroke database.

Quality assessment reports were prepared several times during the study on all major data items[6] to assist quality assurance of the data. To estimate the validity of the data for the assessment of trends, a stroke quality score was calculated that reviewed the following areas: general quality of the data, completeness of the registration of fatal events, completeness of the registration of nonfatal events, reliability of the data for the assessment of trends, and reliability of the data for the classification of events.[21,26]

An overall quality score (with perfection set to a value of 2.0) was calculated to summarize the scores for stroke event trends, demographic data, response rates, and trends in cigarette smoking, systolic blood pressure, total cholesterol, and BMI. The corresponding quality score was also derived for each risk factor separately.[17]

Statistical Analysis

Data for men and women were analyzed separately. Unless otherwise specified, the full age range of 35 to 64 years was used.

To describe population trends in risk factors (Table 1), the sample means were standardized to the world population using the weights 12, 11, and 8 for the three 10-year groups in the 35- to 64-year age range.[27]

When used in analyses of their association with trends in stroke events, risk factors were age standardized by taking the weighted mean of the trends using the weights 1, 3, and 7 for the age groups 35 to 44, 45 to 54, and 55 to 64 years, respectively. Such weighting makes the risk factor trends comparable with the event trends, reflecting the greater contribution of the older age groups to stroke events.[28] Thus, weights used for the analyses of trends in risk factors are different from those used simply to describe the trends in the risk factors in Table 1.

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. The middle survey was not incorporated for the 2 populations in Novosibirsk, where the middle survey data quality was lower than in the initial and final surveys.

Annual rates of stroke events were standardized to the world standard population,[27] with the weights 6, 6, 6, 5, 4, and 4 for the 5-year age groups 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, and 60 to 64, respectively.

Trends in event rates were calculated from the age-standardized annual rates (r_t) with the following model[29]: $\log r_t = a + bt + e_t$, where log denotes the natural logarithm, t is the year, and e_t is the error term with allowance for extra-Poisson variation.[28,30] The parameter b, which is the rate of change of the event rate, is called the trend in the event rates.

Association Between Risk Factor Trends and Stroke Trends

The association between the trends in risk factors and trends in stroke event rates was estimated with the population as the unit of analysis, the trend in event rates as the dependent variable, and the trend in risk factor(s) as the explanatory variable. Several approaches were used. First, the association was analyzed with a simple linear regression model using systolic blood pressure as the explanatory variable. Second, trends in systolic blood pressure and daily smoking were analyzed together as explanatory variables of stroke trends in a multiple linear regression model. Third, the stroke risk score was used as an explanatory variable in a simple regression model.

For proper weighting of the populations, the error term of the regression model was defined as the sum of 2 components: 1 resulting from the known standard errors of the estimates of trends, and 1 representing variation not explained by the model.[31,32] To address data quality issues, analyses were weighted with the quality score.

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 the variation resulting from the known standard errors of the trend estimates and then multiplied by 100.[28,30]

Time Lag

To allow for a time lag between the risk factor changes and event rate changes, the analyses were repeated using a stroke event registration period that started 4 years after the middle of the initial risk factor survey. For the populations in which this would have resulted in a period of <6 years of trends in events, the event period was started 3 years after the initial survey (Table 2).

Sensitivity Analyses

Different analyses were performed to assess the robustness of the study findings with and without weighting data using quality scores, varying end points, different time lag periods, coefficients of risk score, and age groups.

Results

Risk Factor Trends

Average annual trends in risk factors are shown in Table 1. Systolic blood pressure declined in most populations in men and women, with somewhat larger declines in women. The 10-year trends were between −12 and 2 mm Hg in men and between −15 and 2 mm Hg in women. Thus, there was considerable heterogeneity between the populations.

In most populations, the daily cigarette smoking declined in both men and women. The 10-year trends in men ranged from −8% to 16% and in women from −6% to 6%.

Mean levels of serum cholesterol declined in most populations in both men and women. The 10-year trends in men were between −0.7 and 0.9 mmol/L and in women between −0.6 and 0.5 mmol/L.

BMI increased in 11 of the 15 populations in men but in only 6 female populations. The heterogeneity was less in men than in women; the 10-year trends ranged from −1.0 to 0.9 kg/m^2 in men and from −2.6 to 0.6 kg/m^2 in women. A 1-unit change in BMI would correspond to a weight loss or weight gain of about 3 kg in men and 2.5 kg in women.

The risk score changes over 10 years were small, ranging from −2.2% to 1.8% in men and from −2.7% to 0.3% in women.

Stroke Event Trends

Table 2 shows the average annual stroke event rates in the last 5 years of the event registration. The table also shows the trends in stroke event rates during the full registration periods and during the lagged period when the first 3 to 4 years were excluded.

TABLE 2. Stroke Event Registration Periods, Number of Stroke Events, Stroke Event Rates (Average Annual Rate During the Last 5 Years of Registration), and Average Annual Trends for the 35- to 64-Year-Old Group, Age Standardized

		Men				Women			
				Trend (SE)				Trend (SE)	
Population	Event Registration Periods, Full/Lagged	Stroke Events, n	Average Annual Event Rate per 100 000 (SE)	Full Period	Lagged Period	Stroke Events, n	Average Annual Event Rate per 100 000 (SE)	Full Period	Lagged Period
Beijing, China	1987–1993/1988–1993	2542	249 (6.0)	−0.1 (1.1)	−0.1 (1.5)	1802	177 (5.2)	0.5 (1.1)	0.1 (1.6)
Glostrup, Denmark	1982–1991/1986–1991	1168	164 (7.5)	−4.3 (0.6)	−2.9 (1.1)	613	89 (5.5)	−1.9 (1.6)	−3.2 (4.3)
Kuopio Province, Finland	1983–1992/1986–1992	1644	326 (12.0)	−2.5 (0.6)	−3.2 (0.9)	854	142 (7.8)	−4.6 (1.4)	−7.0 (1.6)
North Karelia, Finland	1982–1991/1986–1991	902	268 (13.3)	−1.6 (0.9)	−1.7 (2.2)	430	120 (9.0)	−0.7 (1.5)	−3.1 (2.3)
Turku/Loimaa, Finland	1983–1992/1986–1992	889	225 (11.5)	−1.2 (1.3)	−4.3 (1.8)	479	106 (7.5)	−1.3 (1.5)	0.8 (1.0)
Friuli, Italy	1984–1993/1989–1993	2398	121 (3.6)	−0.7 (0.7)	0 (1.9)	1295	61 (2.5)	−0.6 (0.8)	−1.1 (2.5)
Kaunas, Lithuania	1986–1995/1988–1985	1930	345 (10.4)	2.3 (1.0)	2.9 (1.5)	1261	164 (6.4)	1.6 (0.8)	1.6 (1.4)
Warsaw, Poland	1984–1994/1988–1994	1820	182 (6.4)	0.2 (1.3)	−2.2 (1.7)	1072	97 (4.4)	0.6 (1.1)	1.0 (2.4)
Moscow, Russia (control)	1985–1993/1988–1993	855	233 (11.5)	−3.0 (2.3)	−1.5 (5.7)	598	88 (6.1)	−8.2 (2.7)	−4.2 (6.3)
Moscow, Russia (intervention)	1985–1993/1988–1993	311	206 (16.7)	2.2 (1.6)	7.1 (1.8)	226	91 (9.8)	−3.3 (1.9)	−6.3 (4.3)
Novosibirsk, Russia (control)	1987–1993/1988–1993	721	322 (15.2)	−1.2 (4.1)	−1.5 (5.8)	751	259 (11.9)	0 (3.6)	−3.2 (4.2)
Novosibirsk, Russia (intervention)	1982–1993/1988–1993	1196	458 (20.0)	0.4 (1.1)	−1.9 (0.8)	1303	360 (15.7)	1.7 (1.1)	3.3 (3.3)
Gothenburg, Sweden	1984–1994/1989–1994	1210	147 (6.5)	1.5 (0.7)	2.7 (1.6)	621	68 (4.5)	−0.4 (1.4)	6.9 (1.2)
Northern Sweden	1985–1994/1989–1994	2131	209 (6.6)	0 (0.9)	3.7 (1.1)	1208	127 (5.2)	1.9 (1.1)	5.4 (1.7)
Novi Sad, Yugoslavia	1983–1995/1988–1995	1421	208 (8.8)	−1.0 (0.9)	−2.0 (2.1)	893	112 (6.2)	0.4 (1.2)	2.8 (2.8)

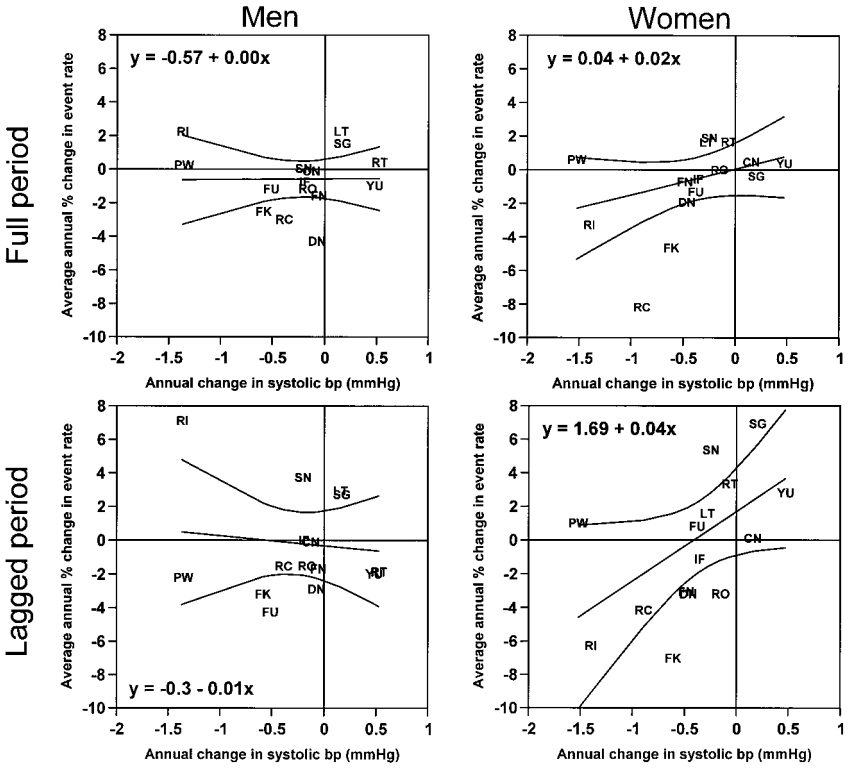

Figure 1. Trends in systolic blood pressure (bp) versus trend in stroke event rate. Abbreviation for countries as given in Table 1.

The trends in stroke event rates were declining in 9 male and 8 female populations. There was considerable heterogeneity in the annual event rate trends, ranging from −4.3% to 2.3% in men and from −8.2% to 1.9% in women. However, the standard errors of the estimates of the trends also were relatively high.

Association Between Trends in Systolic Blood Pressure and Daily Cigarette Smoking and Trends in Stroke Event Rates

During the 10-year period, stroke event rates and levels of systolic blood pressure changed in the same direction (whether upward or downward) in 10 populations in men (67%) and in 9 populations in women (60%) (Figure 1). In the regression analysis, the change in systolic blood pressure did not explain the change in stroke event rates in men (0%) but explained 21% of the change in women (Table 2).

When a 3- to 4-year time lag was taken into account, the change in systolic blood pressure had a small negative association with stroke event trends in men (2% of the variation explained) and strong positive association in women (38% of the variation explained) (Table 2).

Trends in daily cigarette smoking alone did not have an association with trends in stroke event rates. Trends in total cholesterol alone explained 10% of the change in stroke event rates in men and 16% in women. Trends in BMI alone explained 21% of change in stroke events in men and 9% in women, but the association was due mainly to former USSR populations with decreasing BMI trend.[17]

TABLE 3. Regression Between Trends in Different Risk Factor End Points and Trends in Stroke Event Rate (Weighted for Quality)

		Men		Women	
Period	Explanatory Variable	Coefficient (95% CI)	Variation Explained, %	Coefficient (95% CI)	Variation Explained, %
Full	Systolic blood pressure, mm Hg	0.0004 (−0.021–0.021)	0	0.015 (−0.009–0.039)	21
	Multiple regression				
	Systolic blood pressure, mm Hg	0.0003 (−0.023–0.024)	0	0.016 (−0.0099–0.041)	23
	Daily cigarette smoking, %	0.0003 (−0.019–0.019)		−0.0064 (−0.036–0.023)	
	Risk score	−0.014 (−0.99–0.72)	2	0.76 (−0.60–2.09)	19
Lagged	Systolic blood pressure, mm Hg	−0.0059 (−0.041–0.029)	2	0.041 (0.002–0.084)	38
	Multiple regression				
	Systolic blood pressure, mm Hg	−0.0041 (−0.042–0.033)	2	0.040 (0.005–0.085)	38
	Daily cigarette smoking, %	0.0023 (−0.028–0.033)		−0.0071 (−0.057–0.042)	
	Risk score	−0.60 (−1.95–0.74)	9	2.09 (−0.33–4.51)	36

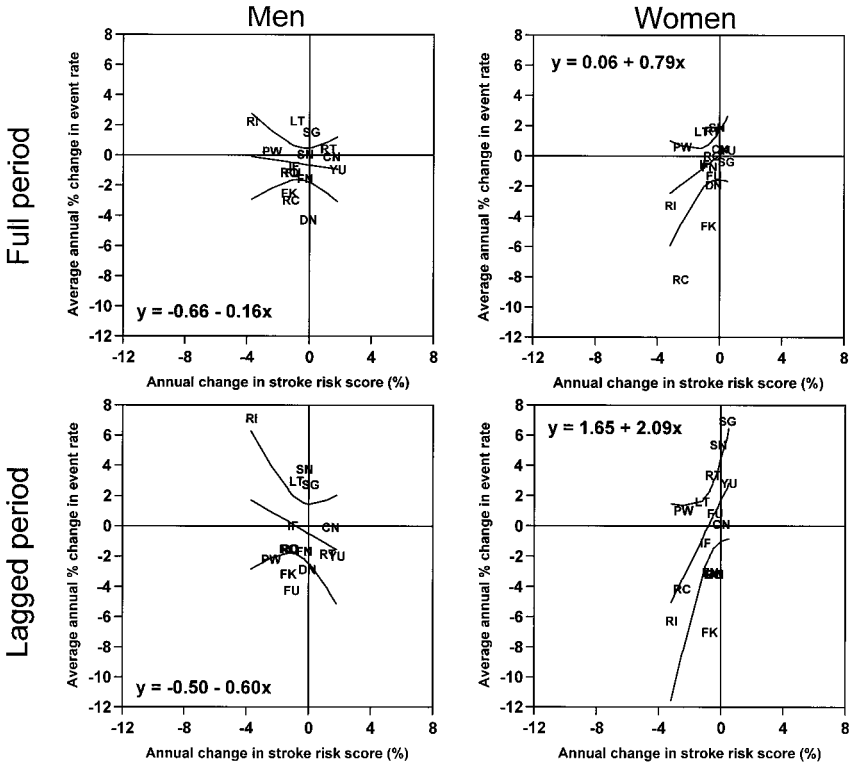

Figure 2. Trend in risk factor score versus trend in stroke event rate. Abbreviation for countries as given in Table 1.

Adding the trends in daily cigarette smoking as explanatory variables to the model with trends in systolic blood pressure did not change the results. For the full 10-year period, the variation explained by these 2 trends together was 0% in men and 23% in women. For the lagged event registration period, the association became stronger than in the full period in women (variation explained, 38%) and remained almost same in men (variation explained, 2%) (Table 3).

Association Between Trends in Stroke Risk Score and Trends in Stroke Event Rates

The effects of all 4 individual risk factors were combined into a risk score. Even though in individual risk factors heterogeneity could be seen in trends between populations, this heterogeneity disappeared when risk factors were combined into a risk score.

In agreement with the observations from analyses of individual risk factors, the association between trends in risk score and trends in stroke event rates during the full 10-year period was weak and negative in men (2% of variation explained) and higher and positive but still moderate in women (20% of variation explained). When a time lag was taken into account, the association increased to 9% of variation explained in men and to 36% of variation explained in women. (Table 3 and Figure 2).

Sensitivity Analyses

All the above results were weighted for data quality. Analyses were repeated without quality weighting, and results remained similar to the analysis with the quality weights. When populations with low data quality (stroke quality score <1.00) were excluded from the analysis and no quality weighting was done, the association between risk factors trends and stroke trends became lower.[17]

When the analyses were repeated with different time lags (1, 2, and 5 years), the results with a 1- and 2-year time lag remained similar to those for full registration periods, and results for the 5-year time lag were similar to those with a 3- to 4-year time lag.

The percentage of variation explained by the model decreased to some extent when events classified as subarachnoid hemorrhages were excluded.[17]

Restricting the analysis to the 55- to 64-year age group had little influence on the association in men, but in women the variation explained increased substantially.[17]

Discussion

Rationale for the Stroke Component of the MONICA Project

When the MONICA study was designed in the late 1970s and early 1980s, a decline in mortality of cardiovascular disorders, including stroke, had been observed in many countries over a number of years. The reduced stroke mortality was commonly ascribed to improved prevention and control of hypertension. More detailed estimations, however, have suggested that 25% of the stroke decline, at the most, is explained by improved detection and treatment of hypertension in the US population.[33] On the other hand, as much as one third of the stroke mortality decline in Finland has been attributed to reduced blood pressure levels in the population.[34] Such estimates based on a single population may be regarded as ecological case reports. Can the observations be reproduced in many diverse populations? The stroke component of the MONICA Project provided a unique opportunity to explore

whether observations on the relationship between secular trends in risk factor levels and stroke rates in the single populations can be generalized.

Strengths and Limitations of the Study Design

The MONICA Project has applied uniform monitoring of risk factors and stroke occurrence in many diverse populations, has been prospective, and has recorded all classic cardiovascular risk factors.

Most previous studies of the impact of risk factors on stroke in the population have been based on mortality rates rather than incidence. It has previously been reported that, in the MONICA populations, changes in early survival are a stronger determinant of stroke mortality trends than changes in incidence rates (C. Sarti, MD, PhD, et al, unpublished data, 2002). Therefore, stroke mortality is not an optimal end point when the impact of risk factor changes over time is analyzed. In the present study, stroke event rate has been used.

There are theoretical reasons why it would be preferable to use incidence rates of first stroke events rather than event rates combining first, recurrent, and indeterminate events. In practice, however, event rates have been easier to measure because, in many MONICA populations, it was not always possible to separate first and recurrent events.

The MONICA approach enables us to quantify the proportion of variation in stroke trends between the populations that can be explained by the variation of the trends in risk factors. The feasibility of doing this depends on heterogeneity in trends across the populations. To have a wide range of contrasting trends, populations that were geographically, culturally, and economically diverse were included in the MONICA Project. Because the participating populations had to have routine death certification, an efficient population census system, and a healthcare system permitting accurate stroke diagnoses, it was not possible to involve developing countries, China being the only exception.

At the inception of the WHO MONICA Project, the focus was on what then was regarded as "premature" cardiovascular disease. An upper age limit was set at 65 years. With aging populations and the median age at onset of stroke being shifted upward, the age range covered by the core MONICA study (35 to 64 years) is excluding most of today's stroke patients in Western countries. However, the relative risks for stroke conferred by modifiable factors such as hypertension and cigarette smoking are at least as high or higher in middle-aged compared with old people,[35,36] so changes in the population load of classic cardiovascular risk factors would be expected to have a particularly great impact on stroke rates in middle-aged populations.

Previous reports from the United States, Europe, and New Zealand[37,38] have shown little change in stroke incidence (or event) rates during the last decades, with few exception like Finland[39] and Australia,[40] where a definite decline in stroke rates has occurred. As the present data show, the changes in stroke event rates were relatively small compared with their precision in most MONICA populations. This modest heterogeneity limits the possibility of demonstrating a relationship between risk factor trends and stroke trends.

Considerable effort was expended on standardizing procedures and monitoring data quality. This concerned collecting demographic data, monitoring of risk factor levels in the population, and recording of stroke events. Of particular relevance for the present analyses is how blood pressure was recorded. Of the 15 populations, 8 populations had a quality score of 2 (highest possible) on blood pressure measurement.[41] Adjusting for data quality in the regression models did not substantially change the results.

Estimated Contribution of Risk Factors Changes to Stroke Trends

To analyze the relation between stroke trends and risk factor trends, we used 3 approaches: (1) simple regression analysis using systolic blood pressure, (2) multiple regression analysis with systolic blood pressure and daily cigarette smoking, and (3) simple regression analysis using risk score derived from individual data from a Finnish database.[17] This Finnish risk score was chosen because it is based on relatively recent data from large cohorts in both men and women and covers both fatal and nonfatal stroke events. Thus, the standard errors of its coefficients were small. The individual risk factors had considerable heterogeneity in trends, but that heterogeneity diminished when the risk factors were combined into the risk score.

Although quantitatively somewhat different, the 3 approaches to studying the relationships between risk factors and stroke events produced the same results in a qualitative sense. Sensitivity analyses using quality weights, excluding populations with low quality, excluding subarachnoid hemorrhage cases, or excluding age groups other than the 55- to 64-year group did not affect the conclusions.

The present results support the existence of a time lag between change in population levels of risk factor and change in stroke event rate. However, the MONICA study was originally designed as a contemporaneous 10-year study, which therefore placed constraints on what time lag could be introduced. We used a 3- to 4-year lag period, analogous to what has been used in the MONICA coronary component.[42] Nevertheless, limited knowledge about the exact time lag and our inability to take these fully into account may have diluted our estimates of the association between risk factor changes and stroke rate changes.

The variation that remains unexplained in the regression analyses is attributed to the imprecision of measurements, complexities in the relationship between risk factor and event rate changes, and other possible factors driving changes in event rates. The present results suggest that, in many populations, factors other than changes in the population load of classic cardiovascular risk factors constitute an important part of the driving force for changes in stroke event rates.

Our observations suggest that relationships between risk factors and stroke occurrence that exist in individuals or within a population do not necessarily apply when time trends are compared between many populations that are vastly different in ethnic background, culture, and socioeconomic factors. It should be noted that, in our analyses, the effects of interventions against risk factors, such as improved detection and treatment of hypertension or campaigns to reduce smok-

ing in the community, are taken into account to the extent that they influence the population distributions of blood pressure and prevalence of smoking.

The relationships deviated from what was expected, particularly in the former USSR populations. Stroke event rates were increasing in former USSR countries despite no adverse trends in classic cardiovascular risk factors but during a time of profound social transition. It seems that the impact of drastic socioeconomic changes on stroke occurrence has been only marginally, if at all, mediated by changes in classic cardiovascular risk factors. Socioeconomic status and other psychosocial factors are difficult to define and measure cross culturally, and data on these have not been collected systematically in the MONICA Project. Changes in biological risk factors not measured in MONICA could perhaps also help explain the poor correlation between trends in classic risk factors and stroke rates.

The MONICA results show that changes in classic cardiovascular disease risk factors explain only a part of the change in cardiovascular disease. There remains an unexplained proportion of the variation that can be due to changes in other risk factors, such as socioeconomic status, ethnic and cultural background, food consumption, or different combinations of some or all of these.

Appendix

Sites and Key Personnel of Contributing MONICA Centers

China: Beijing Heart, Lung and Blood Vessel Research Institute, Beijing: Wu Zhaosu (principal investigator), Wu Yingkai (former principal investigator). Denmark: Center of Preventive Medicine (The Glostrup Population Studies) Copenhagen University: M. Schroll (principal investigator), H. Kirkby, S. Henriksen, D. Jeppesen, G. Vincents, P. Thorvaldsen. Finland: National Public Health Institute, Helsinki: J. Tuomilehto (principal investigator), P. Puska (former principal investigator), P. Immonen-Räihä, E. Kaarsalo, E.V. Narva, K. Salmi, V. Salomaa, C. Sarti, J. Sivenius, J. Torppa. Italy: Institute of Cardiology, Regional Hospital, Udine: D. Vanuzzo (principal investigator), G.A. Feruglio (former principal investigator), L. Pilotto, G.B. Cignacco, M. Scarpa, R. Marini, G. Zilio, M. Spanghero, G. Zanatta. Lithuania: Kaunas Medical Academy, Institute of Cardiology: J. Bluzhas (principal investigator), D. Rastenyte. Poland: National Institute of Cardiology, Warsaw, Department of Cardiovascular Epidemiology and Prevention: S. Rywik (principal investigator), M. Polakowska, G. Broda (coprincipal investigator), B. Jasinski, A. Pytlak, H. Wagrowska. Russian Federation: National Research Center for Preventive Medicine, Moscow: T. Varlamova (principal investigator); Institute of Internal Medicine, Novosibirsk: Yu P. Nikitin (principal investigator), V. Feigin, S. Malyutina, T. Vinogradova, A. Tarasov. Sweden: The Cardiovascular Institute, Göteborg University, Göteborg: L. Wilhelmsen (principal investigator), P. Harmsen, K. Romanus, G. Lappas; Department of Internal Medicine, Kalix Lasarett, Kalix: V. Lundberg; Department of Medicine, Kiruna Hospotal, Kiruna: T. Messner (principal investigator); Umeå University Hospital, Department of Medicine: K Asplund (principal investigator), B. Stegmayr, M. Peltonen, G. Rönnberg. Yugoslavia: Novi Sad Health Center: M. Planojevic (principal investigator), Z. Solak, M. Zikic

MONICA Management Center: World Health Organization, Geneva, Switzerland: S. Mendis (responsible officer), I. Martin (former responsible officer), I. Gyarfas (former responsible officer), Z. Pisa (former responsible officer), S.R.A. Dodu (former responsible officer), S. Böthig (former responsible officer), M.J. Watson, M. Hill, A. Price.

MONICA Data Center: National Public Health Institute, Helsinki, Finland: K. Kuulasmaa (responsible officer), J. Tuomilehto (former responsible officer), E. Ruokokoski, H. Tolonen, A.-M. Rajakangas, M. Mähönen, J. Torppa.

MONICA Quality Control Center for Event Registration: University of Dundee, Dundee, Scotland: H. Tunstall-Pedoe (responsible officer), K. Barrett, C. Brown.

MONICA Stroke Advisory Group: K. Asplund, R. Bonita, D. Eisenblätter, S. Hatano, M. Schroll, P.O. Wester, Wu Zhaosu, H. Tunstall-Pedoe, J. Tuomilehto.

MONICA Steering Committee: K. Asplund (chair), P. Amouyel (publications coordinator), A. Pajak, H. Tunstall-Pedoe (rapporteur), S. Mendis, K. Kuulasmaa, A. Shatchkute (WHO, Copenhagen), A. Evans. Consultant: A. Dobson. Previous Steering Committee members: M. Ferrario, M. Hobbs, S. Sans, F. Gutzwiller, R. Beaglehole, S.P. Fortmann, A. Menotti, P. Puska, S.L. Rywik, U. Keil. Former Chiefs of CVD/HQ, Geneva (listed above), V. Zaitsev (WHO, Copenhagen), J. Tuomilehto. Former consultants: Z. Pisa, O.D. Williams (Birmingham, Ala), M.J. Karvonen (Helsinki, Finland), R.J. Prineas, (Minneapolis, Minn), M. Feinleib (Bethesda, Md), F.H. Epstein (Zürich, Switzerland).

Acknowledgments

The MONICA Centres are funded predominantly by regional and national governments, research councils, and research charities. Coordination is the responsibility of the WHO, assisted by local fund raising for congresses and workshops. WHO also supports the MONICA Data Centre (MDC) in Helsinki. Not covered by this general description is the ongoing generous support of the MDC by the National Public Health Institute of Finland and a contribution to WHO from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md, for support of the MDC and the Quality Control Centre for Event Registration in Dundee. The completion of the MONICA Project is generously assisted through a Concerted Action Grant from the European Community. Likewise appreciated are grants from ASTRA Hässle AB, Sweden; Hoechst AG, Germany; Hoffmann-La Roche AG, Switzerland; the Institut de Recherches Internationales Servier, France; and Merck & Co Inc, New Jersey, to support data analysis and preparation of publications. We thank Esa Ruokokoski and Vladislav Moltchanov for their contribution to the statistical programming and the persons who prepared the quality assessment reports that have been referred to in the text and published as Internet documents.

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Do Trends in Population Levels of Blood Pressure and Other Cardiovascular Risk Factors Explain Trends in Stroke Event Rates?: Comparisons of 15 Populations in 9 Countries Within the WHO MONICA Stroke Project

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Stroke. 2002;33:2367-2375
doi: 10.1161/01.STR.0000033131.27936.7F
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628