Trends in Stroke and Coronary Heart Disease in the WHO MONICA Project

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Background and Purpose—Coronary heart disease (CHD) and stroke are leading causes of death and disability. Because they share major common risk factors, it would be expected that trends in mortality and incidence of these 2 major cardiovascular diseases would be similar.

Methods—Data from the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project were used to compare 10-year trends in mortality, event rates, and case fatality from both CHD and stroke. Fifteen populations in the WHO MONICA Project provided data on both CHD (60,763 events) and stroke (10,442 events) in men and women aged 35 to 64 years (23.4 million person-years of observation in total).

Results—Trends for the 2 cardiovascular diseases varied within and between populations, and when data from all populations were combined, trends in CHD and stroke mortality differed in men (P=0.001) but not in women, whereas trends in event rates differed significantly in both men and women (P<0.001 and P=0.011, respectively). The differences in trends for CHD and stroke case fatality were not statistically significant in either men or women. In sensitivity analyses, differences in trends in event rates remained statistically significant in men (P<0.001) but not in women.

Conclusions—Trends for CHD and stroke mortality rates, event rates, and case fatality differ substantially between and within the study populations.

Stroke and coronary heart disease (CHD) are the leading causes of death and disability among adults. While the cerebral and myocardial vasculature are different, the occurrence of stroke and CHD is related to common risk factors such as level of blood pressure, tobacco smoking, and body mass index, and it could therefore be expected that trends would be similar for these 2 diseases. Nevertheless, studies have found that changes and levels of rates of stroke and CHD may not show similar patterns in a population, suggesting that although the 2 diseases share risk factors, the elements that determine their trends may be more complex.2,3 These findings, however, are based on single populations and may not be representative of trends in cardiovascular disease in other populations.

The World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project was initiated in the 1980s to explain the observed changes in CHD and stroke mortality rates. Ten-year trend data for CHD were collected from 38 populations, and approximately half of the MONICA centers also undertook registration of stroke events. Predefined definitions of stroke and CHD, together with standard procedures for prospective data collection and the development of data quality assessment methods, have enabled comparisons of trends in these populations.4–6

This article explores these issues, addressing the following hypothesis: “For the population reporting units there is no relationship between 10-year trends in event rates or mortality rates between stroke and coronary events”.7

Key Words: cerebrovascular disorders, coronary heart disease, health surveys, mortality, registries, World Health Organization

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Sites and key personnel of the WHO MONICA Project appear in the Appendix, which is available online at http://stroke.ahajournals.org.

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Subjects and Methods
The MONICA populations and registration procedures have been described in detail elsewhere. Standard coding and criteria were applied throughout, with internal and external quality control to validate all suspected coronary and stroke events in individuals aged 35 to 64 years of the defined populations.

Definitions of CHD and Stroke Events
The diagnosis of a coronary event was based on clinical symptoms, ECG findings, cardiac enzymes, necropsy findings, and previous history of CHD. Suspected CHD events were classified as definite acute myocardial infarction, possible acute myocardial infarction or coronary death, no acute myocardial infarction, or unclassifiable coronary death. A detailed description is available elsewhere.\textsuperscript{11} The following coronary events were used in the present analyses: nonfatal and fatal events of definite myocardial infarction, possible coronary deaths, and unclassifiable coronary deaths. This excluded possible nonfatal events because these were not collected completely in all centers.\textsuperscript{11,12}

The WHO definition of stroke was used: rapidly developing signs of focal (or global) disturbance of cerebral function lasting >24 hours (unless interrupted by surgery or death), with no apparent nonvascular cause. This definition excluded patients with transient cerebral ischemia or stroke events in cases of blood disease or brain tumors.\textsuperscript{13} Secondary strokes caused by trauma were also excluded.\textsuperscript{14} Suspected stroke events were classified into 4 diagnostic categories: definite stroke, definite stroke associated with definite myocardial infarction, no stroke event, and unclassifiable event. An event was defined as unclassifiable if there were insufficient data on the event but the diagnosis of stroke could not be fully excluded and there was no other explanation. The category “unclassifiable” was mainly used for fatal events in the absence of autopsy. Nonfatal events were classified in the category “unclassifiable” if it was impossible to determine whether the symptoms were from stroke or other diseases or if the symptoms were typical for a stroke but the duration was uncertain. Unclassifiable stroke accounted for 2.6% of all events. Definite stroke events (fatal and nonfatal) and unclassifiable events (fatal and nonfatal) were used in the analyses.

Stroke and CHD events were defined as fatal if the patient died within 28 days from the onset of symptoms. In this report we present analyses on trends in event rates (first and recurrent events together) of CHD and stroke rather than incidence (first-ever) rates; event rates are easier to measure, and in many MONICA populations it was not always possible to separate first and recurrent events.

Data Quality Assessment
Quality assurance has been a key issue in MONICA. Quality assessment reports are available at the MONICA Web site for stroke events\textsuperscript{9} and for CHD events.\textsuperscript{10} Separate assessments were done for the reliability of trend data. For coronary and stroke events, 10 and 18 separate quality indicators were used to calculate an overall trend quality score, respectively. A perfect score was 2.0, while a score of 0 denoted serious problems with the data.\textsuperscript{15}

Statistical Procedures
Age-standardized event and mortality rates were calculated in 5-year age groups in the range of 35 to 64 years. Mortality rates were grouped by year, and age was determined by the day of death. The weights 6, 6, 6, 5, 4, and 4 were derived from the age distribution of Segi’s world population\textsuperscript{16} representing the age groups 35 to 39, 40 to 44, 45 to 59, 50 to 54, 55 to 59, and 60 to 64 years, respectively.

The annual number of events within each age group was assumed to follow a Poisson distribution with allowance for overdispersion. Trends were calculated from the age-standardized annual rates ($r_t$) with the log-linear model of log $r_t=a+bt+e_t$, where log denotes the natural logarithm, $t$ the year, and $e_t$ the error term of the regression model. The estimate $100b$ is the rate of change of the event rate and is expressed in this report as trend.

Case fatality was standardized to the distribution of MONICA events (weighting 1, 3, and 7 for the age groups 35 to 44 years, 45 to 54 years, and 55 to 64 years, respectively, and divided by 11, with elimination of empty cells by amalgamation when necessary).

Trends were calculated from annual age-standardized case fatality by log-linear regression, with the assumption that the annual case fatality within age groups follows the binomial distribution and with allowance for additional deviation from the regression line, as for trends in event rates. Percentage changes in case fatality are expressed as percentage points relative to the initial value (for example, a change from 50% to 49% is 2%).

The trends in mortality rates, event rates, and case fatality rates were compared by subtracting the percentage trend in CHD rates from the corresponding percentage trend in stroke rates. Thus, if the magnitude and the direction of the trends in the 2 diseases are similar, the difference is low or zero. In contrast, in populations in which the magnitude of the trend is high and has opposite direction for CHD and stroke, the difference is large. When the significance of the differences between trends in CHD and stroke was tested, the variances of the estimates of the trends were assumed to be nonrandom. Accordingly, the $z$ test was used for comparison for a single population, and a $\chi^2$ test was used for overall comparisons.

Results
Fifteen MONICA populations provided trend data on both CHD events and stroke for subjects aged 35 to 64 years. The observation periods and number of years of registration for each population are listed in the Table. For all populations, the registration periods for the 2 series of events were either identical or overlapped considerably. In total, 60 763 CHD events and 10 422 stroke events were recorded during 23.4 million person-years of observation. Data quality scores for stroke and CHD trend data are also listed in the Table. Five populations had scores for either stroke or CHD that were <1, while the remaining 10 populations all had scores >1.

Trends in Stroke and CHD Mortality Rates
Trends in age-standardized stroke and CHD mortality rates for men and women are presented in Figure 1. In men, statistically significant changes in stroke and CHD mortality rates were noted in 5 and 10 populations, respectively. In 4 populations, changes in both stroke and CHD mortality rates were statistically significant. In women, statistically significant changes in CHD mortality rates were noted in 7 populations, and corresponding significant changes in stroke mortality rates were registered in 2 of these.

The differences between the trends for CHD and stroke mortality rates are shown in Figure 2. In both men and women, the differences were marked in several populations and were significant in the Moscow Intervention population, the 2 Swedish populations, and the Beijing population in men and in Turku/Loimaa and Novi Sad populations in women. The explanation for these results varied considerably between the populations. For example, in men from the Moscow Intervention population, the increase in stroke mortality rates was accompanied by a much smaller increase in CHD mortality rates, whereas in the Swedish populations, decreases in CHD mortality rates occurred, while there were opposite changes in stroke mortality rates. The differences for all populations combined were statistically significant in men ($P=0.001$).
Trends in Stroke and CHD Event Rates

Trends in age-standardized stroke and CHD event rates for men and women are presented in Figure 3. In men, 9 populations had decreasing CHD event rates, and in 6 of these the trends for stroke event rates also decreased. In women, there were decreasing stroke event rates in 9 populations, and in 8 of these the trends were paralleled by decreasing CHD event rates. There were statistically significant changes in both stroke and CHD event rates in men in 3 populations and in women in 2 populations.

The differences in the magnitude between trends for CHD and stroke event rates are shown in Figure 4. There were major differences in the trends for the 2 diseases, with the most common reason being decreasing CHD event rates combined with small changes in stroke event rates. The differences for all populations combined were statistically significant in both men \( (P<0.001) \) and women \( (P=0.01) \).

Trends in Stroke and CHD Case Fatality

Trends in age-standardized CHD and stroke case fatality for men and women are shown in Figure 5. In men, statistically significant changes in case fatality for stroke and CHD were noted in 4 and 5 populations, respectively. Stroke case fatality changed significantly in women in 4 populations but in only 3 for CHD case fatality.

![Figure 1. Percent change over 10 years in age-standardized CHD and stroke mortality rates in men and women aged 35 to 64 years. *Statistically significant changes \((2P<0.05)\). Abbreviations are as defined in the Table.](image-url)
The magnitude of the differences between trends in CHD and stroke case fatality rates are shown in Figure 6. In men, the largest differences were reported from the 2 populations in Moscow and Turku/Loimaa; however, only the trends in the Warsaw population were significantly different. In women, trends in CHD and stroke case fatality differed most in Moscow Intervention and Kuopio Province populations; these were significant only in the latter. While trends in case fatality rates for the 2 diseases varied substantially, the differences for all populations combined were not statistically significant in either men or women.

**Sensitivity Analyses**

In 5 study populations, the data quality score for either stroke or CHD was <1 (Table). Although the quality score is arbitrary, it was regarded as an appropriate indicator for the validity of data. To examine whether the inclusion of these 5 populations altered the results, analyses of the differences in pattern and magnitude of stroke and CHD were redone with the omission of these populations. In men, the difference in event rates was significant (P=0.001), while for mortality rates and case fatality the differences were statistically insignificant (P=0.18) and (P=0.78), respectively. In women, the differences in trends for event rates, mortality rates, and case fatality were statistically insignificant (P=0.28, P=0.33, and P=0.54, respectively). Statistical power was lost in the sensitivity analyses because there was a lower number of observations and the range of variations between populations was reduced.

**Discussion**

Data from 15 populations in the WHO MONICA Project, in which data for both stroke and CHD were collected, show that trends in CHD and stroke rates differed substantially between and within the study populations. In men, the magnitude and direction of trends for CHD and stroke event rates and mortality rates differed statistically significantly in analyses of all populations combined. In women, the difference for all populations combined was significant only in event rates. In sensitivity analyses, differences in trends in event rates in men remained statistically significant.
The WHO MONICA Project provides a unique opportunity to study trends in CHD and stroke in different populations in different countries, and the present analyses show the diversity in both magnitude and direction of the changes. The participating centers in the WHO MONICA Project all adhered to common definitions and shared a common study protocol, and the present collection of data may be one of the best sources to address the relationship in trends between CHD and stroke. The strength of the study is the possibility for multicenter analyses, and therefore the discussion refers predominantly to the results for all populations combined.

Stroke and CHD are both cardiovascular diseases related to arteriosclerosis, and it would therefore be expected, at the population level, that trends in one of the diseases would resemble those of the other. In this study, the test for differences between trends in CHD and stroke rates depended both on the magnitude and on the directions of the changes. This means that while, for example, mortality trends in men in the Moscow Intervention population increased significantly for both diseases (the direction), it was the male population with the largest difference because stroke mortality rates increased much more than CHD mortality rates (the magnitude). Testing only the relationship between the directions of the changes in stroke and CHD rates would ignore that the magnitudes of the trends for the 2 diseases were substantially different in several of the study populations.

The pattern of trends for CHD and stroke mortality rates differed significantly only in men in this study. Because the range of the differences was substantial in both men and women, it remains possible that the lack of significance in women may be due to fewer cases and insufficient statistical power rather than indicating that in women there is a common trend for the 2 diseases. A particular finding was that the magnitude and direction of trends were not uniform for men and women within each population. For example, in men in the Moscow Intervention population, there was a substantial increase in CHD mortality rates while only a minor increase in stroke mortality, while in women there were almost no changes. Substantial differences in trends were also observed in the Northern Sweden population; in men these trends were characterized by a marked decrease in CHD mortality rates but a more modest reduction in stroke mortality rates, while in women there were only minor reductions in mortality rates for both stroke and CHD. In Beijing there was a significant increase in CHD mortality rates in men accompanied by a
significant decrease in stroke mortality rates, and the same pattern was shown in women.

Changes in mortality rates are a function of changes in event and case fatality rates, and in the present study we examined trends in these 2 indicators. It has previously been reported that in the MONICA populations two thirds of the changes in stroke mortality rates were explained by changes in case fatality, while one third was explained by changes in incidence rates. In contrast, approximately one third of the changes in the CHD mortality rates were explained by changes in case fatality rates, while two thirds were explained by the changes in CHD event rates. As shown in Figure 3 in the present analyses, event rates for CHD decreased substantially in many populations, while the decreases were less evident for stroke event rates. These analyses indicate that the background for the differences in stroke mortality rates varies markedly between the populations. For example, in men in the Moscow Intervention population, there was an increase in the case fatality for stroke, while the event rates changed only slightly. In comparison, in men in Northern Sweden, case fatality declined in both diseases, but event rates declined only for CHD. Similar variations can be found in many of the other populations.

In the WHO MONICA Project, the upper age limit in most of the participating populations was 65 years. This is a limitation of the present study in that it is unknown whether there is a relationship between trends for CHD and stroke in older people, in whom the majority of events occur. During the study period, advances in prevention and treatment of patients with myocardial infarction have affected the age group in which this disease is frequent, and the impact this may have had on trends in stroke and CHD in the older people is unknown.

Discrepancies between mortality rates for CHD and stroke, as well as their trends, have been reported from other studies. The Chinese Sino-MONICA Project included populations from 17 selected monitoring areas totaling approximately 5 million people. During a 7-year follow-up period from 1987 to 1993, age-standardized mortality rates for CHD were low compared with those of Western industrialized countries, while the stroke mortality rates were high. Routine mortality data from the United States have shown that while the CHD mortality rates continue to decline, stroke mortality rates have remained almost stable since 1990. There is no clear explanation for this difference, but trends in stroke and CHD mortality rates in the United States have differed previously. While there has been a continuous decline in stroke mortality rates since the beginning of the 20th century, age-adjusted death rates for CHD continued to increase into the 1960s and then declined. This indicates that in a population the 2 diseases may be at different stages of the epidemic, which will affect trend analyses.

Epidemiological studies have shown that CHD and stroke share key risk factors such as high blood pressure, tobacco use, and body mass index, which are of particular importance at the population level with their strong effect and high prevalence. However, the strength and directions of the associations may be different for the 2 diseases. Whereas CHD is a disease caused by ischemic changes, the stroke diagnosis refers to a heterogeneous group of cerebrovascular diseases. Previous analyses based on data from 38 MONICA populations in 21 countries showed that from the mid-1980s to mid-1990s, smoking rates decreased in most male populations, while trends were mixed in women, and body mass index increased. The same study found that changes in these classic risk factors partly explained the variation in population trends in CHD. A recent study from 15 populations in the MONICA Project showed that systolic blood pressure trends were strongly associated with stroke event trends in women, but there was no association in men. In addition, trends in daily cigarette smoking were not associated with trends in stroke event rates. Thus, although several risk factors are associated with both diseases, changes in classic risk factors appear to have had a greater impact on CHD event rates than on the stroke event rates in the MONICA populations. A British study has indicated that adverse socioeconomic status in childhood influences mortality from stroke more than from CHD, and socioeconomic status could therefore be another risk factor that may have a different impact on the occurrence of stroke and CHD.

Figure 6. Differences in trends in age-standardized CHD and stroke case fatality in men and women aged 35 to 64 years. Trends in percentage in stroke case fatality rates were subtracted from trends in percentage in CHD mortality rates. *Statistically significant differences for individual populations (2P<0.05). The probability value concerns the null hypothesis that the difference is zero in all populations. Abbreviations are as defined in the Table.
In sensitivity analyses, 5 populations with stroke or CHD quality scores of < 1 were excluded. It was anticipated that if the results were very consistent, exclusion of these populations would have little effect. However, the earlier differences observed in trends in stroke and CHD mortality rates in men and event rates in women were not statistically significant in this subset of analyses, possibly because 3 of the 5 populations excluded were populations that had some of the largest differences in trends in both stroke and CHD. The lack of consistency makes it difficult to conclude with any confidence whether the observed trends in stroke and CHD mortality rates in men and women actually differ. Nevertheless, the present results serve to emphasize the possible complexity of the interactions between biological and socioeconomic risk factors in the causation of stroke versus CHD.

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References

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), Yao Chonghua, Hong Zhaoguang.

Denmark
Center of Preventive Medicine (Glostrup Population Studies), Copenhagen University: M. Schroll (Principal Investigator), P. Thorvaldsen, Mette Madsen, Henrik Bronnum Hansen, M. Kirchoff.

Finland

Italy
Institute of Cardiology, Regional Hospital, Udine: D. Vanuzzo (Principal Investigator), L. Pilotto, G.B. Cignacco, R. Marini, G. Zilio.

Lithuania
Kaunas Medical Academy, Institute of Cardiology: J. Bluzhas (Principal Investigator), D. Rastene, V. Grinius, R. Gruzuleviciene, D. Rasteniene.

Poland
National Institute of Cardiology, Warsaw, Department of Cardiovascular Epidemiology and Prevention: S. Rywik (Principal Investigator), M. Polakowska, G. Broda (Co-Principal Investigator), B. Jasinski, A. Pytlak, H. Wagrowska, P. Kurjata, W. Kupsc.

Russian Federation
National Research Center for Preventive Medicine, Moscow: T. Varlamova (Principal Investigator), V. Naumova, M. Ossokina, N. Serdyuchenko, N. Popova, E. Bolshakova. Institute of Internal Medicine, Novosibirsk: Yu Nikitin (Principal Investigator), V. Feigin, V. Gafarov, S. Malyutina, T. Vinogradova, G. Simonova.

Sweden
The Cardiovascular Institute, Göteborg University: L. Wilhelmsen (Principal Investigator), P. Harmsen, K. Romanus, G. Lappas, S. Johansoon, M. Falkman. Department of Internal Medicine, Kalix Lasarett, Kalix: F. Huhtasaari (Former Principal Investigator), V. Lundberg, E. Jägare Westerberg, B. Wikström, S. Boström. Department of Medicine, Kiruna Hospital, Kiruna: T. Messner (Principal Investigator). Umeå University Hospital, Department of Medicine: K. Asplund (Principal Investigator), P.O. Wester (Former Principal Investigator), B. Stegmayr, M. Peltonen, G. Rönnberg.

Yugoslavia
Novi Sad Health Center: D. Jakovljevic (Principal Investigator), M. Planovec (Principal Investigator).

Other MONICA Centers and Groups
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