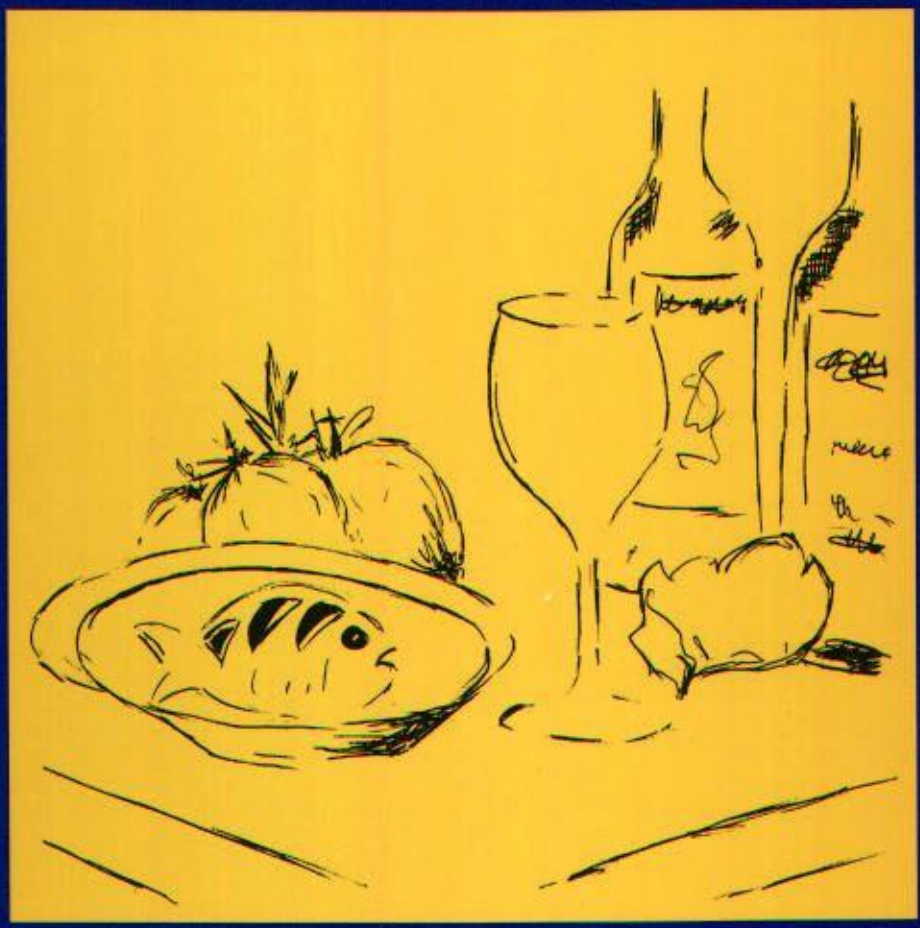
Epidemiology of stroke

The role of blood pressure, alcohol and diet



Sirving O. Keli

STELLINGEN BEHORENDE BIJ DIT PROEFSCHRIFT

1. Het gebruik van één meetmoment om het niveau van een risicofactor te schatten kan tot een substantiële misschatting van het risico op de desbetreffende uitkomst leiden indien het niveau van dit risicofactor sterk fluctueert en het onderliggende mechanisme via een langdurig proces werkt *(dit proefschrift)*.

2. Het concept van herhaalde metingen is sterk inherent aan het onderliggende mechanisme en is derhalve niet heilig. Het veronderstelde onderliggende mechanisme alsmede de haalbare en gehaalde meetprecisie bepalen in eerste instantie welke soort schatting het beste is *(dit proefschrift)*.

3. Matige visconsumptie leidt behalve tot verlaging van de sterfte aan coro-naire hartziekten tevens tot verlaging van het risico op cerebrosculaire accidenten. *(dit proefschrift; stelling onder voorbehoud van milieuverontreiniging)*

4. Langdurige consumptie van grote hoeveelheden flavonoïden leidt tot verlaging van het risico op zowel coronaire hartziekten (M. Hertog, 1994) als op cerebrovasculaire accidenten *(dit proefschrift)*.

5. Perhaps the main hazard to an epidemiologist is to lean too heavily on methodological dogma. .... The only way I can think of to overcome this imminent danger, is to gain subject matter knowledge. *(Albert Hofman, 1983)*.

6. Een epidemioloog zonder voldoende kennis van statistiek en computers gelijkt een vis op een fiets.

7. Momenteel wordt wereldwijd met man en macht en met verfijnde wetenschappelijke methoden aangetoond dat oma gelijk had toen ze als gezondheidsadvies gaf: 'Doe alles met mate'.

8. Wie anderen hun zekerheid ontneemt omdat hij die zelf niet heeft, koketteert tenslotte met zijn eigen eerlijkheid en beseft zijn verantwoordelijkheid niet. *(Godfried Bomans, 1983)*

9. Schurken verrekenen zich gewoonlijk hierdoor dat zij hun eigen bedoelingen ook aan anderen toeschrijven. (Godfried Bomans, 1983)

10. Het aan elkaar gelijkstellen van gelijknamige instituten in de gezondheidszorg op Curacao en Nederland getuigt van weinig inzicht in één of beide systemen van gezondheidszorg.

11. Geloven dat iemand anno 1995 op Curacao van bijstand kan rondkomen betekent zelfbedrog of puur opportunisme.

12. Play it, and Ill show you some unexpected rearrangements.

13. The fact that I look different and sometimes even eye different does not imply /that I am subversive.

Stellingen behorende bij het proefschrift van Sirving O. Keli, 1995.

EPIDEMIOLOGY OF STROKE

THE ROLE OF BLOOD PRESSURE, ALCOHOL AND DIET

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EPIDEMIOLOGY OF STROKE

THE ROLE OF BLOOD PRESSURE, ALCOHOL AND DIET

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in de landbouw- en milieuwetenschappen
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in het openbaar te verdedigen
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des namiddags te vier uur in de Aula
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The investigations described in this thesis were carried out within the Netherlands Institute for Health Sciences (NIHES), at the Department of Chronic Diseases and Environmental Epidemiology of the National Institue of Public Health, Bilthoven.

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Abstract

Epidemiology of stroke. The role of blood pressure, alcohol and diet

Ph.D. thesis Netherlands Insitute for Health Sciences, Agricultural University of Wageningen, and National Instiute of Public Health and Environmental Protection, Bilthoven, the Netherlands.

Sirving O. Keli

This thesis evaluates the recent trends in stroke mortality in the Netherlands Antilles, and the role of long-term blood pressure, alcohol and diet as risk factors for stroke incidence. The official mortality statistics and population data from the Netherlands Antilles over the period 1981-1992 were used to study trends in stroke mortality. The association of long-term blood pressure, alcohol and diet were studied with data from the Zutphen Study, a longitudinal study on risk factors for chronic diseases in the Netherlands. Repeated blood pressure measurements were collected yearly between 1960 and 1970. Information on alcohol and diet was collected in 1960, 1965 and 1970 with the cross-check dietary history method. Stroke incidence data were present for the period 1970-1985.

Age-adjusted stroke mortality declined over the period 1981-1986 in men and women in the Netherlands Antilles. Over the period 1987-1992 a slow down occurred in men, and in older women even an increase was observed. The average of individual repeated systolic blood pressure measurements over a period of 10 years was shown to be a better predictor of stroke incidence than single measurements. The latter understimated the stroke risk by 55%. Moderate alcohol consumption was associated with a non-significant 34% lower stroke risk. Consumption of one serving of fish per week was associated with a 50% lower stroke incidence compared with the consumption of less fish. Men with high intake of dietary flavonoids and men who drank their main source tea frequently had a 70% lower stroke incidence compared with men with a lower intake of flavonoids or tea. Men with high intake of beta-carotene had a 46% lower incidence of stroke, although this was not statistically significant. The effects of blood pressure, fish and flavonoids were independent from each other, and from other risk factors for stroke.

We conclude that the decrease in stroke mortality in the Netherlands Antilles came to a standstill, and that long-term blood pressure and diet are important predictors of stroke.

Contents

Chapter 1

GENERAL INTRODUCTION

After the decline of infectious diseases, cancer and cardiovascular diseases emerged as the most important causes of death worldwide. Currently, stroke has become for many countries the third leading cause of death after coronary heart disease and cancer[1-3]. The 28-day case fatality of stroke is high, varying generally from 15 to 60%[4-7]. The devastating effects of stroke are also reflected by the high proportion of disability resulting from stroke, especially among elderly[8,9]. Although strokes can be subdivided into several subtypes of either ischemic or hemorrhagic nature, in most Western countries the majority of strokes are ischemic. Both in the Netherlands[4] and int the Netherlands Antilles the majority of strokes are ischemic (chapter 2).

The pathogenetic mechanisms which lead to ischemic stroke are generally assumed to act through the complicated processes of atherosclerosis[10] and thrombosis[11]. The known risk factors for stroke include factors which are difficult to treat as well as modifiable lifestyle related risk factors. Factors which are hardly to change include age, sex, race, a history of cardiovascular diseases, diabetes mellitus, socio-economic factors, geographical locations, seasonality and climate[12]. Lifestyle related factors are modifiable and include blood pressure, which is the most important risk factor[13]. Blood pressure has also been proven to be suitable for lowering of stroke incidence and mortality when intervened upon[14]. Other identified lifestyle related or otherwise treatable risk factors for stroke include cigarette smoking, alcohol consumption, and cardiac abnormalities[12,15-18]. Although many of these risk factors are involved in the etiology of stroke and have been established as independent risk factors, identification of others, e.g. snoring[19] and recent infections[20], still prompt for confirmation by other studies and for biologically plausible mechanisms which, separately from or together with atherothrombosis, may explain stroke occurrence.

Diet has been shown to play an important role in the atherothrombotic processes[21]. Since these processes are assumed to be crucial in the pathogenesis of ischemic strokes it should be evaluated which dietary components may reduce or elevate the risk of stroke. The importance of the evaluation of diet in relation to stroke is further enlarged, since diet has already been shown to be crucial in the prevention of not only coronary heart disease, but also of cancer. A relevant role of diet in relation to stroke prevention would imply that dietary intervention should gain more focus, since it enables simultaneous targeting at three major causes of death, responsible for up to 60% or more of total mortality in many countries. Results from recent analyses indicate concordance between mortality trends of coronary heart disease, stroke and cancer, confirming the probability of common risk factors, including diet, and hence of common intervention focus points[22]. With exception of results from correlation studies in the beginning of the eighties[23], and from some cohort studies[15,24], little is known

about the effect of dietary intake on stroke incidence besides alcohol consumption. Furthermore, most of the cohort studies on diet and stroke are based on single measurements of dietary intake, and not on repeated measurements.

A crucial aspect in epidemiological studies estimating the strength of the relationship between one or more exposure variables and disease outcome is the exposure assessment. When the relationship between diet and disease, e.g. stroke, is studied, intra-individual variations in dietary habits over time are also important. Large intra-individual variations in food intake will lead to underestimation of real diet-disease associations.

Even in case of a reliable estimate of the exposure of interest, insight in the biological mechanism(s) which are being held responsible for the relationship with the disease is essential. For the occurrence of slowly developing chronic diseases like stroke, single measurements of risk factors, such as blood pressure and serum cholesterol, may not take into account measurement errors and intra-individual variations over short and long periods of time. For these risk factors, summary variables of different measurements over a long period have been proposed as better risk indicators[25-29]. Therefore, whenever available, repeated measurements have been used in this thesis to estimate the true exposure level of the variables under study.

The aims of this thesis are:

1) to assess recent trends in stroke mortality in the Netherlands Antilles and the Netherlands, given its importance as third leading cause of death in both countries in the Kingdom of the Netherlands;

2) to reappraise the role of blood pressure as a risk factor for stroke, taking into account repeated rather than single blood pressure measurements as has frequently been done;

3) to study the relationship between long-term alcohol consumption and stroke incidence;

4) to explore the relationship between different dietary variables and stroke incidence, given the potentially important implications for the prevention of strokes in particular, and chronic diseases in general.

An update on trends in stroke mortality in the Netherlands Antilles and the Netherlands is provided, based on official mortality statistics (*chapter 2*). Data from the Mortality Registers of the Branch of Epidemiology of the Department of Public Health and Environmental Hygiene of the Netherlands Antilles and the Central Bureau of Statistics from the Netherlands were used for this purpose.

Data from the Zutphen Study, a cohort study designed to investigate the effects of risk factors for chronic diseases in middle-aged men, were gratefully used. The Zutphen Study is conducted by the National Institute of Public Health and Environmental Protection of the Netherlands. Based on yearly blood pressure measurements in middle-aged men between 1960 and 1970 and follow-up from 1970 to 1985, the extent of underestimation of stroke risk by use of single instead of repeated blood pressure measurements is assessed (*chapter 3*). Alcohol consumption and diet were estimated every 5 years between 1960 and 1970. These data made

it possible to use repeated measurements of alcohol and diet in relation to 15-year stroke incidence. The relationship between alcohol consumption and stroke incidence is described in *chapter 4*. As regards diet, the relationship of fish consumption and antioxidant vitamins, including dietary flavonoids, with stroke incidence are described in *chapter 5 and 6*. In the general discussion (*chapter 7*) the results are integrated and the implications for public health and future research are discussed.

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Chapter 2

DECREASE IN STROKE MORTALITY IN THE NETHERLANDS ANTILLES AND THE NETHERLANDS:

Evidence for a recent slow down

Keli SO, Feskens EJM, Naarden EN, Kromhout D. Submitted.

Abstract

Background. Data on stroke mortality for the Netherlands Antilles are scarce and information on trends in stroke mortality does not exist. Stroke mortality characteristics and trends over the period 1981-1992 were studied and compared with data from the Netherlands.

Methods. Stroke mortality rates, calculated from official mortality data from the Netherlands Antilles and the Netherlands (ICD-9 codes 430-438), were adjusted for age according the WHO world population. Stroke mortality trends were assessed by linear regression of log stroke mortality on time.

Results. Age-adjusted stroke mortality was about 50% higher in the Netherlands Antilles compared with the Netherlands. An overall annual decrease of 1.2% ($p=0.08$) was observed for the Netherlands Antilles, and of 1.5% ($p<0.001$) for the Netherlands over the period 1981-1992. In men no consistent trends were observed for the Netherlands Antilles. For the Netherlands the initial 2.8% ($p=0.002$) annual decrease during the period 1981-1986 slowed down to 0.7% ($p=0.03$) during the period 1987-1992. In women from both countries, after an initial decrease during the period 1981-1986 stroke mortality increased during the period 1987-1992, especially in those aged 75 years and older.

Conclusions. Stroke mortality decreased in both the Netherlands Antilles and the Netherlands during the period 1981-1992. This decrease was mainly due to a decrease in the period 1981-1986. In men, the decrease slowed down over the period 1987-1992, while especially in older women an increase was noted.

Introduction

Since the beginning of the 20th century a consistent decline in stroke mortality has been observed in Western industrialized countries[1-3]. This decline was not worldwide, since in different Eastern European Countries an increase in stroke mortality was reported[4]. Although many possible explanations for the trends in stroke mortality have been put forward, specific causes still remain unclear[5].

In developing countries mortality patterns have been very different from those in Western industrialized countries in the past[6]. However, during most recent decades, a shift of mortality patterns towards those in Western countries, the so-called epidemiologic transition, often combined with the resurgence of some infectious diseases, has been reported[6,7]. As a consequence, stroke has become an important cause of death for several developing countries[8].

The mortality patterns of the Netherlands Antilles, a developing country of 5 islands in the Caribbean, are largely in accordance with those observed in the developed countries. Crude data on stroke mortality in the first half of the eighties indicated that it was the third leading cause of death after coronary heart disease and cancer, similar to other industrialized countries like U.S.A[9], and Japan[10]. However, information regarding trends in stroke mortality was lacking.

The Antillean National Mortality Register provides a complete, systematically coded and reviewed death registration for the 5 islands of the Netherlands Antilles, a part of the Kingdom of the Netherlands. Data from this register provided the opportunity to evaluate stroke mortality and its trends during the period 1981-1992. After standardization according to the WHO world standard population of 1992, these data were compared with those on stroke mortality in the Netherlands.

Methods

Mortality and population information sources

The Netherlands Antilles are constituted by 5 islands in the Caribbean, about 60 to 90 kilometers from the coast of Latin America (Venezuela). It has an area of approximately 800 km^2, and is a part of the Kingdom of the Netherlands, together with the autonomous countries Aruba and the Netherlands. Although the Netherlands Antilles are officially classified as a developing country, the lifestyle is comparable to that in Western countries. It has a more or less stable population, although aging tendencies are not as pronounced as seen in Western populations. The study population (midyear-population of all ages) increased from 173,711 in 1981 to 189,911 in 1992.

Information on stroke mortality in the Netherlands Antilles was obtained from the Antillean Mortality Register, maintained by the Branch of Epidemiology at the Department of

Public Health. This is a complete death registration, which includes personal data as well as information on the underlying causes of death and other concurrent diseases of diseased persons. Before inclusion in the Antillean Mortality Register all death certificates are critically reviewed by a team consisting of a registered nurse and two medical doctors. Whenever necessary, information from the corresponding hospital records and/or treating medical specialists are sollicited in order to provide the correct underlying cause of death. After the review and corrections, all certificates are coded according to the 9th revision of the International Classification of Diseases (ICD-9) by the registered nurse, trained especially for this purpose by the WHO, and a medical doctor (whenever necessary). All Antillean mortality data are registered by means of a computer program especially designed for this purpose.

The Antillean population data over the period 1981-1992 were obtained from the Antillean National Bureau of Statistics, and were recently updated according to the last census hold in 1992. Those data contain the population sizes, according to 1-year age classes from 0 up to 84 years, and one remaining category of 85 years and older. All data concerning the mortality and population of the Netherlands were obtained from the Central Bureau of Statistics of the Netherlands.

Stroke mortality was defined as death with ICD-9 codes 430-438 as the underlying cause of death, according to WHO ICD-9 international classification rules. All stroke mortality rates were age-standardized to the recently revised WHO standard world population of 1992[11].

Statistical analysis

Statistical analyses were carried out using the SAS statistical package[12]. Because of the positively skewed distribution of mortality data, all mortality rates were logarithmically transformed. The average annual change in stroke mortality over the period 1981-1992 was calculated by linear regression of log stroke mortality on time (0-11 years). The annual change in age-adjusted mortality was calculated from the regression model by dividing the difference of the age-adjusted mortality of one year and the previous year by the age-adjusted mortality for the previous year, expressed as percentage. The age-adjusted mortality was calculated from the intercept and the coefficient from the regression model.

Graphical inspection of the trend curves over the period 1981-1992 indicated possible changes in stroke mortality trends after 1986 for both the Netherlands Antilles and the Netherlands. Therefore also separate trend analyses for the periods 1981-1986 and 1987-1992 were carried out. The annual changes are percentual changes based on the age-adjusted stroke mortality level of 1981 for either the period 1981-1992 or 1981-1986, and based on 1987 when the period 1987-1992 is referred to. The p-values for trends in stroke mortality for 1992 with increasing age, were derived from the regression coefficient of a linear regression model, regressing the logarithmically transformed age-specific mortality on an age-scale. This age-

scale had 5-year age-classes and an open-ended age class of 75 years and older.

Results

In 1992 stroke mortality accounted for 11% of all deaths in the Netherlands Antilles, and 10% in the Netherlands. In both countries it ranked as the third major cause of death after coronary heart disease and cancer. The majority of all strokes in the Netherlands Antilles and in the Netherlands was ischemic. Table 1 shows the age-standardized mortality rates according to the WHO new standard population of 1992 for the Netherlands Antilles and the Netherlands. Generally stroke mortality was nearly 50% higher for the Netherlands Antilles compared with the Netherlands (table 1). Stroke mortality increased statistically significant with age in both men and women, and in the Netherlands Antilles as well as in the Netherlands.

Table 1. Sex specific age standardized stroke mortality rates# for the Netherlands Antilles and the Netherlands over the period 1981-1992.*

YEAR	The Netherlands Antilles			The Netherlands		
	Men	Women	Total	Men	Women	Total
1981	49.3	80.8	65.3	41.2	48.3	44.6
1982	76.4	50.0	62.6	39.4	48.4	43.8
1983	61.2	65.1	62.8	38.0	45.7	41.7
1984	54.5	59.4	56.8	38.4	46.3	42.3
1985	63.9	64.8	63.9	35.9	44.2	39.9
1986	53.3	50.4	51.4	35.6	43.4	39.4
1987	48.4	56.7	52.3	33.7	41.6	37.6
1988	63.3	45.6	54.0	34.0	42.3	38.1
1989	52.2	59.9	55.6	33.9	42.3	38.0
1990	54.3	64.7	59.2	33.3	42.5	37.9
1991	41.1	65.7	53.5	33.2	42.7	37.9
1992	56.5	62.6	59.4	32.6	43.8	38.2

* Standardized according to the corresponding WHO new standard world population of 1992.
\# All death rates per 100,000 persons per year.

In the Netherlands Antilles an annual decrease of age-standardized mortality of 1.2% (p=0.08) was observed over the period 1981-1992 (tabel 2, figure 1). This was due to a 3.5% (p=0.10) annual decrease over the period 1981-1986 and a 2.0% (p=0.14) annual increase over the period 1987-1992. In the Netherlands, an annual decrease of 1.5% in WHO age-adjusted stroke mortality was observed over the period

1981-1992 ($p<0.001$, figure 1). A 2.5% ($p=0.002$) decrease over the period 1981-1986 was followed by a non-significant 0.2% ($p=0.22$) increase over the period 1987-1992 .

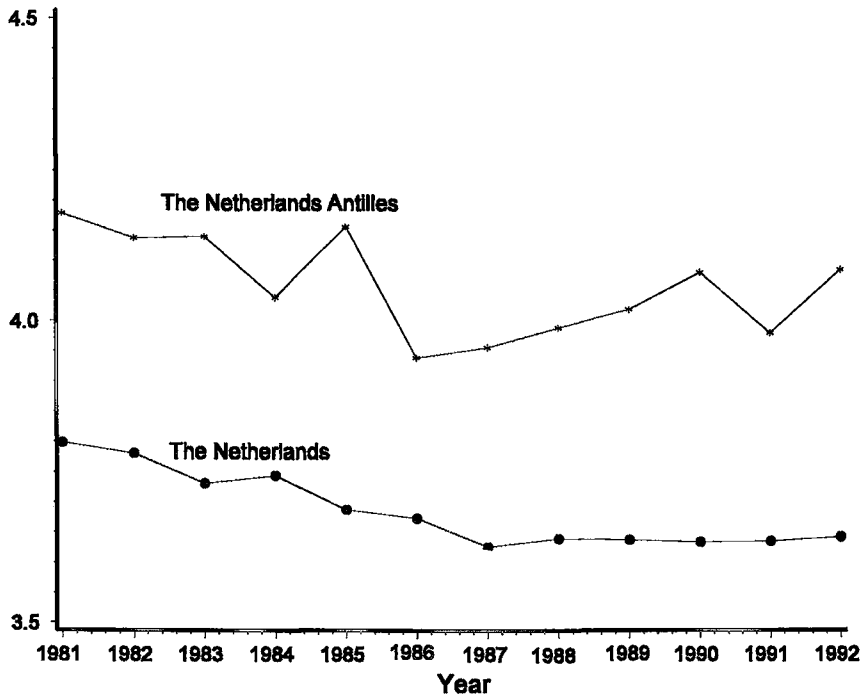

Figure 1. Trends in stroke mortality in the Netherlands Antilles and the Netherlands over the period 1981-1992 in the total population.

In Antillean women, a non-significant 4.7% decrease in stroke mortality during 1981-1986 ($p=0.31$) was followed by a 4.9% ($p=0.16$) increase over 1987-1992. In men no consistent trends were observed. In the Netherlands, stroke mortality was lower in men than in women. The annual decrease in men slowed down from 2.8% ($p=0.002$) during the period 1981-1986 to 0.7% ($p=0.03$) during the period 1987-1992. In women the 2.3% ($p=0.004$) annual decrease during the period 1981-1986 was followed by an annual increase of 0.8% ($p=0.01$) from 1987 to 1992.

During the period 1981-1992 an average annual decrease of 3.2% ($p=0.003$) in stroke mortality was observed for Antillean persons under 75 years. This was mainly due to a 7.5% ($p=0.03$) annual decrease over the period 1981-1986, followed by a 3.2% ($p=0.10$) annual decrease over the period 1987-1992. Both men and women under 75

years showed a decrease in stroke mortality, although none of these decreases separately was statistically significant. Antillean persons aged 75 years and older showed an 1.6% (p=0.09) annual increase in stroke mortality during the period 1981-1992, which was mainly due to a 2.9% (p=0.03) annual increase for women (table 2).

Table 2. Age and sex specific trends in log stroke mortality for the Netherlands Antilles and the Netherlands over the period 1981-1992.

AGE	The Netherlands Antilles		The Netherlands	
	Intercept#	Coefficient#	Intercept#	Coefficient#
Men				
25-44	2.4	-0.080	1.3	-0.015
45-64	4.8	-0.046	3.8	-0.035 ***
65-74	6.3	-0.013	5.7	-0.027 ***
75+	7.1	0.000	7.2	-0.013 ***
0-75+@	4.1	-0.018	3.7	-0.021 ***
Women				
25-44	1.8	0.049	1.4	0.002
45-64	4.3	-0.064	3.4	-0.027 ***
65-74	5.9	-0.041	5.3	-0.033 ***
75+	7.0	0.025*	7.1	-0.005
0-75+@	4.1	-0.005	3.9	-0.012 **
Total				
25-44	1.8	0.005	1.4	-0.006
45-64	4.6	-0.053*	3.6	-0.031 ***
65-74	6.1	-0.028*	5.5	-0.030 ***
75+	7.0	0.016	7.1	-0.008 **
0-75+@	4.1	-0.012	3.8	-0.015 ***

Log stroke mortality for 1981 and regression coefficient as estimated by linear regression of log stroke mortality over the period 1981-1992. All intercepts have a $p < 0.001$.
@ Standardized according to the WHO new standard world population of 1992.
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

In the Netherlands, the overall decrease of age-adjusted stroke mortality over the period 1981-1992 was due to a decrease in both men and women of all ages during the period 1981-1986. From 1987 to 1992 stroke mortality increased annually by 0.6% (p=0.32) in women under 75 years, and by 1.0% (p=0.03) in women aged 75 years and older. In men younger than 75 years the annual decrease in stroke mortality during the period 1981-1986 of

2.1% (p=0.75) slowed down to 0.8% (p=0.25) during 1987-1992. No trend was observed in men aged 75 years and older during the period 1987-1992.

Discussion

The data used for the present study are derived from vital statistics. The registration of births, deaths, migrations and several other important life events are mandatory in the Netherlands Antilles and the Netherlands. Consequently, these data are very complete. The accuracy of diagnosis may have influenced the observed results. However, only the total category of strokes (ICD codes 430-438) was used in the present study, whithout reference to specific subtypes. Although diagnoses of specific subtypes of stroke on death certificates are not considered accurate, the category of strokes as a whole is generally accepted to be reliable[13]. Besides, in the present study all death certificates were carefully reviewed and if necessary corrected after retrieving more detailed information. It has been shown that inquiry procedures increase the validity of vital statistics[14]. Also, it has been shown that routinely collected mortality statistics on stroke give a good estimate of stroke mortality in the population when compared with population-based stroke registries[3,15].

Stroke mortality accounted for 11% of the total mortality in the Netherlands Antilles and 10% in the Netherlands. This is comparable with countries like Australia and New Zealand[4], but is lower than in Japan (15%)[10]. Stroke mortality in the Netherlands Antilles is higher than the average WHO estimate for selected developing countries in the American continent (7% for men and 8% for women)[8]. The rank of strokes as the third leading cause of death after coronary heart disease and cancer is comparable to that in most industrialized countries, e.g. U.S[9], Japan[10], Australia, and New Zealand[4].

Stroke mortality during the period 1981-1992 was lower in the Netherlands compared with the Netherlands Antilles. This is in accordance with several reports showing industrialized countries to have lower stroke mortality rates than developing countries[11,16]. However, when viewed in an international perspective, the level of stroke mortality in the Netherlands Antilles can be considered to be intermediate[1,2,8,17].

Although the difference was not statistically significant, the overall decline in stroke mortality in the Netherlands Antilles was stronger in men compared with women, but differed when separate age groups were considered. In several developing countries, including Latin America and the Caribbean, a stronger overall decline was observed in women[8,18]. In the Netherlands a stronger decline in overall stroke mortality was observed in men, but this was not the case for all age groups. The stronger overall decline in men but also the differences in trends in men and women between age groups observed in the Netherlands is in agreement with observations in other industrialized countries e.g. U.S. and Canada[4,9,19], and for

Shanghai[20]. Thus, it appears that the rates of the decline of stroke mortality in men and women differ not only between countries, but also between age groups within countries.

In the Netherlands Antilles the observed annual decrease of 1.2% (p=0.08) over the period 1981-1992 was mainly due to a decrease in the period 1981-1986, caused primarily by a significant 7.5% decrease in persons younger than 75 years. During the period 1970-1985 Japan, which has a much higher stroke mortality rate, experienced a comparable annual decrease (7%) in stroke mortality[4]. In Netherlands the decrease over the period 1981-1986 was the consequence of a decrease in all age groups. On global level, most countries, including U.S., Canada, countries in the Central American, South American, English and Latin Caribbean regions, have experienced a downward trend, in contrast to some Eastern European countries where an upward trend was observed[2].

The observed downward trend in stroke mortality of the last decades has generally been attributed to the success of stroke prevention programs, especially hypertension treatment programs. However, this may not be a sufficient explanation, since declines in stroke mortality rates prior to the start of such programs have been reported[21]. Besides, only a small part of the decline can be explained by treatment of hypertension[22].

During the period 1987-1992, the observed decrease in Antillean stroke mortality slowed down. Also in the Netherlands, the initial strong decrease in stroke mortality during the period 1981-1986 disappeared after 1987, and in women even a statistically significant increase was observed. Recently, Cooper and coworkers reported a similar finding for the United States over the period 1978-1986[16]. There is some evidence that the incidence of stroke increased during the last decade in industrialized countries[23,24]. Assuming a continuing decline in stroke mortality in the Netherlands, Niessen and coworkers predicted a continuing decline in stroke incidence up to the year 2005 with a single-state transition model which included empirical data on stroke from several sources[25]. This assumption is in contrast with recent the slow-down in stroke mortality in men and the increase in stroke mortality in women we observed. It must be assumed that changes in the same, hitherto mostly unknown, factors initiating and prolonging the decline in stroke mortality since the beginning of this century are responsible for the slow down in the decline.

We conclude that a decrease in stroke mortality was observed in the Netherlands Antilles for the persons younger than 74 years over the period 1981-1992, which was mainly due to a 7.5% annual decrease over the period 1981-1986. In persons aged 75 and older an increase in stroke mortality was observed, especially in women. In the Netherlands, a decrease in stroke mortality over the period 1981-1986 was followed by a slower decrease in men, and by an increase in women between 1987 and 1992. Primary prevention of stroke remains therefore important in both the Netherlands Antilles and the Netherlands.

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Chapter 3

PREDICTIVE VALUE OF REPEATED SYSTOLIC BLOOD PRESSURE MEASUREMENTS FOR STROKE RISK

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Abstract

Background. The strength of the association between blood pressure and stroke incidence is dependent on the number of blood pressure measurements. Different summary variables of repeated blood pressure measurements taken during 10 years were evaluated in relation to the long-term risk of stroke in the Zutphen Study.

Methods. During the period 1960-1970 repeated blood pressure measures were taken yearly in 603 men aged 50 to 69 years in 1970 in the town of Zutphen, The Netherlands. The individual average systolic blood pressure between 1960 and 1970, the predicted systolic blood pressure for 1970 (based on regression of blood pressure readings on time) and the single observed systolic blood pressure in 1970 were used as systolic blood pressure estimates. Their strength in predicting the 15-year stroke incidence was assessed using Cox proportional hazards models. Adjustment was made for the confounding effect of age, cigarette smoking, and serum total cholesterol.

Results. The average systolic blood pressure between 1960 and 1970 was the strongest predictor of 15-year stroke incidence. The strength of the association was underestimated with 55% when a casual systolic blood pressure measurement was used instead of 11 yearly measurements.

Conclusions. It can be concluded that a casual blood pressure measurement leads to a substantial underestimation of the long-term stroke risk of an individual.

Introduction

Cohort studies have shown that casual blood pressure measurements have a strong predictive power for stroke incidence and mortality[1-8]. This has also been reported for the Netherlands[9-11]. Randomised clinical trials on the effect of treatment of hypertension have shown that lowering blood pressure by drug treatment is an effective measure to decrease stroke incidence and mortality within a few years[12-17]. Blood pressure can therefore be considered an important independent predictor of stroke.

Most studies on the relationship of blood pressure and stroke are based on a single baseline blood pressure measurement and subsequent follow-up of the study subjects[1-11]. However, blood pressure has a large intra-individual variation and is also subject to measurement errors[18-22]. Single blood pressure measurements, therefore, do not reflect the true blood pressure level of an individual and do not take into account changes in blood pressure level during follow-up. Summary variables of several blood pressure readings have been proposed as better risk indicators than a single blood pressure measurement[18-22]. In most studies, periods of 4-5 years at a maximum were used to summarize the blood pressure readings. However, it is of great interest to study the effect of blood pressure on stroke incidence based on blood pressure measurements during a longer period prior to the baseline measurement in order to get a better estimate of the true blood pressure. This could be done in the Zutphen Study. The predictive power of three blood pressure estimates on the stroke incidence during the subsequent 15 years was studied in uni- and multivariate analyses. The results of these analyses are reported here.

Methods

Since 1960, a longitudinal investigation of risk factors for chronic diseases has been carried out among middle-aged men from the town of Zutphen in the Netherlands. The Zutphen Study is the Dutch contribution to the Seven Countries Study[23-25]. In 1960 a random sample of 1,088 men born between 1900 and 1919 was drawn out of a total of 24,500. A cohort of 878 men from 40 to 59 years was eventually medically examined.

Blood pressure was measured with an ordinary mercury sphygmomanometer at the end of the physical examination on the right arm with the men in supine position, according to the protocol of the Seven Countries Study[23]. Only the result of the last of two measurements was recorded. Between 1960 and 1970 the blood pressure was measured yearly. The average systolic blood pressure was calculated as the sum of the systolic blood pressure readings from 1960 to 1970 divided by the number of measurements, provided that the subject had a total of

at least four readings during this period. At least one of these readings should have been taken in the last five years prior to or in 1970. In order to include trends in systolic blood pressure during the period 1960-1970, the predicted systolic pressure was calculated from the linear regression equation of the systolic pressure readings from 1960 to 1970 on time.

Information on cigarette smoking was collected in a standardized way[23]. Exposure to smoke was operationalized by calculating the variable packyears of cigarette smoking. Serum cholesterol determinations were carried out according to the method of Abell-Kendall in the period 1960-1965[26], and the method of Zlatkis[27] between 1966 and 1970, also providing values equivalent to the Abell-Kendall method. The average total serum cholesterol level over the period 1960-1970 was calculated in the same way as the average systolic blood pressure.

During follow up, the men were medically examined yearly between 1960 and 1973, in 1977/1978, and in 1985. Questionnaires about their health status were filled in by the men in 1980 and 1982. No one was lost to follow up. All morbidity and mortality data collected in the period 1960-1985 were coded by one physician in a standardized way in 1986. Stroke was defined as a sudden onset of neurological paralyses lasting longer than 24 hours or leading to death. All stroke diagnoses were confirmed in letters from a neurologist in the hospital of Zutphen to the general practitioner of the participant. Fatal strokes were coded according to the eighth revision of the International Classification of Diseases (ICD-8 codes 430-438). Data on stroke incidence, being either the first non-fatal or fatal event, are presented here.

From the 755 men who were alive and free of stroke in 1970, 143 were excluded either because of missing blood pressure readings in 1970, or because of having more than 7 missing values during the period 1960-1970. Nine of the remaining 612 persons were excluded because of missing data needed to correct for confounders, leaving 603 men for the final analyses.

Statistical analyses were performed using the SPSS/PC+, and BMDP package programs[28,29]. Stroke risk was assessed by survival analysis, using the Kaplan-Meier product limit estimator and the Cox proportional hazards model[30,31]. Correction for confounding by age, cigarette smoking, and serum total cholesterol was performed in multivariate Cox models. The following cut-off points were used for the single observed systolic blood pressure in 1970: <130 mmHg (lowest quartile) 130-156 mmHg (two middle quartiles) and ≥ 156 mmHg (highest quartile). These categories will be referred to as low, middle and high systolic blood pressure. The same cut-off points were used for the other systolic blood pressure estimates.

Regression dilution bias is defined as the percentage decrement in risk when a single measurement of a potential risk factor is used to study the association with a disease[18]. This

bias is due to intra-individual variation and measurement variability, causing regression towards the mean[18,22]. Regression dilution bias was assessed by calculation of the percentage underestimation of the regression coefficient for systolic blood pressure in the Cox model when the single observed systolic blood pressure is used instead of the average systolic blood pressure between 1960 and 1970 or the predicted systolic blood pressure for 1970. Systolic blood pressure was entered as a continuous variable in these models.

Results

Between 1970 and 1985 46 out of the 603 men aged 50-69 in 1970 had a first stroke. Fourteen of these men died due to the stroke. The overall stroke incidence rate was 6.2 per 1000 person-years. The 46 men who developed a stroke were older but had not significantly higher single observed diastolic and systolic blood pressures in 1970 compared with non-cases (table 1). The predicted systolic blood pressure for 1970 and the average systolic blood pressure between 1960 and 1970 were significantly higher in the stroke cases. This was not the case for the predicted and average diastolic blood pressure values. Therefore only the results for systolic blood pressure were used in further analyses.

Table 1. Systolic blood pressure estimates and other risk factors in 603 men aged 50-69 in 1970 in relation to 15-year stroke incidence. The Zutphen Study.

Risk factor	No Stroke n=557	Stroke n=46
Age (yr)	59.4 ± 5.3	62.0 ± 5.4**
Observed SBP in 1970 (mmHg)	145.7 ± 19.9	152.4 ± 25.4
Observed DBP in 1970 (mmHg)	88.6 ± 11.4	90.4 ± 13.2
Predicted SBP in 1970 (mmHg)	147.6 ± 18.4	156.0 ± 25.2*
Predicted DBP in 1970 (mmHg)	89.3 ± 10.3	91 ± 11.9
Average SBP 1960-1970 (mmHg)	141.9 ± 14.1	148.3 ± 19.2*
Average DBP 1960-1970 (mmHg)	86.9 ± 7.7	88.8 ± 8.9
Cigarettes/day x years till 1970	443.8 ± 325.3	457.2 ± 329.0
Average serum cholesterol 1960-1970 (mg/dl)	237.5 ± 36.4	235.7 ± 37.9

SBP = Systolic blood pressure
DBP = Diastolic blood pressure
@ Slope of the regression line obtained by regression of systolic pressure on time
* $p < 0.05$; ** $p < 0.01$

The highest relative risk for stroke was observed for the average systolic blood pressure between 1960 and 1970. Men with high levels had a 4.01 times higher 15-year stroke incidence than those with low levels (table 2). When adjustment was made for age, cigarette smoking and average serum total cholesterol between 1960 and 1970, the stroke incidence was 3.11 times higher. For the predicted systolic blood pressure in 1970 a 2.52 times higher stroke incidence was found in the men with high levels compared with those with low levels. After adjustment for confounders this relative risk was reduced to 2.34. For the observed systolic pressure in 1970 these risk ratios 1.99 and 1.84 respectively. The survival curves for the different average systolic blood pressure categories in the period 1960-1970 are shown in figure 1. The 15-year stroke survival was significantly higher in men with average systolic blood pressures levels above 156 mmHg in the period 1960-1970.

Table 2. Crude and adjusted relative risks for stroke incidence for different systolic blood pressure estimates in 603 men aged 50-69 years in 1970 in Zutphen.

SYSTOLIC BLOOD PRESSURE (mmHg)	CRUDE RR	95%CI	ADJUSTED RR	95%CI
Observed in 1970				
< 130	1.00	-	1.00	-
130 - 155	0.55	0.24 - 1.27	0.56	0.24 - 1.29
≥ 156	1.99	0.92 - 4.31	1.84	0.85 - 3.99
	X_t^2=6.39*		X_t^2=5.20*	
Predicted systolic pressure for 1970				
< 130	1.00	-	1.00	-
130 -155	0.74	0.29 - 1.88	0.76	0.30 - 1.96
≥ 156	2.52	1.03 - 6.17	2.34	0.95 - 5.76
	X_t^2=9.87**		X_t^2=8.14**	
Average systolic pressure 1960-1970				
< 130	1.00	-	1.00	-
130 - 155	1.29	0.53 - 3.13	1.26	0.52 - 3.06
≥ 156	4.01	1.54 - 10.45	3.11	1.17 - 8.24
	X_t^2=9.74**		X_t^2=6.42*	

RR	Relative risk, calculated from Cox proportional hazards model.
95% CI	95% Confidence Interval of relative risk.
ADJUSTED	Adjusted for age in 1970, average serum total cholesterol between 1960 and 1970 and cigarette smoking.
X_t^2	Chi-square test for linear trend
*	p<0.05; ** p<0.01

If the average systolic blood pressure between 1960 and 1970 was used as an estimate of the true systolic blood pressure instead of the observed systolic blood pressure in 1970, the strength of the association with 15-year stroke incidence increased by 55% (Cox coefficient 0.0151 compared with 0.0234). The predicted systolic blood pressure for 1970 showed a 26% stronger association with stroke incidence than the observed systolic blood pressure in 1970.

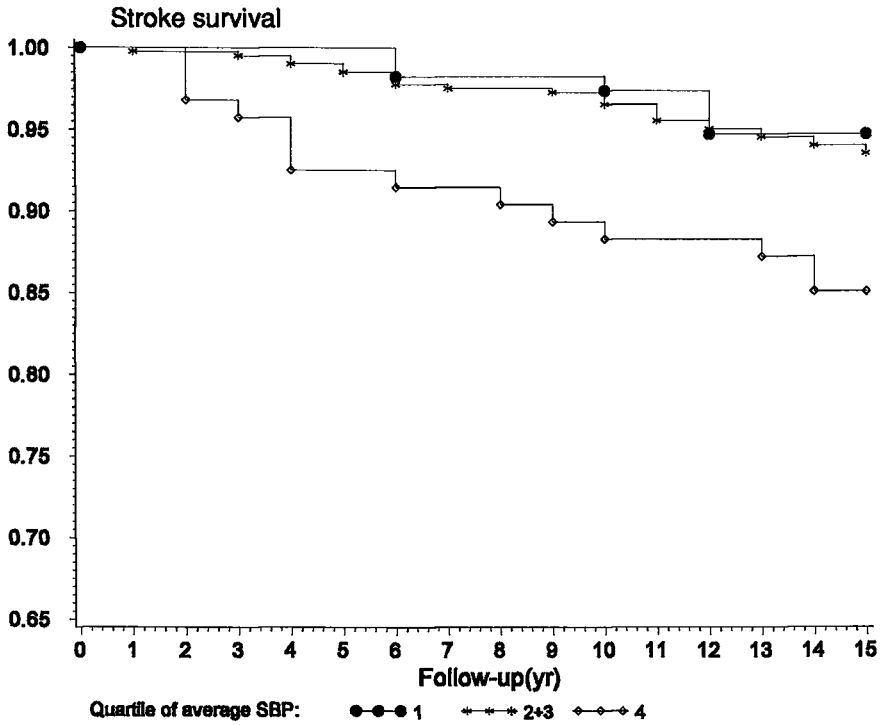

Figure 1. Average systolic blood pressure (SBP) 1960-1970 and 15-year stroke incidence among 603 men aged 50-69 in 1970.

Discussion

The results of the present study showed that the average systolic blood pressure of 11 yearly readings was more strongly related to stroke incidence than a single systolic blood pressure measurement. Also other studies reported a better assessment of stroke risk by a

cumulative measure of blood pressure over a prolonged period instead of a single observed blood pressure measurement[18-21,32]. Although the estimates of the true blood pressure used in these studies are somewhat different, the findings are consistent with those observed in the present study.

Yearly blood pressure values were strongly correlated ($r>0.6$). This means that in hypertensives the blood pressure is correlated with the duration of hypertension. This was especially the case in the 1960's, because at that time only very high blood pressure levels were treated. However the effect of the duration of hypertension should not be overstated, because hypertensive patients are still prone to the variability in blood pressure and measurement errors, which cause regression dilution bias[18,33,34].

MacMahon and coworkers reported an increase of 60% in the strength of the association between diastolic blood pressure and stroke risk when bias due to regression dilution was taken into account. They adjusted for regression dilution bias by using repeated diastolic blood pressure measurements in a subsample of the examined populations[18,35]. Our estimate of a 55% increase in the strength of the association was based on 11 yearly blood pressure measurements prior to 1970. Although different methods were used to take regression dilution bias into account similar results were obtained in both studies.

The stroke risk rose sharply above systolic blood pressure values of 156 mmHg, suggesting a possible threshold effect around this cut-off point(table 2, figure 1). This effect was stronger for the average systolic blood pressure than for the single observed or predicted blood pressure for 1970. This cut-off point is in accordance with the commonly used cut-off point of 160 mmHg for systolic hypertension[36]. In the guidelines for the management of hypertension prepared by the Guidelines Sub-Committee of the WHO/ISH Mild Hypertension Liaison Committee diastolic blood pressure was used to diagnose hypertension[37]. However, the findings of the present study and several other epidemiological studies suggest that systolic hypertension is a stronger predictor for stroke risk than diastolic hypertension[8,21,32,38].

The findings of the present study clearly showed that a casual systolic blood pressure measurement is not sufficient to predict stroke risk. The average systolic blood pressure measured over a long period of time provides a much better estimate of the true pressure. When considering treatment most clinicians do not rely on a single blood pressure reading[33,34]. The best estimate of the long-term stroke risk of a patient in clinical practice is achieved when his average systolic blood pressure over a period of several years is taken into account.

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Chapter 4

LONG-TERM MODERATE ALCOHOL CONSUMPTION, DIETARY HABITS AND STROKE INCIDENCE

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Abstract

Background. There is some evidence that moderate current alcohol consumption is inversely associated with risk of ischemic stroke. Selection bias due to a higher risk in ex-drinkers has been put forward as an explanation of this finding. Information on present and past characteristics of ex-drinkers is almost non-existent. The aim of the present study was to assess dietary and other characteristics of moderate alcohol drinkers, ex-drinkers and never-drinkers, and to study their risk of stroke.

Methods. In 1960, 1965 and in 1970, cardiovascular risk factors including alcohol and diet were assessed in 514 men born between 1900 and 1919 in Zutphen, The Netherlands, who consumed less than 30 grams of alcohol per day. Alcohol consumption and dietary habits were estimated with the cross-check dietary history method. Differences in risk factors and dietary habits between alcohol consumption categories were tested with analysis of variance. The association of long-term alcohol consumption habits and 15-year incidence of stroke was analyzed with Cox proportional hazards models. Confounding effects of age, socio-economic status, and life style related factors, e.g. diet and smoking, were taken into account.

Results. Of all men, 69.7% drank alcohol, 9.7% were ex-drinkers, and 20.6% never-drinkers. Alcohol use was positively associated with cigarette smoking, total fat and fish intake, and inversely with carbohydrate intake. There was no difference in risk factors, chronic disease prevalence and dietary pattern between never- and ex-drinkers. Moderate alcohol drinkers (less than 3 glasses/day) had a non-significant 34% lower stroke risk (adjusted relative risk 0.66; 95% CI 0.30-1.47) compared to never-drinkers.

Conclusions. Moderate alcohol drinking was associated with smoking habits and dietary pattern. A non-significant 34% lower stroke incidence was observed for alcohol consumers compared to never-drinkers.

Introduction

Several studies have reported that heavy alcohol consumption is associated with an increased risk of stroke[1,2]. For the hemorrhagic type of stroke a dose-response relation was observed[3], whereas for the ischemic type of stroke current moderate alcohol consumption seems to be protective[4].

Although a preventive effect of current moderate alcohol consumption on cardiovascular diseases has repeatedly been shown, the interpretation of the finding is subject to persistent discussion[5-8]. Especially selection bias towards the category of non-drinkers has been put forward as an alternative explanation for the apparent higher risk[7,8]. Non-drinkers consist of never- and ex-drinkers. Most studies could not provide information on the composition of the category of non-drinkers and its subsequent relation with risk factors and stroke incidence.

In the Zutphen Study extensive information on long-term alcohol consumption, other risk factors including dietary habits, and stroke incidence has been collected. These data provide the possibility to separate the group of non-drinkers into never-drinkers and ex-drinkers, and to study the 10-year history of dietary habits, biological risk factors, and chronic disease prevalence. Furthermore, the group of current moderate alcohol drinkers could be divided into beginners and always-drinkers and the relation between habitual alcohol consumption and other risk factors and the effect of moderate alcohol consumption on stroke incidence were investigated.

Methods

Study population

Since 1960, a longitudinal investigation of risk factors for chronic diseases has been carried out among middle-aged men from the town of Zutphen in the Netherlands. The Zutphen Study is the Dutch contribution to the Seven Countries Study[9,10]. In 1960 a random sample of 1,088 men born between 1900 and 1919 was drawn out of a total of 2,450. A cohort of 872 men from 40 to 59 years participated in both the medical examination and the dietary survey. From the 755 men who were alive and free of stroke in 1970, 172 were excluded because they did not participate in the dietary survey in 1960, 1965, or 1970. Thirty-four of the remaining 583 men were excluded because data on confounding variables were lacking. After exclusion of 35 men with a daily alcohol intake outside the studied range, i.e. more than 30 grams/day, 514 men remained for the final

analysis.

Alcohol and food intake

Alcohol and food intake data were collected in 1960, 1965 and 1970 using the cross-check dietary history method[11], adapted to the Dutch situation[12]. This method provides information about the usual pattern of food and alcohol consumption in the 6 to 12 months prior to the interview. Each participant was interviewed together with his wife about his usual food and alcohol consumption patterns on weekdays and weekends. The participant was also interviewed about his usual food and alcohol consumption away from home. The estimated average consumption of foods and alcoholic drinks during a day or a week was checked with the quantities of foods bought per week for the whole family. The food consumption during a typical weekday was calculated on the basis of this information. The interviews were carried out by trained dietitians in the months May, June and July. The dietitians also recorded any special diet of the participant, prescribed by his general practitioner or specialist. An extended computerized version of the Netherlandsfood table, containing the energy and nutrient composition of Dutch foods in the period 1960-1970, was used to convert the food intake data into energy and nutrients[12].

Risk factors

Blood pressure was measured with an ordinary mercury sphygmomanometer at the end of the physical examination on the right arm with the men in supine position, according to the protocol of the Seven Countries Study[9]. Between 1960 and 1970 the blood pressure was measured yearly. The average systolic blood pressure was calculated as the sum of the systolic blood pressure readings from 1960 to 1970 divided by the number of measurements, provided that the subject had a total of at least four readings during this period. At least one of these readings should have been taken in the last five years prior to or in 1970. Information on cigarette smoking was collected by a questionnaire[9]. Serum cholesterol determinations were carried out according to the method of Abell-Kendall in the period 1960-1965[13], and the method of Zlatkis[14] between 1966 and 1970, also providing values equivalent to the Abell-Kendall method. The average serum total cholesterol level over the period 1960-1970 was calculated in the same way as the average systolic blood pressure. Body mass index was calculated as weight divided by height squared (kg/m^2). Men with either an academic or comparable education, or with management positions in commerce, industry or public service, were classified as members

of the highest socio-economic class.

Follow-up

The men were medically examined yearly between 1960 and 1973, in 1977/1978, and in 1985. Questionnaires about their health status were filled in by the men in 1980 and 1982. No one was lost to follow-up. All morbidity and mortality data collected in the period 1960-1985 were coded by one physician in a standardized way in 1986. Stroke was defined as a sudden onset of neurological paralyses, lasting longer than 24 hours or leading to death. All stroke diagnoses were confirmed in letters from a neurologist or internist in the hospital of Zutphen to the general practitioner of the participant. Fatal strokes were coded according to the eighth revision of the International Classification of Diseases (ICD-8 codes 430-438). Data on stroke incidence being either the first non-fatal or fatal event, are presented here.

Angina pectoris was defined as a specific medical history of typical chest pain from cardiac origin based on the Rose-questionnaire[15]. Myocardial infarction was considered as definite when two of the following three criteria were met: a specific medical history, i.e., severe chest pain during more than 20 minutes and not disappearing during rest; characteristic electrocardiographic changes and specific enzyme level elevations.

Statistical Analysis

Statistical analyses were performed using the SAS statistical package[16]. Men were divided into different categories according to their alcohol consumption habits reported in the dietary surveys in 1960, 1965 and 1970. Those men who on all surveys reported not to drink were classified as never-drinkers. The men who did not drink in 1970, but had drunk either in 1960, 1965 or both years, were classified as ex-drinkers. Men who started to drink either in 1965 or in 1970 were considered beginners, while always drinkers had reported drinking alcohol in 1960, 1965 and 1970.

Risk for stroke incidence was assessed by survival analysis, using the Kaplan-Meier product limit estimator and Cox proportional hazards models[17]. The possible confounding effect of other risk factors was taken into account.

Results

In 1970, about 70% of the 514 men were alcohol users. The group of 156 non-drinkers consisted of 32% ex-drinkers who had stopped drinking prior to baseline in

1970. Of the current alcohol users, about 44% had always used alcohol during the period 1960-1970. The average alcohol consumption in 1970 in the total study population amounted to 7.1 grams/day, which is less than 1 drink/day (table 1). The most important source of alcohol was spirits (4.1 grams/day), followed by beer (2.6 grams/day) and wine (0.4 grams/day). Always drinkers took on average about 1 drink per day (table 2). They also had the highest fish consumption (about one serving of fish/week) and fat intake, and the lowest intake of carbohydrates. Never-drinkers and ex-drinkers did not differ in dietary intake pattern.

Table 1. Dietary characteristics in 514 men free of stroke aged 50-69 years in 1970 in relation to alcohol consumption habits in Zutphen.

DAILY INTAKE	ALCOHOL INTAKE IN 1970			
	Never n=106	Ex-drinkers n= 50	Beginners n=200	Always n=158
Alcohol (g)	0	0	7.6 ± 6.3	13.3 ± 8.5
Energy (MJ)	10.7 ± 2.2	10.9 ± 2.6	11.0 ± 2.2	11.1 ± 2.0
Protein (en%)	12.6 ± 2.0	12.6 ± 1.9	12.5 ± 1.6	12.4 ± 1.9
Total Fat (en%)	41.8 ± 5.5	41.0 ± 6.7	41.2 ± 5.2	42.9 ± 4.6**
Saturated (en%)	17.0 ± 2.6	16.8 ± 3.2	16.9 ± 2.9	17.4 ± 2.8
Monounsaturated (en%)	17.6 ± 3.1	17.4 ± 3.5	17.4 ± 2.8	18.2 ± 2.5*
Polyunsaturated (en%)	7.1 ± 2.6	6.6 ± 2.2	6.6 ± 1.9	7.0 ± 2.0
Carbohydrates (en%)	44.9 ± 5.5	45.6 ± 6.7	43.6 ± 5.3	40.6 ± 5.1***
Monosaccharides (en%)	22.3 ± 6.1	24.5 ± 6.4	21.2 ± 5.3	19.7 ± 5.2***
Polysaccharides (en%)	22.6 ± 4.8	21.1 ± 4.0	22.4 ± 4.3	20.9 ± 4.2***
Dietary cholesterol (mg)	392.1 ±68.2	416.0 ±95.5	415.2 ±72.3	437.1 ±63.3
Dietary fibe r(g)	24.3 ± 7.5	24.8 ± 7.3	25.5 ± 7.4	25.1 ± 7.4
Fish (g)	15.2 ±15.7	14.1 ±14.2	16.5 ±15.5	21.2 ± 25.0*

* $p < 0.05$
*** $p < 0.001$

Among always-drinkers there were significant more cigarette smokers compared with the other alcohol intake categories (table 2). Alcohol drinking was not related to

socio-economic status. The risk factor levels in ex-drinkers did not differ from those in never-drinkers. When disease history was compared, the prevalence of angina pectoris, myocardial infarction and cancer at baseline in 1970 did not differ according to alcohol consumption category.

Table 2. Risk factors in 514 men free of stroke aged 50-69 years in 1970 according to categories of alcohol consumption habits in Zutphen.

RISK FACTORS	ALCOHOL INTAKE IN 1970			
	Never n=106	Ex-drinkers n=50	Beginners n=200	Always n=158
Age 1970 (yr)	59.5 ± 5.5	59.4 ± 5.3	59.9 ± 5.5	59.1 ± 5.3
Body Mass Index (kg/m^2)	24.6 ± 2.8	25.1 ± 3.0	25.2 ± 2.6	25.4 ± 2.6
Average SBP (mmHg)#	141.2 ± 14.5	143.1 ± 13.5	143.2 ± 14.4	141.7 ± 13.2
Average SChol (mg/dl)#	231.6 ± 35.2	240.2 ± 42.4	235.3 ± 34.7	241.2 ± 37.0
Cigarette smokers (%)	44.3	44.0	47.0	60.8*
Highest SES (%)	14.2	16.0	19.0	17.7

SBP Systolic blood pressure.
\# All averages are over the period 1960 to 1970.
SChol Serum total cholesterol.
SES Social economic status indicator; highest = professionals.
* $p<0.05$.

During 15 years of follow-up 40 events of stroke occurred in the 514 men. The beginners had the lowest 15-year stroke incidence (table 3). Stroke incidence in alcohol drinkers (beginners and always-drinkers together) was 34% lower (unadjusted relative risk 0.66, 95% CI: 0.30-1.47) compared with never-drinkers. The stroke risk in ex-drinkers was 29% lower (relative risk 0.71, 95% CI: 0.23-2.24) compared with never-drinkers. The risk ratios did not change after adjustment for potential confounders in multivariable Cox models. Men with a history of myocardial infarction, angina pectoris or cancer may have changed their alcohol drinking habits and have a increased risk for stroke. However, adjustment for history of myocardial infarction, angina pectoris or cancer prevalence in 1970 did not change the risk ratio (relative risk 0.67, 95% CI: 0.30-1.48). The risk ratio also changed little when average systolic blood pressure and serum cholesterol were taken additionally into account in multivariable models (relative risk 0.76, 95% CI : 0.24-2.42).

Table 3. Long-term alcohol consumption habits in relation to 15-year stroke incidence in 514 men aged 50-69 years in 1970 in Zutphen.

Alcohol intake in 1970	N(cases)	Inc	CRUDE RR	95%CI	ADJUSTED* RR	95%CI
Never	106(11)	9.3	1.00		1.00	
Ex-drinkers	50(4)	6.7	0.71	0.23-2.24	0.74	0.23-2.32
Beginners	200(14)	5.9	0.63	0.29-1.39	0.65	0.28-1.51
Always drinkers	158(11)	6.1	0.65	0.28-1.50	0.69	0.26-1.80
			p_{trend}=0.29		p_{trend}=0.39	

* Adjusted for age, cigarette smoking, fish consumption, intake of carbohydrates and total fat, body mass index, and socio-economic status at baseline in 1970.

Inc Incidence of stroke per 1000 person-years.

RR Relative risk.

CI Confidence interval.

Discussion

In the present study men with different long-term moderate alcohol consumption habits were compared with regard to their dietary habits, other risk factors and incidence of stroke. Although no data on stroke subtype are available in the present study, other population-based studies have reported that ischemic strokes are the predominant subtype of strokes in the Netherlands[18]. The present study was limited to men with moderate alcohol consumption. The always-drinkers had a higher fish consumption, a higher intake of fat, a lower intake of carbohydrates and smoked more cigarettes compared with the other categories of alcohol drinkers. Moderate alcohol drinkers tended to have a lower stroke incidence compared with never-drinkers.

Data on dietary habits of moderate alcohol consumers are scarce. In the Dutch National Food Consumption Survey, Veenstra and coworkers found no differences in nutrient intake between non- drinkers and moderate drinkers, but a slightly higher intake of total and saturated fat in the weekends[19]. As in the present study, no differences in body mass index were observed, whereas more moderate drinkers smoked cigarettes compared with non-drinkers. Stampfer and coworkers[4] and Rimm and coworkers[20] observed a higher

intake of fat with increasing alcohol consumption, while the percentage of smokers was higher in moderate drinkers compared with non-drinkers. In the present study fish consumption was positively associated with alcohol intake. Shekelle and coworkers reported a similar observation in the Western Electric Study[21]. These results suggest that moderate alcohol consumption is associated with a different dietary pattern and heavier cigarette smoking compared with non-drinking.

Regarding the 15-year stroke incidence, after adjustment for potential confounders a 34% lower stroke risk was observed in moderate alcohol drinkers (always-drinkers and beginners together) compared with the never-drinkers, although this difference was not statistically significant. It is important to consider the relatively low alcohol consumption in the Zutphen cohort for the always-drinkers with an average of about 1 drink/day. In other studies these men would belong to the category of light drinkers. In The Netherlands, Herman and coworkers found a weak inverse association between life long light alcohol consumption and two-year stroke incidence[22]. Gill and coworkers reported a J-shaped relationship between alcohol consumption and stroke risk[2]. When considering the range of 10-90 grams and 100-300 grams of alcohol per week, risk ratios of 0.50 (95% CI 0.2-1.1) and 0.73 (95% CI-0.4-1.2) were observed. Palomaki and coworkers observed an odds ratio of 0.54 (95% CI 0.28-1.05) for alcohol consumption up to 150 grams/week[23]. In the present study the relative risks were 0.65 for beginners (8.4 grams/day in 1970) and 0.69 for always drinkers (13.3 grams/day in 1970). Furthermore, similar findings were reported in the Nurses' Health Study, and studies in Japan, California and Hawaii[3,4,24]. So, although the numbers in the present study are small and therefore have a limited power, the findings in relation to stroke incidence are similar with most other larger studies when the alcohol consumption range is taken into account.

The interpretation of the higher risk reported for non-drinkers compared with moderate drinkers for coronary heart disease and for stroke has persistently been subject of discussion. In case-control studies, selection bias due to unsuitable choices of the control groups and incorrect matching procedures has been suggested[5,6,25]. For cohort studies the category of non-drinkers could be biased, because these studies could not separate ex-drinkers from never-drinkers[7,8]. Reasons to stop drinking could be related to disease prevalence. A worse profile of risk factors and disease prevalence at baseline in ex-drinkers has been held responsible for the observed higher risk of not only coronary heart disease, but also of stroke[8]. In the present study, the differences in risk factor levels between never- and ex-drinkers, however, were small and not significant. When we adjusted for the risk

factors and prevalence of myocardial infarction, angina pectoris and cancer at baseline in 1970, the 26% lower risk of stroke for ex-drinkers compared with never-drinkers increased to 31%. Therefore, our findings do not support the hypothesis that the worse health status of ex-drinkers might artificially increase the risk of stroke in the category of non-drinkers when they are analyzed together with never-drinkers, as is done in most cohort studies.

Since in the present study similar relative risks were observed for the always drinkers and the beginners, and studies on current alcohol levels report comparable results, the data suggest that current alcohol intake is as important as long-term alcohol intake. This is compatible with one of the presumed biological mechanisms by which alcohol consumption might affect cardiovascular risk, which is by inhibition of platelet aggregation[26,27]. It has been shown that alcohol inhibits the induction of platelet aggregation by adenosine diphosphate and collagen[27] . Besides, alcohol inhibits release of thromboxane A_2 and stimulates fibrinolysis[28].

The inverse association of moderate alcohol consumption with cardiovascular diseases has also been explained by an increase of the total HDL serum cholesterol level by alcohol, especially of the HDL_{-2} and HDL_{-3} subfractions, explaining about 50% of the protective effect of alcohol[29]. Although some studies reported a protective effect of HDL cholesterol on stroke incidence[30], more studies on this subject are needed.

Moderate to light alcohol consumption has been reported to elevate blood pressure[31]. In the present study, blood pressure levels were similar in all alcohol consumption categories, probably due to the low level of alcohol consumption. No change occurred in the risk ratio's for alcohol consumption when the average systolic blood pressure, which is a strong predictor of stroke incidence[32], was included in the Cox models. Therefore, systolic blood pressure as an intermediate in the relationship between alcohol consumption and stroke incidence may not explain our observations.

These combined effects of alcohol on platelet aggregation, HDL cholesterol and blood pressure on atherosclerotic complications may not provide the complete biological mechanism. Recently a direct and independent inverse association of moderate alcohol consumption with atherosclerosis was reported[33]. This association remained after correction from blood pressure, HDL serum cholesterol, hemostatic factors and other cardiovascular risk factors.

We conclude that alcohol consumption was significantly correlated with higher fish and fat intake, a lower intake of carbohydrates and heavier cigarette smoking. After adjustment for potential confounders a reduction of 34% in stroke risk was observed for

moderate alcohol consumers compared to never-drinkers, although it was not statistically significant. Our findings could not support the hypothesis that a worse health status of ex-drinkers is responsible for the increased risk of stroke reported in non-drinkers.

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Chapter 5

FISH CONSUMPTION AND RISK OF STROKE

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Abstract

Background. A low to moderate average daily fish consumption has been reported to convey protection against coronary heart disease incidence and mortality. Currently there is no information about its effect on stroke risk.

Methods. In 1960, 1965 and 1970 cross-check dietary histories were obtained in 552 men aged 50 to 69 years in 1970 in the town of Zutphen, The Netherlands. The association between fish consumption and stroke incidence in the period 1970-1985 was assessed by Cox proportional hazards models. Adjustments were made for confounding by age, systolic blood pressure, cigarette smoking, serum total cholesterol, energy intake, alcohol consumption and prescribed diet.

Results. The mean fish consumption in 1970 was 17.9 grams/day. Men who consumed more than 20 grams of fish per day in 1970 had a reduced risk of stroke compared to those who consumed less fish. The relative risk (RR) amounted to 0.49 (95% CI 0.24-0.99), and did not change after adjustment for potential confounders. Among the 301 men who always reported fish consumption between 1960 and 1970 fewer strokes occurred than among the men who changed fish consumption habits between 1960 and 1970 or did not consume fish at all (RR 0.63; 95% CI 0.34-1.16).

Conclusions. These results suggest that consumption of at least one portion of fish per week may be associated with a reduced stroke incidence.

Introduction

Stroke incidence on a haemorrhagic basis is higher among Greenland Eskimos compared with Danes[1]. A prolonged bleeding time due to a high intake of N-3 polyunsaturated fatty acids could be an explanation for this phenomenon[1,2]. The effect of a small amount of these fatty acids, as may be derived from low to moderate daily fish consumption is, however, not known.

Compared to a group of subjects using no fish, the average daily intake of a small amount of fish was shown to be protective for coronary heart disease mortality in a number of prospective studies, including the Zutphen Study[3-6]. It can therefore be hypothesized that an low to moderate average daily fish intake is also protective for thrombotic stroke. This hypothesis was tested in the Zutphen Study, a long-term follow-up study in which dietary data have been collected repeatedly.

Methods

Study population

Since 1960, a longitudinal investigation of risk factors for chronic diseases has been carried out among middle-aged men from the town of Zutphen in the Netherlands. The Zutphen Study is the Dutch contribution to the Seven Countries Study[7-9]. In 1960, a random sample of 1,088 men was drawn from a total of 2,450 inhabitants born between 1900 and 1919. A cohort of 872 men aged 40 to 59 years participated in both the medical examination and the dietary survey. Information on dietary habits, risk factors and disease incidence was collected repeatedly over the period 1960-1985.

For the present purpose, the dietary intake in the period 1960-1970 was investigated in relation to the incidence of stroke during the follow-up period 1970-1985. Of the 755 men who were alive and free of stroke in 1970, 172 men were excluded because they had not participated in the dietary survey in 1960, 1965 or 1970. Thirty-one of the remaining 583 men were excluded because data on confounding variables were lacking, leaving 552 men for the final analyses.

Dietary methods

In 1960, 1965 and 1970, food intake data were collected by the cross-check dietary history method[10], adapted to the Dutch situation[11]. This method provides information about the usual pattern of food consumption in the 6 to 12 months prior to the interview. Each

participant was interviewed together with his wife about his usual food consumption patterns on weekdays and weekends. Also the usual food consumption away from home was asked for. The estimated average consumption of foods during a day or a week was checked against the quantities of food bought per week for the whole family.

The food consumption during a typical weekday was calculated on the basis of this information. The interviews were carried out in the months May, June and July of each year, and were taken by trained dietitians, six in 1960, six in 1965, and nine in 1970. The dietitians also recorded any special diet of the participant, prescribed by his general practitioner or specialist. An extended computerized version of the Netherlandsfood table database, containing the amounts of energy and nutrients in Dutch foods between 1960 and 1970, was used to convert the food intake data into nutrients and energy[12] .

Medical examinations

Blood pressure was measured with an ordinary mercury sphygmomanometer at the end of the physical examination at the right arm with the subject in the supine position, according to the protocol of the Seven Countries Study[7] . Between 1960 and 1970 blood pressure was measured annually. For each subject, the average systolic blood pressure was calculated as the sum of the annual systolic blood pressure readings in the period 1960-1970 divided by the number of measurements, provided that a total of at least four readings were taken during this period. At least one of these readings had to have been taken in the last five years prior to or in 1970.

Serum cholesterol determinations were carried out according to the method of Abell-Kendall in the period 1960-1965[13] and the method of Zlatkis[14] between 1966 and 1970. The latter provides values equivalent to the Abell-Kendall method. The average serum cholesterol level over the period 1960-1970 was calculated in the same way as the average systolic blood pressure. Information on cigarette smoking was collected in a standardized way[7]. Exposure to smoke was quantified by multiplying the amount of cigarettes smoked with the duration of cigarette smoking.

Follow-up

During follow up, the men were medically examined annually between 1960 and 1973, in 1977/1978 and in 1985. Questionnaires about their health status were filled in by the men in 1980 and 1982. No one was lost to follow up. All morbidity and mortality data collected in the period 1960-1985 were coded by one physician in a standardized way in

1986. Stroke was defined as a sudden onset of neurological paralysis of more than 24 hours duration or leading to death. All diagnoses of stroke were confirmed in a letter from a neurologist of the hospital of Zutphen to the general practitioner. Fatal strokes were coded according to the eighth revision of the International Classification of Diseases (ICD-8 codes 430-438). Data on the incidence of stroke, being either the first non-fatal or fatal event within the study period, are presented here.

Statistical analyses

Statistical analyses were carried out with the SAS statistical package version 6 on a DEC 5000 minicomputer[15]. The fish consumers were initially divided into three categories of fish intake: no fish, low fish consumption (20 grams of fish per day or less) and high fish consumption (more than 20 grams of fish per day). The 'no fish' and the 'low fish' categories did not differ from each other in stroke survival analysis. In the final analyses these two groups were taken together. The 301 subjects who reported to consume fish at each survey were considered as subjects who always ate fish during 1960-1970. The 39 subjects who did not consume fish during 1960-1970 were grouped together with the subjects who changed their fish consumption habits, to a total of 251 subjects.

Student's t-test was used to compare levels of risk factors and nutrient intake by incidence of stroke and by fish consumption. In case of skewed variables the Wilcoxon rank statistic was used. The relationship between fish consumption and the risk of stroke was assessed by survival analysis, using the Kaplan-Meier product limit estimator and the Cox proportional hazards model[16,17]. Additional adjustments for potential confounding effects of age, systolic blood pressure, serum cholesterol, cigarette smoking, intake of energy and vegetable protein, alcohol consumption and prescribed diet were carried out. Because the average systolic blood pressure had previously been shown to be the strongest predictor of stroke[18], this variable was used as covariate instead of the single observed systolic blood pressure in 1970. So was done with the average of serum total cholesterol over the period 1960-1970 and life long smoking habits. All p-values were derived from two-tailed tests of significance.

Results

During the 15-year follow-up period, 42 first strokes occurred among the 552 men, resulting in an incidence rate of 6.65/1000 person-years. The age in 1970 and the average systolic blood pressure between 1960 and 1970 were significantly higher for the men who

developed stroke compared to the men who remained free of stroke (table 1). Fish consumption in 1970 was significantly lower among the future stroke cases (table 2). No other significant differences in macronutrient intake or in percentage on prescribed diet between incident cases of stroke and men without stroke were observed.

Table 1. Risk factors in 552 men aged 50-69 yr in 1970 in relation to 15-yr incidence of stroke. The Zutphen Study.

Risk factor	No Stroke (n=510)	Stroke (n=42)
Age (yr)	59.3 ± 5.3	61.9 ± 5.5**
Systolic BP 1960-1970 (mmHg)	142.2 ± 14.1	148.9 ± 20.1*
Total cholesterol 1960-1970 (mmol/l)	6.1 ± 0.9	6.1 ± 1.0
Cigarette years till 1970 (packyears)	438 ±327	433 ±293

* $p<0.05$, ** $p<0.01$

Comparing the 393 men who consumed fish in 1970 with non-fish eaters, no differences in risk factors were observed (table 3). Concerning dietary factors, fish consumption was significantly associated with the intake of energy, animal protein, polyunsaturated fatty acids and linoleic acid. Significant inverse associations with the intake of vegetable protein and dietary cholesterol were observed. These nutrients were not associated with the incidence of stroke.

The 220 men who consumed more than 20 grams of fish per day in 1970 had a significantly lower risk of stroke compared to those who ate less fish (relative risk (RR): 0.49; 95% confidence interval (CI): 0.24-0.99, $p=0.048$, table 4). Figure 1 shows the survival curves for these men. After adjustment for confounding by age, average systolic blood pressure, average serum cholesterol, cigarette smoking, energy intake, alcohol consumption and prescribed diet, the relative risk did not substantially change, although the result just failed to reach statistical significance ($p=0.052$). Additional analysis showed that the results were also unaffected by body mass index and history of myocardial infarction and diabetes mellitus.

Spearman correlation coefficients between fish consumption in 1960, 1965 and 1970 decreased with increasing time between dietary surveys, varying from 0.41 ($p<0.001$) for 1960 and 1965 to 0.32 ($p<0.001$) for 1960 and 1970. As the survival curves in figure 2

illustrate, the 301 men who always ate fish between 1960 and 1970 had a reduced risk of stroke compared with the 251 men who either changed their fish eating habits or never ate fish between 1960 and 1970. The relative risk was 0.63, and increased to 0.71 after adjustment for potential confounders (table 4).

Table 2. Fish consumption and other dietary variables in 552 men aged 50-69 years in 1970 in relation to 15-year incidence of stroke. The Zutphen Study.

Daily dietary intake	No Stroke (n=510)	Stroke (n=42)
Fish consumption (g)	18.3 ± 19.8	12.8 ± 12.3*
Energy intake (MJ)	11.0 ± 2.2	10.4 ± 2.2
Total protein (en%)	12.4 ± 1.9	12.3 ± 1.5
Animal protein	8.3 ± 1.9	8.4 ± 1.8
Vegetable protein	4.1 ± 0.8	4.0 ± 0.9
Total fat (en%)	41.5 ± 5.3	42.8 ± 6.1
Saturated fatty acids	16.9 ± 2.9	17.3 ± 3.4
Monounsaturated fatty acids	17.6 ± 2.8	18.4 ± 3.2
Polyunsaturated fatty acids	6.8 ± 2.2	7.0 ± 2.0
Linoleic acid	5.9 ± 2.1	5.9 ± 1.9
Total carbohydrates (en%)	42.8 ± 6.0	42.0 ± 6.0
Oligosaccharides	21.1 ± 5.7	20.8 ± 6.1
Polysaccharides	21.7 ± 4.4	21.2 ± 5.1
Alcohol consumption (en%)	2.7 ± 4.0	2.3 ± 3.3
Dietary cholesterol (mg/MJ)	38.6 ± 15.3	36.2 ± 13.2
Prescibed diet (%)	11.0	7.1

* $p<0.05$

Discussion

In the present study, men who consumed more than 20 grams of fish per day had a lower risk of stroke than men who ate less fish. This association remained essentially

unchanged after adjustment for potential confounders.

Table 3. Baseline characteristics of fish consumers and non-fish consumers in 552 men aged 50-69 yr in 1970. The Zutphen Study.

Characteristic	No fish n=159	Fish n=393
Age (yr)	59.6 ± 5.4	59.5 ± 5.3
Systolic BP 1960-1970 (mm Hg)	142.4 ± 15.0	142.8 ± 14.7
Total cholesterol 1960-1970(mmol/l)	6.2 ± 1.1	6.1 ± 0.9
Cigarette-years until 1970	429 ± 329	441 ±323
Energy intake (MJ)	10.5 ± 2.3	11.1 ± 2.2**
Total protein (en%)	12.2 ± 2.0	12.5 ± 1.8
Animal protein	8.0 ± 1.9	8.4 ± 1.9*
Vegetable protein	4.2 ± 0.9	4.1 ± 0.8*
Total fat (en%)	41.4 ± 5.9	41.8 ± 5.2
Saturated fatty acids	17.1 ± 3.2	16.9 ± 2.8
Monounsaturated fatty acids	17.5 ± 3.1	17.7 ± 2.8
Polyunsaturated fatty acids	6.4 ± 2.0	7.0 ± 2.2**
Linoleic acid	5.5 ± 1.9	6.0 ± 2.2*
Total carbohydrates (en%)	43.0 ± 6.7	42.6 ± 5.6
Oligosaccharides	20.8 ± 6.5	21.2 ± 5.5
Polysaccharides	22.1 ± 4.8	21.4 ± 4.3
Alcohol intake (en%)	2.8 ± 5.4	2.6 ± 3.2
Dietary cholesterol (mg/MJ)	37.2 ± 16.2	38.9 ± 14.6*
Prescribed diet (%)	13.8	9.4

* $p<0.05$, ** $p<0.01$

Besides the data on fish consumption in 1970 also information on fish consumption in 1965 and 1960 was available. Subjects who always ate fish between 1960 and 1970 had a lower risk of stroke than subjects who either changed their fish consumption patterns or

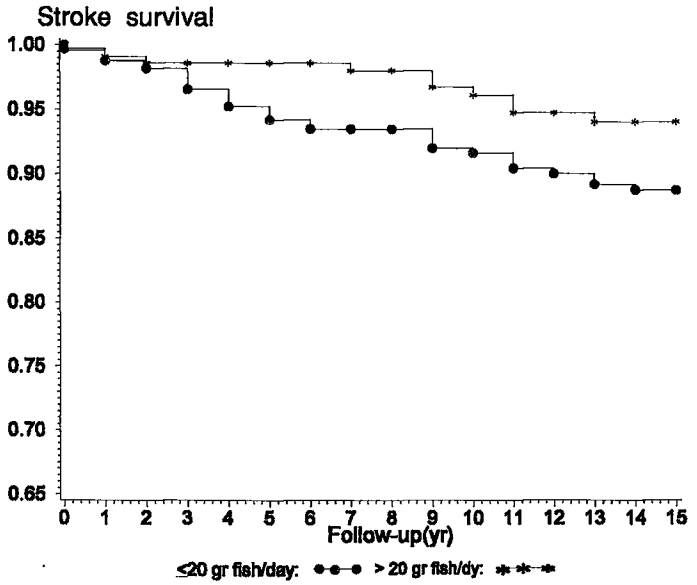

Figure 1. 15-Yr stroke incidence by categories of fish consumption in 1970 in 552 men aged 50-69 yr. The Zutphen Study.

used no fish during this period, but this difference was not statistically significant using a two-sided test. Beforehand, it was hypothesized that the average fish consumption was a better predictor of stroke risk than the single year fish consumption, due to reduction of random measurement error[19]. This would have been comparable to what we had observed for the association between blood pressure and stroke [18]. However, the association between fish consumption in 1970 and 15-yr stroke risk was stronger. This suggests a larger effect of the more recent (1970) fish consumption than of the longer habitual (1960-1970) fish consumption on the incidence of stroke, which may be plausible in the light of the etiology of the disease.

To our knowledge, this is the first time that an inverse relationship between fish consumption and stroke incidence has been reported. These results are, however, in accordance with those from other prospective studies reporting an inverse association between fish consumption and coronary heart disease, including our own cohort [3-5]. In

those studies, an inverse dose-response relationship was found between consumption of small amounts of fish and long-term mortality form coronary heart disease. In Eskimos however, who consume large amounts of seafood, a higher incidence of haemorrhagic strokes was reported compared with Danes[1]. It may therefore be hypothesized that small amounts of fish intake may reduce the incidence of coronary heart disease and the ischemic subtypes of stroke, whereas consumption of large amounts of seafood may increase haemorrhagic subtypes of stroke. Unfortunately, no information on the type of stroke is available for the Zutphen men. However, an extensive study showed that 82% of the strokes in the Netherlandsis thrombotic[20], and it is very likely that this was also the case in the Zutphen Study.

Table 4. Crude and adjusted relative risks (RR) for stroke incidence for different fish intake estimates in 552 men aged 50-69 years in 1970 in Zutphen.

	N	Fish (g/dy)	CRUDE RR	CRUDE 95%CL	ADJUSTED* RR	ADJUSTED* 95%CL
Fish consumption in 1970(g/dy)						
≤20	332	6.3	1.00	-	1.00	-
>20	220	35.4	0.49	0.24-0.99	0.49	0.24-1.01
Fish consumption 1960-1970						
Not always	251	7.5#	1.00	-	1.00	-
Always	301	26.5	0.63	0.34-1.16	0.71	0.38-1.33

* Relative risk adjusted for age, average systolic blood pressure 1960-1970, average serum cholesterol 1960-1970, cigarette smoking until 1970, and intake of energy and vegetable protein, alcohol consumption and prescribed diet in 1970.

\# Fish consumption in 1970 (grams/day); average fish consumption 1960-1970 10.0 and 27.4 g/day respectively

Experimental studies in vitro and in humans showed that N-3 polyunsaturated fatty acids, of which especially eicosapentaenoic acid and docosahexaenoic acid are present in fish, reduce the formation of thromboxane A_2 [21,22]. This leads to a reduced aggregability of blood platelets [21,22]. In addition, eicosapentaenoic acid can be transformed to thromboxane

A_3, which does not have aggregating abilities, and competes with thromboxane A_2 in vessel walls[21-23] . Besides, it also increases the synthesis of the antithrombotic agent PGI_3 [21-23]. Thromboxane A_2 is a mediator of thrombosis and vasospasm occurring in stroke and myocardial infarction[23]. Reduction of the thromboxane A_2 production by small amounts of aspirin has been shown to lower the risk of stroke and myocardial infarction [24-28]. Therefore, a protective effect of fish consumption on thrombotic stroke and coronary heart disease through this mechanism is conceivable. An effect of fish intake on thrombotic processes is supported by the results from a secondary intervention study among myocardial infarction patients [29].

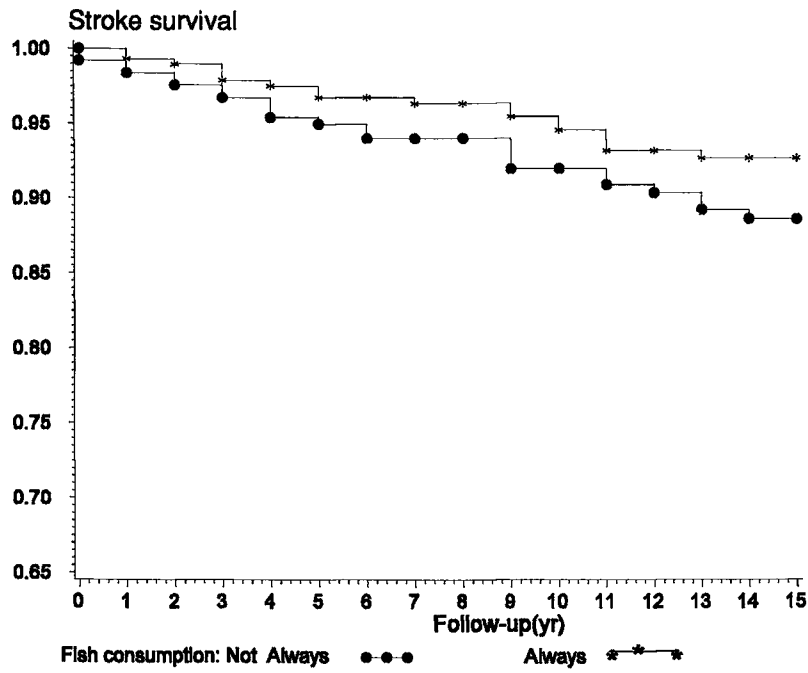

Figure 2. 15-Yr stroke incidence by ten-year habitual fish consumption in 552 men aged 50-69 yr. The Zutphen Study.

Other mechanisms may also play a role. Even small amounts of fish intake increase the concentration of N-3 polyunsaturated fatty acids in phospholipids[23,26,30,31]. This may lead to altered fluidity and activity of membrane-associated enzymes and receptors, resulting in protection of the vessel wall against ischemic damage[23]. N-3 polyunsaturated fatty acids have been shown to reduce the plasma lipids, especially triglycerides and VLDL lipoproteins[23]. It is, however, not very likely that this mechanism is of importance in stroke, since in general the association between serum triglycerides and stroke risk is not very strong. It has also been suggested that fish (oils) may lower blood pressure[32]. As also shown in the present study, blood pressure is one of the most important risks for stroke[18]. However, in intervention studies large amounts of fish oils are needed to achieve blood pressure lowering[32]. In the present study fish consumption was not associated with blood pressure. Thus, it is unlikely that blood pressure may play a role in explaining the protective effect of a small amount of fish on stroke incidence. Finally, it can be hypothesized that the effect may be partly caused by effects of fish intake on insulin resistance and glucose tolerance[33,34], which are also independent risk factors for stroke[35]. The present results were, however, not affected by adjustments for presence of diabetes mellitus, and the possible intermediate pathway by carbohydrate metabolism remains to be studied.

The results of the present study suggest that an inverse relationship exists between fish consumption and incidence of stroke. The possible protective effect of low to moderate fish consumption in both stroke and coronary heart disease is intriguing. More research is needed on mechanisms explaining this inverse relationship. With respect to prevention of cardiovascular disease, evidence is accumulating that the consumption of at least one portion of fish per week may have a protective effect.

Acknowledgements

The authors are indebted to the many people who cooperated in this longitudinal study, including the field work team in Zutphen, especially E.B. Bosschieter, MD; the late professor F.S.P. van Buchem, MD, PhD, the principal investigator of the study in the period 1960-1975; professor A.C. Arntzenius, MD, PhD, for his advice on coding of the morbidity data; M. Drijver, MD, for coding the morbidity data; and C. de Lezenne Coulander, MSc, for database management.

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Chapter 6

DIETARY FLAVONOIDS, ANTIOXIDANT VITAMINS AND INCIDENCE OF STROKE

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Abstract

Background. Epidemiologic studies suggested that consumption of fruit and vegetables may protect against stroke. The hypothesis that dietary antioxidant vitamins and flavonoids account for this observation is investigated in a prospective study.

Methods. A cohort of 552 men aged 50-69 years was examined in 1970 and followed for 15 years. Average nutrient and food intake was calculated from cross-check dietary histories taken in 1960, 1965 and 1970. The association between (non)nutritive antioxidants, selected foods and stroke incidence was assessed by Cox proportional hazards regression analysis. Adjustment was made for confounding by age, systolic blood pressure, serum cholesterol, cigarette smoking, energy intake and consumption of fish and alcohol.

Results. Forty-two cases of first fatal or non-fatal stroke were documented. Dietary flavonoids (mainly quercetin) were inversely associated with stroke incidence after adjustment for potential confounders, including antioxidant vitamins. The relative risk of the highest vs the lowest quartile (28.6 mg/dy or more vs less than 18.3 mg/dy) was 0.27 (95 % CI 0.11-0.70). A lower stroke risk was also observed for the highest quartile of beta-carotene (RR=0.54, 95% CI 0.22-1.33). The intake of vitamin C and E was not associated with stroke risk. Black tea contributed about 70% to flavonoid intake. The relative risk for a daily consumption of 4.7 cups or more of tea vs less than 2.6 cups of tea was 0.31 (95% CI 0.12-0.84).

Conclusions. The habitual intake of flavonoids and its major source tea may protect against stroke.

Introduction

Population data from the United Kingdom suggested that the decline in stroke mortality during the last decades may be due to an increase in the consumption of fruit and vegetables[1]. In a prospective study in Norway a high intake of fresh fruit and vegetables was associated with a low stroke mortality[2]. Results of the Rancho Bernardo Study in the US have suggested that the intake of potassium may be responsible for this observation[3].

Besides minerals, fruit and vegetables are important sources of antioxidants, e.g. beta-carotene, vitamin C and flavonoids[4,5]. Antioxidants prevent LDL-oxidation and may therefore reduce the occurrence of coronary heart disease and ischemic stroke[6-10]. Information from prospective studies on stroke is limited but suggests that low levels of plasma beta-carotene may be associated with a higher stroke risk[9].

Flavonoids are non-nutritive compounds with antioxidant properties, occurring in plant foods[4,5]. Recently we have shown that the intake of flavonoids was inversely associated with the risk of coronary heart disease in elderly men[10]. We investigated the hypothesis that the intake of antioxidants, including flavonoids, is inversely associated with the risk of stroke. For this purpose we used data from a cohort of middle-aged men of which information from repeated dietary surveys was available.

Methods

Study population

Since 1960, a longitudinal investigation of risk factors for chronic diseases has been carried out among middle-aged men from the town of Zutphen in the Netherlands. The Zutphen Study is the Dutch contribution to the Seven Countries Study[11,12]. In 1960 a random sample of 1,088 men born between 1900 and 1919 was drawn out of a total of 2,450. A cohort of 872 men from 40 to 59 years participated in both the medical examination and the dietary survey. From the 755 men who were alive and free of stroke in 1970, 170 were excluded because they did not participate in the dietary survey in 1960, 1965, or 1970. Thirty-one of the remaining 583 men were excluded because data on confounding variables were lacking, leaving 552 men for the final analyses.

Dietary intake

Food intake data were collected in 1960, 1965 and 1970 by the cross-check dietary history method[13], adapted to the Dutch situation[14]. This method provides information about the usual pattern of food consumption in the 6 to 12 months prior to the

interview. Each participant was interviewed together with his wife about his usual food consumption patterns on weekdays and weekends. The participant was also interviewed about his usual food consumption away from home. The estimated average consumption of foods during a day or a week was checked with the quantities of foods bought per week for the whole family. The food consumption during a typical weekday was calculated on the basis of this information. The interviews were carried out by trained dietitians in the months May, June and July. The dietitians also recorded any special diet of the participant, prescribed by his general practitioner or specialist. An extended computerized version of the Netherlands food table, containing the energy and nutrient composition of Dutch foods in the period 1960-1970, was used to convert the food intake data into energy and nutrients, including vitamin C[14]. The food table was updated in 1993 for beta-carotene, vitamin E (alpha-tocopherol equivalents) and flavonoid data. Flavonoids are defined as the sum of quercetin, kaempferol, myricetin, luteolin and apigenin. A recently developed and validated HPLC method was used to determine the flavonoid content of plant foods and drinks, e.g. fruit, vegetables, black tea and wine[15].

Risk factors

Blood pressure was measured with an ordinary mercury sphygmomanometer at the end of the physical examination on the right arm with the men in supine position, according to the protocol of the Seven Countries Study[11]. Between 1960 and 1970 the blood pressure was measured yearly. The average systolic blood pressure was calculated as the sum of the systolic blood pressure readings from 1960 to 1970 divided by the number of measurements, provided that the subject had a total of at least four readings during this period. At least one of these readings should have been taken in the last five years prior to or in 1970.

Information on cigarette smoking was collected in a standardized way[11]. Exposure to smoke was quantified by multiplying the amount of cigarettes smoked by the duration of cigarette smoking. Serum cholesterol determinations were carried out according to the method of Abell-Kendall in the period 1960-1965[16], and the method of Zlatkis[17] between 1966 and 1970, also providing values equivalent to the Abell-Kendall method. The average total serum cholesterol level over the period 1960-1970 was calculated in the same way as the average systolic blood pressure.

Follow-up

During follow-up, the men were medically examined yearly between 1960 and 1973, in 1977/1978, and in 1985. Questionnaires about their health status were filled in by the men in 1980 and 1982. No one was lost to follow-up. All morbidity and mortality data collected in the period 1960-1985 were coded by one physician in a standardized way in 1986. Stroke was defined as a sudden onset of neurological paralyses, lasting longer than 24 hours or leading to death. All stroke diagnoses were confirmed in letters from a neurologist or internist in the hospital of Zutphen to the general practitioner of the participant. Fatal strokes were coded according to the eighth revision of the International Classification of Diseases (ICD-8 codes 430-438). Data on stroke incidence being either the first non-fatal or fatal event, are presented here.

Statistical Analysis

Statistical analyses were performed using the SAS statistical package[18]. To reduce within-person variation information of the repeated dietary surveys was used. The long-term consumption of beta-carotene, vitamin C, vitamin E, flavonoids and their major food sources was estimated by calculating the average intake of 1960, 1965 and 1970 for each item. The intake of these antioxidants in 1970 did not differ from the average intake in 1960, 1965 and 1970. However, the standard deviation of the average intake was smaller, indicating a reduced intra-individual variation of nutrient intake data, e.g. the intake (±standard deviation) of flavonoids in 1970 was 22.0 (± 9.1) mg/dy compared to the average of 23.5 (±7.6) mg/dy in 1960, 1965 and 1970.

Men were divided into quartiles of antioxidant and food intake. The second and third quartiles were combined and referred to as the medium intake group. Risk for stroke incidence was assessed by survival analysis, using the Kaplan-Meier product limit estimator and Cox proportional hazards models[19]. Previously the 10-year average systolic blood pressure was shown to be a strong predictor of the stroke risk, while fish consumption was inversely associated with stroke incidence[20,21]. Therefore these variables were added to multivariate Cox models adjusting also for age, cigarette smoking, serum cholesterol, alcohol consumption and energy intake.

Results

During 15-years of follow-up 42 first fatal or non-fatal strokes occurred in 552 men. The average intake of beta-carotene, vitamin C and vitamin E were lower in stroke

cases compared with non-cases, but these differences did not reach statistical significance (table 1). Men with a high intake of beta-carotene over the period 1960-1970 had a lower risk of stroke compared with men in the lowest quartile (RR=0.54, 95 percent confidence interval, 0.22 to 1.33, table 2). This association was independent of flavonoid intake. The intake of vitamin C and E was not associated with stroke risk. Adjustment for potential confounders did not influence these results.

Table 1. Characteristics of 552 men aged 50-69 years in 1970 in relation to 15-year incidence of stroke. The Zutphen Study.

Characteristic	No Stroke (n=510)	Stroke (n=42)
Age 1970 (yr)	59.3 ± 5.3	61.9 ± 5.5**
Average SBP 1960-1970(mmHg)	142.2 ± 14.1	148.9 ± 20.1*
Average serum cholesterol 1960-70(mmol/l)	6.1 ± 0.9	6.1 ± 1.0
Cigarette/day x years till 1970 (packyears)	437.7 ±327.2	433.3 ± 292.7
Alcohol consumption 1970 (g/dy)	9.9 ± 14.0	7.7 ± 10.9
Fish consumption 1970 (g/dy)	18.3 ± 19.8	12.8 ± 12.3*
Average total energy intake 1960-1970 (MJ)	12.2 ± 2.1	11.5 ± 1.9
Average antioxidant intake 1960-1970 (mg/dy)		
B-Carotene	1.2 ± 0.3	1.1 ± 0.3
Vitamin C	93.5 ± 30.2	86.0 ± 26.1
Vitamin E	17.9 ± 4.7	17.4 ± 4.3
Flavonoids	23.8 ± 7.6	20.7 ± 7.7*
Average food consumption 1960-1970 (g/dy)		
Solid fruit	77.2 ± 53.9	57.4 ± 42.6*
Citrus fruit	64.3 ± 47.4	58.0 ± 62.6
Vegetables	187.4 ± 48.9	178.4 ± 44.4
Tea	472.0 ±200.6	409.4 ± 209.5*

SBP Systolic blood pressure
* $p \leq 0.05$
** $p < 0.01$

Table 2. Crude and adjusted relative risks for 15-year stroke incidence to intake of antioxidants in 552 men aged 50-69 years in 1970 in Zutphen.

VARIABLE			CRUDE		ADJUSTED*	
Category	N(cases)	Mean intake	RR	95%CI	RR	95%CI
Average beta-carotene intake 1960-1970 (mg/dy)						
<1.01	135(15)	0.86	1.00		1.00	
1.01-1.36	280(20)	1.19	0.66	0.34-1.28	0.69	0.35-1.36
≥1.37	137(7)	1.58	0.51	0.21-1.25	0.54	0.22-1.33
			p_{trend}=0.12		p_{trend}=0.15	
Average vitamin C intake 1960-70 (mg/dy)						
<74	137(13)	59.3	1.00		1.00	
74-107.6	277(16)	90.5	0.60	0.29-1.26	0.66	0.32-1.40
≥107.7	138(13)	131.2	1.04	0.48-2.25	1.21	0.55-2.66
			p_{trend}=0.93		p_{trend}=0.67	
Average vitamin E intake 1960-70 (mg/dy)						
<14.4	138(8)	6.0	1.00		1.00	
14.4-21.2	276(26)	8.0	1.73	0.79-3.84	1.99	0.88-4.52
≥21.3	138(8)	10.7	1.11	0.42-2.95	1.64	0.54-4.97
			p_{trend}=0.81		p_{trend}=0.30	
Average flavonoid intake 1960-1970 (mg/dy)						
<18.3	139(18)	14.2	1.00		1.00	
18.3-28.5	270(18)	23.2	0.50	0.26-0.96	0.46	0.24-0.90
≥28.6	143(6)	33.3	0.33	0.13-0.82	0.27	0.11-0.70
			p_{trend}=0.009		p_{trend}=0.004	

* Adjusted for age, average systolic blood pressure, serum cholesterol, energy intake, lifetime cigarette smoking exposure until 1970, fish consumption in 1970 and alcohol consumption habits during the period 1960-1970. All averages are over the period 1960-1970.

RR relative risk

CI confidence interval.

The intake of flavonoids in 1970 was 19.8±9.2 mg/dy in stroke cases compared to 22.2±9.1 mg/dy in non-cases (p=0.10). The difference in flavonoid intake between stroke cases and non-cases was statistically significant when the average flavonoid intake over the period 1960-1970 was used (table 1). A dose-dependent inverse association between average flavonoid intake over the period 1960-1970 and stroke risk was noted (table 2). After adjustment for confounders men in the highest quartile had a relative risk of 0.27 (95 percent confidence interval, 0.11 to 0.70) compared with those in the lowest quartile. These results were essentially unchanged after additional adjustment for vitamin C, vitamin E and beta-carotene. Also exclusion of 40 men with a history of myocardial infarction in 1970 did not influence the results (RR=0.25, 95 percent confidence interval, 0.09 to 0.69). The survival curves showed a long-term effect of flavonoid intake, starting early in the follow-up period (figure 1). A comparable inverse association with stroke risk was observed when the men who always (1960, 1965 and 1970) used 28.6 mg/dy or more of flavonoids were compared with those who always used less than 18.3 mg/dy of flavonoids (RR=0.23, 95 percent confidence interval, 0.06 to 0.85).

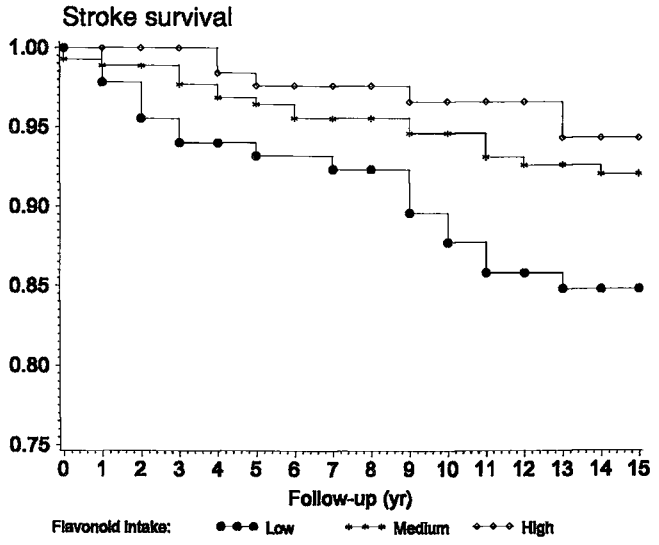

Figure 1. Relation between average flavonoid intake and 15-year stroke incidence in 552 men aged 50-69 years in 1970. The Zutphen Study.

Table 3. Crude and adjusted relative risks for 15-year stroke incidence to long-term intake of antioxidants in 552 men aged 50-69 years in 1970 in Zutphen.

VARIABLE			CRUDE		ADJUSTED*	
Category	N(cases)	Mean intake	RR	95%CI	RR	95%CI
Average solid fruit consumption 1960-1970 (g/dy)						
<41	137(14)	21.6	1.00		1.00	
41-99.7	277(21)	67.0	0.73	0.37-1.43	0.83	0.41-1.66
≥99.8	138(7)	147.1	0.49	0.20-1.21	0.52	0.21-1.31
			p_{trend}=0.12		p_{trend}=0.17	
Average citrus fruit consumption 1960-1970 (g/dy)						
<28	137(12)	11.2	1.00		1.00	
28-91.6	278(20)	58.9	0.79	0.38-1.61	0.91	0.44-1.89
≥91.7	137(10)	126.3	0.84	0.36-1.94	0.93	0.39-2.22
			p_{trend}=0.67		p_{trend}=0.86	
Average vegetable consumption 1960-1970 (g/dy)						
<153.2	138(13)	128.1	1.00		1.00	
153.2-215.7	276(20)	184.4	0.78	0.39-1.57	0.75	0.37-1.51
≥215.8	138(9)	249.9	0.76	0.32-1.78	0.82	0.35-1.94
			p_{trend}=0.50		p_{trend} =0.60	
Average tea consumption 1960-1970 (g/dy)						
<330	120(14)	207.8	1.00		1.00	
330-586.6	302(22)	453.1	0.60	0.31-1.18	0.52	0.26-1.05
≥586.7	130(6)	739.5	0.38	0.15-0.99	0.31	0.12-0.84
			p_{trend}=0.04		p_{trend}=0.02	

* Adjusted for age, average systolic blood pressure, serum cholesterol, energy intake, lifetime cigarette smoking exposure until 1970, fish consumption in 1970 and alcohol consumption habits during the period 1960-1970. All averages are over the period 1960-1970.

RR Relative risk.

CI Confidence interval.

The intake of beta-carotene was strongly correlated with consumption of vegetables (r=0.90, p<0.001), while for vitamin C intake strong correlations were found with the consumption of citrus fruit (r=0.88, p<0.001) and vegetables (r=0.48, p<0.001). The intake of flavonoids correlated strongly with consumption of tea (r=0.94, p<0.001) and solid fruit (r=0.31, p<0.001). Tea contributed about 70% to flavonoid intake and apples about 10%. An inverse association between tea consumption in the period 1960-1970 and stroke risk was observed (table 3). Men who on average drank 4.7 or more cups of tea per day (highest quartile) had an adjusted relative risk of 0.31 (95 percent confidence interval, 0.12 to 0.84) compared to those who on average drank less than 2.6 cups of tea per day (lowest quartile). The adjusted relative risks and trends remained unaffected when average solid fruit consumption was taken into account. Also when the 40 men with a history of myocardial infarction in 1970 were excluded from the analyses the association with tea did not change (RR=0.28, 95 percent confidence interval, 0.10 to 0.81).

Solid fruit consumption was significantly lower in stroke cases compared with non-cases (table 1). Men in the highest quartile of solid fruit consumption had a lower stroke risk compared with men who had a low solid fruit consumption (RR=0.52, 95 percent confidence interval, 0.21 to 1.31, table 3). No associations were observed between the average citrus fruit and vegetable consumption over the period 1960-1970 and stroke incidence.

Discussion

We investigated the association of long-term intake of different antioxidants and their food sources with stroke incidence. Although no data on stroke subtype are available in our study, other population based studies have reported that ischemic strokes are the predominant subtype of strokes in The Netherlands[22]. We observed a siginificant inverse association between the long-term intake of flavonoid antioxidants and stroke incidence. Men with a high intake of flavonoids had a 73% lower risk of stroke during 15 years of follow-up compared with those on a low flavonoid intake. The intake of beta-carotene was, independent from flavonoid intake, associated with a 46% lower stroke risk, although this was not statistically significant. No association of either vitamin C or E intake with stroke risk was observed.

We used the cross-check dietary history method to obtain information on food consumption[13,14]. The validity and the reproducibility of this method are well established[23,24].

To further enhance the power of the study we used three repeated measurements on each individual, by averaging the intake in 1960, 1965 and 1970. We hypothesized that this would reduce the within-person variation in dietary intake[25] and therefore strengthen the association with stroke risk. This was confirmed by the results. Although the intakes were similar, the standard deviation of the average flavonoid intake of three measurements was smaller compared with the single intake in 1970, and its association with stroke risk was stronger.

Few studies have reported on the association between antioxidant vitamins and stroke risk. Gey and coworkers reported a higher stroke mortality for middle-aged men with low plasma levels of beta-carotene in the Basel Study[9]. We observed a similar non-significant association in the present study. Both studies had a small number of cases and therefore a limited power to detect an association. In a preliminary report of the Nurses' Health Study a combined antioxidant score, with beta-carotene as the predominant contributor, was associated with a 45% lower stroke incidence[26]. Based on the available data an inverse association between beta-carotene and stroke seems likely. Results of other studies are needed to confirm this association.

We observed no relationship between vitamin E and stroke incidence. Neither common intake levels nor high levels through vitamin E supplementation were associated with ischemic stroke incidence in the Nurses' Health Study[27]. Also in the Basel Study[9] and in a Dutch nested case-control study using stored plasma samples[28] vitamin E was not related to stroke mortality. In the present study no association between vitamin C intake and stroke incidence was found. This is not surprising because it has been hypothesized that vitamin C protects primarily against hemorrhagic stroke[1,2,29].

The present study is the first that showed a protective effect of flavonoid intake on stroke incidence. We reported earlier that the intake of flavonoids reduced coronary heart disease risk in Dutch elderly men[10]. We also observed that the mean flavonoid intake in the 16 cohorts of the Seven Countries Study was inversely related with long-term mortality from coronary heart disease[30]. These results suggest that dietary flavonoids may protect against both coronary heart disease and stroke.

The most important food sources of flavonoids and vitamin antioxidants, e.g. fruit, vegetables and black tea, were also analyzed in relation to stroke incidence. Black tea was with 70% the major source of flavonoids in the present study and tea consumption was inversely associated with stroke risk. Men who drank more than 4.7 cups of tea per day had a 69% reduced risk of stroke compared with men who drank less than 2.6 cups per day.

Tea also contains other antioxidative compounds such as the catechins (-) epicatechingallate and (-) epigallocatechingallate[31] which may explain this inverse association. Similarly, the high consumption of solid fruit (mainly apples) predicted independently from tea consumption a non-significant 48% lower stroke risk. A number of solid fruits including apples also contain antioxidant catechins which may explain this result[32]. However, we could not investigate this in more detail because no quantitative data on the catechin content of foods was available.

Khaw and Barrett-Connor observed an inverse association between dietary potassium intake and stroke-associated mortality in the Rancho Bernardo Study and hypothetisized that consumption of one serving or more of fresh fruit and vegetables might be protective against stroke[3]. In the present study fruit and vegetable data, however, showed very low correlations with potassium, while potassium intake itself was not associated with stroke incidence. Our findings suggest that potassium does not explain the inverse relation between fruit and vegetable consumption and the occurrence of stroke.

The inverse association between intake of antioxidants and stroke incidence may be explained by their protective effect against lipid peroxidation in early atherosclerosis[6,33]. Low Density Lipoprotein (LDL) is modified by free radicals which oxidize the polyunsaturated fatty acids in the LDL molecule. Modified LDL is easily absorbed by macrophages and is toxic to the vessel endothelium[6]. This may ultimately lead to the formation of atherosclerotic plaques. Free radicals have also been reported to enhance thrombogenesis by affecting platelet aggregation[34]. Antioxidants, including flavonoids, inhibit the oxidative modification of LDL and reduce the cytotoxicity of LDL to the vessel wall[6,35-37]. Furthermore, flavonoids reduce platelet aggregation by inhibiting lipoxygenase and cyclo-oxygenase activity[38]. Data on the absorption of flavonoids are scarce but suggest that at least some quercetin is absorbed in the human gastro-intestinal tract[39].

We conclude that long-term intake of flavonoids and consumption of black tea may protect against stroke. A possible beneficial effect of dietary beta-carotene and the consumption of solid fruit on stroke risk merits further investigation.

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Chapter 7

GENERAL DISCUSSION

Stroke is an important public health problem in the Netherlands Antilles; about 11% of total mortality is due to stroke. The purpose of this thesis was to assess recent trends in stroke mortality in the Netherlands Antilles, to reappraise the role of blood pressure as a risk factor for stroke with correction for regression dilution bias, and to investigate the role of alcohol and diet in the occurrence of stroke.

Stroke can be divided into different subtypes, with ischemic and hemorrhagic strokes being the most important ones. In both the Netherlands Antilles (chapter 2) and the Netherlands[1] more than 80% of the strokes are ischemic. Ischemic strokes are caused by occlusion of cerebral blood vessels, with damage to the cerebral tissues as a consequence. Atherosclerotic processes in the cerebral vessels can lead to severe stenosis of the cerebral blood vessels, but often this process is more complicated and accelerated by local thrombosis on ulcerated atherosclerotic plaques, with subsequent reduction of cerebral blood flow causing stroke[2,3]. Besides, thrombotic processes from other locations in the cardiovascular system may also cause (thrombo-embolic) ischemic stroke when the emboli reach the cerebral vessels through the circulation[2,3]. However, these processes may not totally encompass the biological mechanisms leading to ischemic stroke.

Atherothrombotic processes also play a role in the pathogenesis of myocardial infarction. However, ischemic stroke generally occurs at an older age than myocardial infarction. The later occurrence of stroke compared with myocardial infarction may also be a consequence of different risk factors on the underlying processes of atherosclerosis and thrombosis. The resemblance of and difference between risk factors for ischemic stroke and myocardial infarction will be discussed.

Stroke mortality

Stroke still is the third leading cause of death in the Netherlands Antilles as well in the Netherlands, being responsible for approximately 10% of all deaths (chapter 2). Stroke mortality in the Netherlands decreased by 47% in men and by 62% in women during the period 1950-1990[4]. In the present study we observed a slow-down in the decline of age-adjusted stroke mortality in the Netherlands during the period 1987-1992 in men and even a significant 0.8% annual increase in women (chapter 2). In the Netherlands Antilles we also observed a slow-down in the decline for men, while in women a significant increase was noted during the period 1987-1992 (chapter 2). As put forward in chapter 2, also in other

industrialized countries this phenomenon is being noted[5].

Like other Western countries, the population of the Netherlands is already subject to aging[6], while also the population of the Netherlands Antilles is expected to become older in the near future[7]. Consequently, stroke, being a disease of old age and already now an important public health problem both in terms of deaths and quality of life, will become a much more serious public health problem in the near future. Therefore more efforts are needed to elucidate risk and protective factors for primary and secondary stroke prevention. If effective stroke prevention program are not developed in the near future, health care will be faced with serious increase of stroke cases and deaths due to aging of the population. Moreover, the observed increase in age-standardized mortality in women and the slow-down in the decline of the stroke mortality in men which are independent from the effect of aging, will deterioriate the situation.

Blood pressure and serum cholesterol

The results presented in this thesis show that the use of a single systolic blood pressure measurement instead of repeated measurements in cohort studies can lead to a substantial underestimation of 55% of the association between systolic blood pressure and stroke (chapter 3). This is in agreement with calculations from meta-analyses of cohort studies using single measurements[8]. This implies that the long-term mean individual blood pressure levels are more important than results of single measurements have suggested. The strong association between long-term repeated measurements and stroke provides additional support for the hypothesis that a chronic atherosclerotic rather than a short-term thrombotic process mediates the relationship between blood pressure and stroke. Our findings also indicate that after successful treatment of hypertension in clinical practice sustained control of systolic blood pressure far beyond a few years after the patient has become normotensive is needed to keep the risk low.

The use of single measurements of serum total cholesterol to study its association with stroke is subject to similar methodological issues as discussed for systolic blood pressure. In the present study we observed no relationship of serum total cholesterol with stroke incidence (chapter 3). The use of repeated measurements did not change this observation. Although serum total cholesterol has been linked to atherosclerosis[9] and has been proven to be a potent risk factor for coronary heart disease[10], its relationship with stroke has always been unclear. Based on single measurements some studies reported an elevated ischemic stroke risk for high serum total cholesterol levels[11,12]. Most studies found however no association with ischemic stroke[13-15], while others observed only an increased mortality from hemorrhagic strokes at extremely low levels of serum total cholesterol[16,17]. Our observations indicate that the lack of

association between serum total cholesterol and ischemic stroke, as reported also by most other studies, is not a consequence of underestimating the risk due to regression dilution bias. Also in a recent meta-analysis of well-designed randomized trials of cholesterol lowering on stroke risk which included 36,000 individuals and 435 strokes reported no effect of a 6-23% lowering of serum total cholesterol on stroke risk (relative risks 1.0 [95% CI 0.8-1.2] for all strokes and 1.1 [95% CI 0.8-1.6] for fatal strokes)[18]. Even in case a global meta-analysis based on a much larger sample size including also non-published trials (as anounced[18]) would show a shift in the currently observed effects towards statistical significance, the population attributable risk for stroke due to serum total cholesterol would still remain low. As a consequence, cholesterol lowering would reduce the number of strokes only slightly. Therefore the relevance of serum total cholesterol in prevention of stroke should be questioned.

Alcohol, diet and stroke

The quality of the estimation of alcohol consumption and dietary intake in the present study can be considered adequate, since it has been shown to have appropriate reproducibility and validity[19,20]. The use of repeated measurements provided the possibility to take possible disadvantages of single measurements into account[21]. Moderate alcohol consumption was associated with a non-significant lower stroke risk (chapter 4), being consistent with findings from larger studies[22,23]. Long-term moderate alcohol consumption was not stronger associated with stroke incidence than current moderate alcohol consumption. This suggests a short-term influence of alcohol on thrombosis rather than an influence on the chronic process of atherosclerosis. This was sustained by the fact that adjustment for blood pressure which influences stroke risk rather through atherosclerosis[24] and which has been associated with alcohol intake[25], did not influence the effect of alcohol consumption on stroke incidence. Recent observations of an inverse association between moderate alcohol consumption and carotid atherosclerosis[26] indicate that the explanation of the association between alcohol and stroke may be more complicated.

The short-term consumption of moderate amounts of fish conveyed a 50% lower stroke risk (chapter 5). In cohort studies, fish consumption was associated with coronary heart disease mortality[27,28], but as discussed earlier, this was not the explanation for our observation. The protective effect of fish consumption was also independent of new risk factors for stroke such as dietary flavonoids and vitamin antioxidants (chapter 6). Although the underlying biological mechanism explaining the association between fish consumption and stroke remains to be elucidated, as was discussed extensively in chapter 5 an anti-thrombotic effect seems a likely candidate. Because fish consumption is generally accepted as a natural part of diet, our observation of a protective effect of one or two servings of fish per week provides a simple

message in terms of stroke prevention, in addition to lowering of coronary heart disease risk.

Dietary flavonoids and their main source, tea, were inversely related to stroke incidence (chapter 6). Although dietary flavonoids have proven to be strong antioxidants[29], an effect through thrombosis or a combined effect on atherosclerosis and thrombosis can not be ruled out[30]. An antioxidant effect of flavonoids would convey further evidence for the 'antioxidant hypothesis in atherosclerosis'[31], which assumes reduction or regression of oxidative processes in atherosclerosis by substances with antioxidant properties. These substances include beta-carotene and vitamin E. We observed a 46% reduction of stroke risk by beta-carotene, although the association was not statistically significant (chapter 6). We found no relationship between vitamin E and stroke incidence, but as discussed in chapter 6, results from studies on stroke as well as on coronary heart disease suggest that only extremely high intake of vitamin E, reached only through daily vitamin supplementation, may lower coronary heart disease risk but not stroke risk[32]. Thus, in terms of prevention by diet, consumption of tea, the main source of dietary flavonoids in the present study, is of interest, also because it is widely available and drunk. Other sources of flavonoids, e.g. onions, apples and red wine, could also be important for stroke prevention.

The observed protective effects of fish consumption and antioxidant intake, in the present study suggest that lowering of stroke incidence by changes in diet is possible. Since no effective therapy exists for stroke, diet must be considered an important means of prevention. Furthermore, unlike interventions using pharamacological agents, no adverse side effects are to be expected from diet, while the nature and quantities of the food components as required do not increase the risk for obesity.

The effects of the different risk factors on stroke incidence were independent from each other (chapter 6). Prevalence of myocardial infarction did not change our observations (chapter 4, 5 and 6), also not in models including all the studied risk factors. Unfortunately we had no data on physical activity[33], a possible protective factor for stroke. We included energy intake in our multivariable models. This can be viewed as a proxy for physical activity. Although we can not rule out residual confounding may have played a role, it is unlikely that this would explain our observations. Also, no significant interactions between any of the analysed risk factors were noted.

Stroke and coronary heart disease

Several risk factors for stroke, including diet, have also been shown to be risk factors for coronary heart disease, although the relative importance may differ differ. Blood pressure is a strong predictor for both stroke (chapter 3) and coronary heart disease. Other common risk factors for stroke and coronary heart disease include cigarette smoking, diabetes mellitus, atrial

fibrillation, clotting factors and heavy alcohol consumption. Known common protective factors include moderate alcohol consumption, moderate fish consumption, dietary flavonoid and beta-carotene intake and physical activity . Besides those common risk factors, stroke and coronary heart disease differ with respect to others. Serum cholesterol, obesity, and the intake of saturated fatty acids are established as risk factors for coronary heart disease, but not for stroke. On the other hand migraine has been suggested as a risk factor for stroke, although plausible biological mechanisms are still lacking.

The resemblance and difference between risk factors for coronary heart disease and stroke imply that in terms of prevention and intervention some risk factors may be suitable for intervention on both diseases. In this light the difference in mean age of occurrence may be an advantage, since early intervention on common risk factors for coronary heart disease may also have a beneficial effect on stroke, especially when these interventions are sustained over a longer period of time.

Stroke prevention in the Netherlands Antilles and the Netherlands

The observed associations between diet and stroke form an additional reason to promote a healthy diet and healthy lifestyle as a means of chronic disease prevention. There is already a lot of evidence that diet is important for the prevention of the two other major causes of death in the Western world, coronary heart disease and cancer. Analyses of age-adjusted death rates of different countries lead to the observation of concordant trends in the mortality of these three chronic diseases on an international level back to the fifties suggesting common causes and hence the need to identify common risk factors for simultaneous prevention of these chronic diseases[34]. The results of the present study are in accordance with this suggestion. Stroke may be a much better preventable chronic disease than hitherto known. As discussed earlier, the possibility of intervention on risk factors for stroke, including diet besides blood pressure and smoking, must be utilized intensively, given the recent trends in stroke mortality observed in the Netherlands and the Netherlands Antilles.

Information on cardiovascular risk factors is not available for the Netherlands Antilles, but is available for Aruba that also belongs to the Kingdom of the Netherlands. In Aruba age-adjusted mortality rates from cardiovascular diseases were lower compared with the Netherlands Antilles, the Netherlands and the U.S.A.[35] In a cross-sectional study conducted in 626 subjects aged 15-74 years a prevalence of 6% of uncontrolled hypertension (defined as systolic blood pressure 160 mmHg or above and/or diastolic blood pressure phase V 95 mmHg or above) was observed in both men and women. The prevalence of controlled hypertension, i.e. normotensive and treated with diet and/or drug therapy, was 11%. Twelve percent of the men and 11% of the women had severe hypercholesterolemia (≥6.5 mmol/l). Mild

hypercholesterolemia (5.2-6.4 mmol/l) was observed in 23% of men and 28% of women. The rates of cigarette smoking were 32% for men and 13% for women. Diabetes mellitus was defined as as non-fasting glucose level $\geq$ 11.1 mmol/l and/or treatment with diet or drugs). The prevalence of diabetes mellitus was 6%, and 60% of the study population was obese. A body mass index between 26 and 30 was observed in 35% and severe overweight (a body mass index above 30) in 23% of the study population [35]. The prevalence rates of Aruba may not be applicable to the Netherlands Antilles, since in contrast to the Antillean population, the Aruban population is mainly Hispanic, and the Antillean cardiovascular mortality rates are higher than those on Aruba. Besides, although not confirmed yet, the overall clinical impression is that hypertension, obesity and diabetes mellitus are very prevalent in the Netherlands Antilles. Therefore it is of vital importance to start risk factor monitoring programs at the national level in the Netherlands Antilles.

Currently, no specific prevention programs exist for hypertension treatment and smoking cessation in the Netherlands Antilles. Also dietary prevention programs are lacking. Therefore, in addition to the existing stroke mortality registration and the efforts to establish a population-based register for stroke incidence and mortality at the national level, intensive stroke prevention programs must be started as soon as possible. Given the vital and national importance, they must be initiated and coordinated on a national level in cooperation with the individual islands. A proper assessment of food consumption in the Netherlands Antilles is necessary. Also a nutrient database, in cooperation with other Caribbean countries is needed. This is facilitated by the relative large part of all foods that is imported from abroad, about which the information on micronutrients already is available. It is clear that prevention of stroke in particular and of cardiovascular diseases and cancer in general, must become a national priority as soon as possible. Given the importance for the Antillean public health, initiation and coordination of research at the national level is required. An essential factor for success is proper funding for these programs.

Epilogue

The possibilities for prevention of stroke have been underestimated. Therefore stroke prevention programs need more attention and better funding. In fact, this thesis only described the tip of the iceberg of the existing questions and answers regarding the role of diet in stroke occurrence and prevention. Partly due to the lack of appropiate dietary data, but far more due to lack of funding and scientific attention, investigations on the relationship between diet and stroke now only start seeing the first day light. It is clear that this area of research is a promising one for the near future.

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SUMMARY

In the Netherlands Antilles stroke mortality contributes 11% to the mortality from all causes. Because data concerning trends in stroke mortality for the Netherlands Antilles were lacking, we used the period 1981-1992 to study recent trends in stroke mortality. The trends in the Netherlands Antilles were compared with those in the Netherlands. Blood pressure has been established as a major risk factor for stroke incidence in cohort studies, which were based on either a single or a few blood pressure measurements. The strength of the association will be underestimated when single measurements of blood pressure are used. Therefore we investigated the magnitude of the underestimation using repeated measurements in a cohort study. We also investigated the role of long-term alcohol and diet in stroke occurrence, since little is known about the role of diet in the etiology of stroke. Establishment of an association between diet and stroke would provide new opportunities for prevention of this disease.

We used official mortality statistics on the category of stroke (ICD-codes 430-438) from the Netherlands Antilles and the Netherlands for men and women after age-adjustment according to the World Standard Population of the WHO for 1992. Generally stroke mortality was nearly 50% higher for the Netherlands Antilles compared with the Netherlands. Over the period 1981-1986 age-adjusted stroke mortality decreased annually by 3.5% (p=0.10) in the Netherlands Antilles, and 2.5% (p=0.002) in the Netherlands. These decreases were followed by a 2.0% (p=0.14) annual increase for the Netherlands Antilles and a 0.2% increase for the Netherlands(p=0.22) over the period 1987-1992. The increases were mainly due to a 4.9% annual increase (p=0.16) for Antillean women and a 0.8% annual increase (p=0.01) in women in the Netherlands. These data indicate that the initial decrease in age-adjusted stroke mortality, which was in the same order of magnitude in the Netherlands Antilles and the Netherlands, came to a standstill over the period 1987-1992, and showed even an increase in women.

We used repeated blood pressure measurements, taken yearly between 1960 and 1970 in 603 men aged 50 to 69 years in 1970 in the Zutphen Study, to evaluate the effect of regression dilution bias on the association between systolic blood pressure and stroke incidence with repeated measurements. In other studies, the effect of regression dilution bias had only been calculated in a meta-analysis using studies with single or few measurements. In the Zutphen Study the occurrence of stroke was established from 1970 to 1985. As estimates of systolic blood pressure we used the single observed systolic blood pressure in 1970, the individual average systolic blood pressure between 1960 and 1970, and the predicted systolic blood pressure for 1970 based on linear regression of blood pressure readings on time. After adjustment for age, cigarette smoking and serum total cholesterol in Cox proportional hazards models, the average systolic blood pressure was the strongest predictor of 15-year stroke

incidence. When the single observed systolic blood pressure was used instead of the average systolic blood pressure, the strength of the association with stroke incidence was underestimated by 55%, compared with 26% when the predicted systolic blood pressure for 1970 was used. From these observations we concluded, that the long-term stroke risk of an individual is substantially underestimated with a single blood pressure measurement.

The assessment of the role of alcohol and diet in the occurrence of stroke was also based on data from the Zutphen Study, of men aged 50 to 69 years in 1970, who had a medical examination, and participated in all dietary surveys of 1960, 1965 and 1970. In these dietary surveys, the cross-check dietary history method was used, and the alcohol and food intake data were converted into energy and nutrients by an extended computerized version of the Netherlands food table.

The number of men who reported moderate alcohol consumption (30 grams alcohol/day or less) in 1960, 1965 and in 1970 was 514. Alcohol consumption was positively associated with cigarette smoking, total fat intake and fish consumption, and inversely associated with carbohydrate intake. Risk factors, chronic disease prevalence and dietary patterns were not different in never-drinkers (20.6% of the men) compared with ex-drinkers (9.7% of the men). Moderate alcohol drinkers (69.7% of the men, three glasses alcohol/day or less) had a relative risk of 0.66 (95% confidence interval 0.30-1.47) compared with non-drinkers. Although not statistically significant, this reduced risk was in the same order of magnitude as in other prospective studies.

Dietary data of the 552 men from the Zutphen Study who participated in the dietary surveys in 1960, 1965 as well as 1970, were used to investigate the association between diet and stroke occurrence. Men who consumed more than 20 grams of fish per day in 1970 (about one serving per week) had a relative risk of 0.49 (95% confidence interval 0.24-0.99) for 15-year stroke incidence, compared with those who consumed less fish. The relative risk was 0.63 (95% confidence interval 0.34-1.16) for the men who reported to consume always fish between 1960 and 1970 compared with those who did not consume fish at all. We concluded that consumption of at least one portion of fish per week was associated with a lower stroke incidence, and that the effect of recent fish consumption was stronger than the effect of long-term fish consumption.

When we studied the long-term dietary intake of antioxidants, the results from Cox proportional hazards models showed a dose-dependent inverse association between 10-year habitual intake of dietary flavonoids and 15-year stroke incidence, with a relative risk of 0.27 (95% confidence interval 0.11-0.70) for consumption of 28.6 mg/day or more (highest quartile) compared to consumption of less than 18.3 mg/day (lowest quartile). This association was independent from other risk factors for stroke, including beta-carotene, antioxidant vitamins C and E, and fish consumption. A dose-dependent inverse association was also

observed with tea, which contributed 70% to the dietary flavonoid intake. Men who drank 4.7 or more cups of tea per day (highest quartile) had a 69% lower stroke incidence (relative risk 0.31, 95% confidence interval 0.12-0.84) compared with those who drank less than 2.6 cups of tea per day (lowest quartile). The intake of vitamin C and E was not associated with stroke risk, while men in the highest quartile of 10-year beta-carotene intake (1.37 mg/day or more) had a relative risk of 0.54 (95% confidence interval 0.22-1.33) compared with those in the lowest quartile (less than 1.01 mg/day). Adjustment for other risk factors for stroke, including fish consumption, moderate alcohol consumption, and also exclusion of 40 prevalent cases of myocardial infarction in 1970 did not change these results.

With regards to alcohol and diet, we concluded from these results that moderate alcohol consumption was associated with a non-significant 34% reduction in stroke incidence, while fish consumption, dietary flavonoids and their main source tea, were independent protective factors for stroke. For beta-carotene a non-significant 46% risk reduction was observed. The protective effects of different dietary components on stroke incidence indicate that diet is an important, hitherto underestimated means of stroke prevention. Especially when taking into account the aging populations in industrialized countries and the recent trends in stroke mortality, stroke is likely to become a more serious public health problem in the near future. Therefore healthy diet has to be promoted as an important means for the prevention of stroke.

SAMENVATTING

In Nederlandse Antillen nemen cerebrovasculaire accidenten (CVA) 11% van de totale sterfte voor hun rekening. Op de Nederlandse Antillen was geen informatie over trends in de sterfte aan CVA aanwezig. Recent zijn gegevens over de periode 1981-1992 beschikbaar gekomen die het mogelijk maakten om de recente trends in de sterfte aan CVA te bestuderen. De trends in de Nederlandse Antillen werden vergeleken met die in Nederland. Bloeddruk wordt als een belangrijk risicofactor voor CVA beschouwd. De informatie hierover is voornamelijk afkomstig uit cohort onderzoeken die gebruik maakten van één of slechts enkele bloeddrukmetingen. De sterkte van de associatie tussen bloeddruk en CVA wordt echter onderschat bij gebruik van één of enkele bloeddrukmetingen. Daarom bestudeerden wij met herhaalde metingen binnen een cohort de mate waarin deze associatie onderschat wordt wanneer geen herhaalde metingen worden gebruikt. Wij onderzochten ook de verbanden tussen alcohol, voeding en het ontstaan van CVA, omdat hierover weinig bekend is. Het bestaan van een associatie tussen voeding en CVA zou nieuwe mogelijkheden voor de preventie van CVA bieden.

Wij maakten gebruik van de officiële sterftestatistieken voor CVA (ICD-codes 430-438) van de Nederlandse Antillen en Nederland die met behulp van de standaard wereldbevolking van de Wereldgezondheidsorganisatie (WHO) voor mannen en vrouwen gestandaardiseerd werden voor leeftijd. De sterfte aan CVA op de Nederlandse Antillen was ongeveer 50% hoger dan in Nederland. Gedurende de periode 1981-1986 nam de voor leeftijd gestandaardiseerde sterfte aan CVA jaarlijks af met 3,5% (p=0,10) in de Nederlandse Antillen en met 2,5% (p=0,002) in Nederland. Gedurende de periode 1987-1992 volgde echter een jaarlijkse toename van 2,0% (p=0,14) in de Nederlandse Antillen en 0,2% (p=0,22) in Nederland. Deze toenames waren voornamelijk het gevolg van een jaarlijkse toename van 4,9% (p=0,16) onder Antilliaanse vrouwen en een jaarlijkse toename van 0,8% (p=0,01) onder Nederlandse vrouwen. Deze gegevens laten zien dat de daling in sterfte zoals waargenomen voor de periode 1981-1986 zowel in de Nederlandse Antillen als in Nederland sterk verminderde gedurende de periode 1987-1992 en onder vrouwen zelfs een toename vertoonde.

Wij gebruikten herhaalde bloeddrukmetingen die tussen 1960 en 1970 jaarlijks in het kader van de Zutphen Studie waren verricht bij 603 mannen van 50-69 jaar in 1970 om het effect van 'regression dilution bias' op de associatie tussen systolische bloeddruk en incidentie van CVA in een cohort onderzoek te kunnen bestuderen. Voorheen was het effect van regression dilution bias alleen geschat in een meta-analyse van onderzoeken met één of enkele bloeddrukmetingen. De follow-up voor incidentie van CVA vond tussen 1970 en 1985 plaats. Als schatters van de bloeddruk werden gebruikt de enkelvoudige meting in 1970, de individuele gemiddelde bloeddruk over de periode 1960-1970 en de voorspelde bloeddruk voor 1970 zoals berekend uit lineaire regressie van jaarlijkse bloeddrukken gemeten tussen

1960 en 1970 op de tijd. Na correctie voor leeftijd, serum totaal cholesterol en roken in Cox proportional hazards modellen bleek de individuele gemiddelde bloeddruk de sterkste voorspeller van de incidentie van CVA te zijn. Gebruik van een enkelvoudige bloeddrukmeting leidde tot een onderschatting de associatie tussen bloeddruk en 15-jaars incidentie van CVA met 55%. Bij gebruik van de voorspelde bloeddruk voor 1970 in plaats van de gemeten bloeddruk in 1970 bedroeg de onderschatting 26%. Wij concludeerden uit deze resultaten dat het lange-termijn risico op een CVA aanzienlijk wordt onderschat indien een enkelvoudige bloeddrukmeting wordt gebruikt.

Voor bestudering van het verband tussen alcohol en voeding enerzijds en de incidentie van CVA anderzijds gebruikten wij eveneens gegevens van de Zutphen Studie. Voor dit onderzoek werden mannen geselecteerd die in 1970 50 tot 69 jaar oud waren en aan zowel de medische als aan de voedselconsumptie onderzoeken van 1960, 1965 en 1970 hadden deelgenomen. Bij deze voedselconsumptie onderzoeken werd de kruisvraag methode gebruikt. De verzamelde gegevens over alcohol en voeding werden met behulp van een aangepaste gecomputeriseerde versie van de Nederlandse voedingsmiddelentabel omgerekend naar energie en nutriënten.

Het aantal mannen dat zowel in 1960, 1965 als in 1970 matig alcohol (30 gram of minder per dag) consumeerde bedroeg 514. De alcoholconsumptie was positief geassocieerd met sigaretten roken, inname van totaal vet en visconsumptie en negatief met koolhydraat inname. Ex-drinkers (9,7% van de mannen) en nooit-drinkers (20,6% van de mannen) verschilden niet van elkaar in niveaus van risicofactoren, prevalentie van chronische ziekten en voedingspatroon. Matige drinkers (69,7% van de mannen) hadden een relatief risico van 0,66 (95% betrouwbaarheidsinterval 0,30-1,47) op een CVA vergeleken met niet-drinkers.

Voedingsgegevens van 552 mannen die zowel in 1960, 1965 en 1970 aan het voedingsonderzoek hadden deelgenomen werden gebruikt om het verband tussen voeding en incidentie van CVA te bestuderen. Mannen die meer dan één portie vis per week consumeerden hadden een relatief risico van 0,49 (95% betrouwbaarheidsinterval 0,24-0,99) op een CVA na 15 jaar vergeleken met mannen die minder of geen vis consumeerden. Het relatief risico was 0,63 (95% betrouwbaarheidsinterval 0,34-1,16) bij mannen die tussen 1960 en 1970 altijd vis consumeerden vergeleken met mannen die nooit vis consumeerden. Wij concludeerden dat het eten van minstens één portie van vis per week geassocieerd was met een lagere incidentie van CVA en dat recente visconsumptie een sterker effect had dan lange-termijn visconsumptie.

Bij het bestuderen van het verband tussen antioxidanten uit de voeding gedurende 10 jaar en de 15-jaars incidentie van CVA met Cox proportional hazards modellen werd een inverse dosis-response relatie (p_{trend}=0,004) gevonden tussen de inname van flavonoïden en CVA. Het relatief risico voor een inname van 28,6 mg/dag of meer (hoogste quartiel)

vergeleken met een inname van minder dan 18,3 mg/dag (laagste quartiel) bedroeg 0,27 (95% betrouwbaarheidsinterval 0,11-0,70). Dit verband was onafhankelijk van andere potentieel verstorende variabelen (waaronder visconsumptie) en de andere antioxidanten beta-caroteen, vitamine C en vitamine E. Ook tussen consumptie van thee, waarvan 70% van de flavonoïden afkomstig waren, en incidentie van CVA werd een invers dosis-respons relatie gevonden. Consumptie van 4.7 of meer kopjes thee per dag ging gepaard met een 69% lagere incidentie van CVA (relatief risico 0,31; 95% betrouwbaarheidsinterval 0,12-0,84) vergeleken met consumptie van minder dan 2,6 kopjes thee per dag. De inname van vitamine C en vitamine E was niet geassocieerd met de incidentie van CVA. Een 10-jaarsinname van 1,37 mg beta-caroteen per dag of meer (hoogste quartiel) gaf een relatief risico van 0,54 (95% betrouwbaarheidsinterval 0,22-1,33) vergeleken met een inname van minder dan 0,86 gram per dag (laagste quartiel). Ook na correctie voor andere risicofactoren voor CVA en uitsluiting van 40 prevalente gevallen met een myocardinfarct veranderden deze resultaten niet.

Visconsumptie, flavonoïden en hun belangrijkste bron thee bleken onafhankelijke risicofactoren te zijn voor de incidentie van CVA. Beta-caroteen gaf een niet-significante 46% reductie van het risico op CVA. De beschermende effecten van voeding ten aanzien van het optreden van CVA geven aan dat voeding een belangrijk en tot op heden onderschat middel ter preventie van CVA is. Vooral indien de thans optredende vergrijzing van geïndustrialiseerde bevolkingen en de recente trends in CVA-sterfte in acht worden genomen, dan kan verwacht worden dat CVA een belangrijker volkszondheidsprobleem zal worden dan tot nu toe het geval was. Daarom dient gezonde voeding als een belangrijke middel ter preventie van CVA te worden gestimuleerd.

NAWOORD

Allereerst was het promoveren een plezierig, maar ook zeer leerzaam proces, met alle nodige ingredienten: momenten om te concentreren, relativeren, lachen, blij zijn, maar soms ook teleurgesteld zijn. Het leerde mij bovendien te beseffen dat meer weten ook betekent zeker(der) ervan zijn dat er veel meer is wat je (nog) niet weet, en hoe fnuikend oppervlakkigheid kan zijn. Het vaak voorkomen van CVA's, hun belang ervan voor de volksgezondheid en mijn persoonlijke belangstelling hebben ertoe geleid dat ik destijds dit onderwerp heb gekozen. Het was een goede keuze.

Het was een voorrecht om te realiseren dat de eerste ronde van het veldwerk van de Zutphen Studie gelijk met mijn foetale ontwikkeling in 1960 is begonnen. Door het actief meewerken aan de Zutphen Ouderen Studie is een hechtere band ontstaan. Echter zonder het werk van allen betrokkenen bij de Zutphen Studie zou dit proefschrift er niet zoals nu hebben uitgezien. Aan alle participanten, veld- en andere medewerkers hierbij betrokken gaat dan ook een woord van dank uit.

De GGD Curacao en het Eilandgebied Curacao hebben het verbijf in Nederland voor dit onderzoek mogelijk gemaakt, en verdienen daarom de nodige erkentelijkheid. Met de nodige medewerking kan nu dan ook meer dan voorheen tot stand worden gebracht.

Een speciaal woord van dank gaat uit naar prof dr ir Daan Kromhout. Daan, je niet aflatende enthousiasme is heel belangrijk geweest. Ook je kritische kijk op zaken en met name je bewonderenswaardig geheugen ("Als ik me niet vergis...", en "Ik zou dit voor alle zekerheid toch nog even nalopen, ..." heb ik leren interpreteren als zeer belangrijk, soms natuurlijk tot schrik) zijn onschatbaar gebleken. Je niet aflatende inspanning om manuscripten grondig na te kijken en alles van alle kanten te bekijken zijn heel belangrijk geweest. Het heeft geleid tot vruchtbare discussies en het vinden van nieuwe wendingen.

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Bennie Bloemberg, je hulp met name aan het begin, maar ook gedurende de rit heeft veel bijgedragen. Je inzicht in de statistiek (naast epidemiologie) kon daarbij niet onopgemerkt blijven. Ook bij jou, Cor de Lezenne-Coulander, kon ik altijd binnenlopen met een methodologisch of software probleem, en je had alle tijd en geduld. De Zutphen analyse club komt ook dank toe, uiteraard voorzover ik met name in het begin erbij kon zijn. Jan Dorssers, Ruud Romme, Frits van den Heuvel en Adriaan van Kessel, jullie hebben alle pc-, netwerk- en

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Amado Römer, op Curacao heb je steeds als belangrijke stimulerende kracht gefungeerd. Dit is altijd van grote waarde geweest.

Met name de laatste trajecten konden plaatsvinden dankzij jullie dierbare hulp, Wim en Dini Gorissen-van Delden, Edwin Vermaes en Myriam Dietvorst, Klasien Bergman, Fekki en Geraldine Davelaar-Pourier, en Vito en Evelyn Koeijers-Schotborgh, omdat jullie mij opvingen met verblijfplaats na mijn (weder) aankomst in Nederland. Dank gaat ook uit naar al mijn andere vrienden die mij zeer dierbaar zijn, en ook op cruciale momenten voor de nodige ontspanning hebben gezorgd.

Last but not least ben ik veel aan jou verschuldigd, Marlia de Jonge. Met name de zeer moeilijke momenten van het eindtraject, waar de loodjes het zwaarst waren. Je luisterende oor, je geduld en goede bui hebben wonderen gedaan.

CURRICULUM VITAE

Sirving Odulpho Keli was born on June 12th 1961 on Curacao, Netherlands Antilles. After attending secondary school at the Maria Immaculata Lyceum (VWO) in Willemstad, Curacao, he started to study Medicine in September 1979 at the Catholic University of Nijmegen in the Netherlands. He obtained his M.D. degree in August 1986.

After working for a short time as attending general practitioner, and as a Mother and Child Health Physician, he designed and programmed the first automated version of the Immunisation Programme Administration of Curacao, while being insular program coordinator for routine immunisation and special immunisation campagnes. In 1987 he was granted a Special Training Award by the insular gouvernment of Curacao to specialize in Social Medicine in the Netherlands.

From January 1988 until June 1991 he specialized in Social Medicine, with main areas general Public Health and Epidemiology, at the Netherlands Institute for Preventive Medicine (NIPG-TNO), including several courses (1989, 1990, 1991) at the Johns Hopkins School of Hygiene and Public Health in Baltimore, USA. Also in January 1988 he started his research at the Medical Faculty of of the University of Leiden (Head: prof D. Kromhout). He moved to the Dept of Epidemiology of the National Institute of Public Health in January 1989. In June 1991 he was registered as a certified Social Medicine specialist by the Royal Dutch Society of Medicine (KNMG, SGRC) with Epidemiology as special area. In 1990 he started this PhD program at the National Institute of Public Health.

From July 1992 to October 1994 he performed several functions at the Medical and Public Health Service of Curacao, including deputy chief medical officer and Head of the Control & Prevention of Communicable Diseases Department. He was also employed at the Ministry of Public Health and Environmental Hygiene of the Netherlands Antilles as part-time national medical epidemiologist, in charge of the national mortality and morbidity registers.

During the period October 1994-May 1995 he finished his PhD thesis at the National Institute of Public Health and Environmental Protection. Thereafter he resumed his positions as Head of the Control & Prevention of Communicable Diseases Department in Curacao, and as part-time national medical epidemiologist at the Department of Public Health and Environmental Hygiene of the Netherlands Antilles.

In September 1995 he started as Head of Staff Bureau in the Sint Elisabeth Hospitaal in Curacao, also in charge of Clinical Epidemiology.