ELECTROCARDIOGRAPHIC INDICATORS OF AUTONOMIC BALANCE AND MORTALITY

Aan Ella

ELECTROCARDIOGRAPHIC INDICATORS OF AUTONOMIC BALANCE AND MORTALITY

A CASE-COHORT APPROACH

ELECTROCARDIOGRAFISCHE INDICATOREN VAN AUTONOME BALANS EN MORTALITEIT

EEN CASE-COHORT BENADERING

Proefschrift

Ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de Rector Magnificus

Prof.Dr. C.J. Rijnvos

en volgens besluit van het College van Dekanen.

De openbare verdediging zal plaatsvinden op

woensdag 26 juni 1991, om 16.00 uur

door

Evert Gerrit Schouten

geboren te Apeldoorn

Promotiecommissie

Promotor:	Prof. Dr. J. Pool
Promotor:	Prof. Dr. J.P. Vandenbroucke
Overige leden:	Dr. Ir. F.J. Kok
	Prof. Dr. M.L. Simoons

Electrocardiographic indicators of autonomic balance and mortality.
A case-cohort approach / Evert G. Schouten - Lienden.
Thesis Rotterdam - With summary in Dutch.
ISBN - 90-9004250-4
Subject headings: epidemiology/electrocardiography/mortality

Druk: Hassink-Haaksbergen, 1991
Omslag ontwerp: Jim Berkhout, Tubbergen

This study was financially supported by the Netherlands Heart Foundation (grant 86.060)
Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

TABLE OF CONTENTS

PREFACE

This thesis should start with the many thanks I owe to those who have contributed to the "APEX project". A single name printed on the cover does no justice to the fact that it is the result of the cooperation of many.

To professor Jan Pool from the Thoraxcenter of the Erasmus University Rotterdam, I am grateful for his stimulating guidance an personal interest throughout the the period the study was conducted. He is not only an excellent cardiologist, but also knows about epidemiology, a rare combination indeed.

I thank Professor Jan P. Vandenbroucke from the Department of Clinical Epidemiology, University Hospital of Leiden, an authority in the field of methodology, for his creative contribution to the investigation as a whole, and particularly to the methodological part. Moreover, without his efforts in the past, the data of the Amsterdam civil servants would not have been available for epidemiological studies.

Dr. Frans J. Kok meant a lot to me during the preparation, as a tutor as well as a personal friend. Although electrocardiography was not at all his primary field of interest he provided the critical reflection I needed, especially in the analysis and in the writing of the thesis.

To professor Maarten L. Simoons I am indepted for his expert criticism on the electrocardiographic subject matter and his valuable comments on the text.

My cooperation with Jacqueline M. Dekker Msc deserves special mention. She had an important contribution to the study, as an intelligent investigator and to the thesis as a critical reader and now continues the research on the subject of electrocardiography and epidemiology.

I am very much indepted to Dr. Robert M van der Heide, who, by performing the original health examination in 1953-1954, made this study possible and to both him and his wife Dr. Cornelia van der Heide-Wessel for their willingness to dig into their memories as well as their active participation in the follow up of the survival and of the causes of death.

To professor Klaas Biersteker and to all the colleagues of the Department of Epidemiology and Public Health of the Agricultural University Wageningen, I am grateful for having given me the opportunity to prepare this thesis and for their stimulation and support. Jos van Hutten is thanked warmly for her editorial assistance and for the expert final preparation of the manuscript. Foky T. Feddes-van Klaarbergen Msc and Petra Naber-van den Heuvel Msc were of great help with the documentation, Ada P.H. Vos-Wolse Msc with computer assistance and Dr. Jan Burema for statistical advice. The contribution of the students Irene E.M. Bosselaars, Regina M.C. in 't Veld, Catja Broekhoff, Astrid M.P. Heijnen, Peter Meppelink MD, Rix ten Veen, Caroline Vreugdenhil, Mirjam Stoel, and Mariette van Ommering and Cecile Beckers to

the papers collected in this thesis has been a great help and enabled me to combine their preparation with my teaching responsibilities.

The pleasant and fruitful cooperation with Dr. Saskia le Cessie and Professor Hans C. van Houwelingen of the Department of Medical Statistics of the University of Leiden was crucial in the mathematical underpinning of the case-cohort methods used in the study.

The Netherlands Heart foundation is gratefully acknowledged for financial support, as well as for taking the initiative to establish the survival of the Amsterdam civil servants, more than ten years ago.

I thank my late father and my mother for their support and for the opportunity they provided to undertake medical studies.

My wife Ella and our children Jasper, Rutger, Minke and Taco have shared my efforts all these years and were more important than they realize themselves. They were a great support, furnished the necessary touch of relativity and managed to cope with an often absent-minded husband and father in an admirable way.

ACKNOWLEDGEMENTS

The help and support of the following persons and institutions is gratefully acknowledged:

Dr. Simone van der Putten, Dr. Gerard Bles, Dr. Peter Nierop and Jasper Schouten for the coding of the electrocardiograms.

Dr. Ale Algra for his advice in the choice of the electrocardiographic parameters, their coding and in the data entry.

Mrs Tineke Tromp, legal adviser of the Agricultural University for her advice with respect to agreement with the Central Bureau of Statistics (C.B.S.).

The Central Bureau of Statistics (C.B.S.), in particular Dr. J.T.P. Bonte and Dr. L.M. Friden-Kill and John de Jong from the Department of Health statistics, for their role in the assessment of the causes of death and for providing hospitality during the data analysis.

The Central Bureau of Genealogy (C.B.G.) for establishing the death certificate numbers.

The Civil Servants Pension Fund (A.B.P.) and in particular Dr. Peter van der Putten for the follow up of the survival.

The municipal offices of the city of Amsterdam for their contribution to the follow up of the causes of death.

Professor Coumel from Paris, for his expert help in the interpretation of the results regarding the PQ interval.

1. INTRODUCTION

The electrocardiogram is primarily used as an instrument for diagnosis of atherosclerotic and other heart disease in patients suspected of having these disorders. In addition it can be used for prediction in patients with established heart disease. Certain electrocardiographic characteristics in myocardial infarction patients, i.e. arrhythmia, depolarization and repolarization abnormalities, and QT-interval prolongation appear to indicate increased risk of (sudden) death (1-3). In populations of apparently healthy individuals the electrocardiogram is also increasingly utilized for screening purposes, in search of subclinical heart disease. Moreover, epidemiological studies among (apparently) healthy individuals demonstrated, that electrocardiographic characteristics are indicators of cardiovascular morbidity and mortality risk. These studies almost exclusively classified electrocardiographic findings according to the Minnesota Code. Usually neglected minor abnormalities in heart rate PQ interval, QT interval, ST-segmet level and T-wave amplitude, not meeting Minnesota criteria are prevalent in healthy individuals. These abnormalities may also be indicators for cardiovascular risk, since they possibly are a reflection of the functional state of the autonomic nervous system, which is related to the electrical stability of the myocardium. The present study investigates the prognostic value of these minor electrocardiographic characteristics in 28 years of follow up of the mortality of 1,583 men and 1,508 women. The population consisted of apparently healthy middle-aged civil servants of the city of Amsterdam, The Netherlands, and their spouses, participating in a general health examination in 1953/1954.

Measurement and coding of electrocardiograms on a large number of items in all 3,091 subjects was not feasible. In order to reduce the amount of exposure that has to be evaluated, i.e. the number of electrocardiograms, in epidemiology two sampling designs are available: the "case-control" design and the more recently developed, less well known "case-cohort" design. In the present study the case-cohort design was used and the special methodology required for this design was explored and further developed.

In observational epidemiologic research, cost-efficient designs like the nested case-control and the case-cohort design, are increasingly used nowadays. They require processing of covariate data on only a part of a cohort. The case-cohort design, although being conceptually superior over the case-control design, until now falls short where the completeness of the methods of estimation is concerned.

This thesis therefore consists of two parts: a main part reporting the results on electrocardiography and cardiovascular mortality, and another part addressing the case-cohort design and its methodology.

1.1 Background

Electrocardiography and cardiovascular mortality

Electrocardiography is a widely used non-invasive procedure for diagnosis in patients with suspected or known heart disease. In addition, it is valuable in determining prognosis, once heart disease has been established. For many pathologic conditions like myocardial ischemia, infarction, conduction disturbances and ventricular hypertrophy, typical electrocardiographic patterns have been recognized. The sensitivity and specificity, however, of many of these findings are relatively low, because they are not necessarily present in all patients and because they occur in persons without other evidence of heart disease (4). This implies that in an apparently healthy population there may be a considerable prevalence of electrocardiographic abnormalities, partly representing persons with latent heart disease, often however, individuals without any heart disease.

In epidemiological studies investigating populations of apparently healthy individuals, electrocardiographic findings like ventricular hypertrophy, left bundle branch block and ST-T abnormalities have been suggested to carry an increased risk of future cardiovascular morbidity and/or mortality (4-5). Until now, these studies almost invariably used the Minnesota Code for classification of electrocardiographic findings (6). The Minnesota Code is a classification system, which is based on similar criteria as used for clinical diagnosis. The electrocardiogram, however, may hold more information with respect to cardiovascular risk than is extracted through the Minnesota Code items.

The present study deals primarily with electrocardiographic parameters, not covered by the Minnesota Code or not meeting Minnesota criteria, as risk indicators for mortality. These parameters are heart rate, lengths of PQ interval and QT interval, level of ST segment and amplitude of T wave (Figure 1.1). Probably they are modulated by the autonomic nervous system.

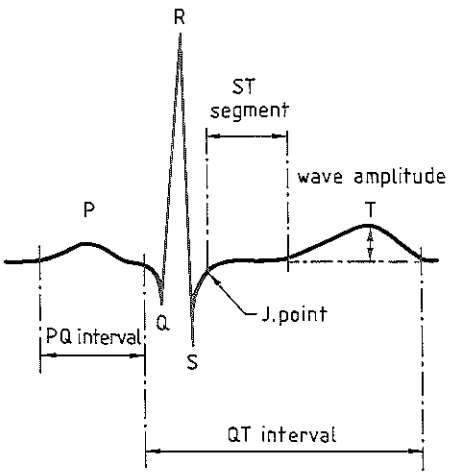


Figure 1.1 The segments of the electrocardiogram

Autonomic nervous system

In general the balance of autonomic influences on the heart may be compromised in two ways. Both kinds of imbalance may lead to an increased risk of cardiovascular and coronary heart disease mortality and may be of endogenous or exogenous origin.

1. Imbalance between the sympathetic and the parasympathetic part of the autonomic nervous system. Usually this relates to a condition in which sympathetic activity is not properly opposed by parasympathetic counteractivity. This may lead to ventricular vulnerability and electrical instability, increasing susceptibility of life-threatening ventricular arrhythmias. In myocardial infarction patients this indeed was observed to result in an increased incidence of arrhythmias and sudden death because of ventricular fibrillation (7-10).

2. Imbalance between left and right sympathetic innervation of the heart. Left and right cardiac sympathetic nerves serve different parts of the heart. Activation of one side has effects different from activation of the other. In animal experiments it was demonstrated that relative predominance of left sympathetic activity, produces electrical instability and lowered ventricular fibrillation threshold, with simultaneous prolongation of the QT interval (11-13).

A human example of this type of autonomic imbalance is the presumably hereditary Idiopathic Long QT Syndrome (14,15). It is characterized by a prolonged QT interval and frequent attacks of ventricular arrhythmias, often leading to ventricular fibrillation and sudden death (16-18). This is to be distinguished from acquired QT-interval prolongation may occur because of use of anti-arrhythmic drugs, electrolyte disturbances, disorders of the central nervous system and

after myocardial damage because of infarction. QT prolongation was reported to be associated with poor survival in post infarction patients (19,20).

As previously mentioned, there is evidence that electrocardiographic manifestations of both kinds of autonomic imbalance, are prognostic of survival in heart-disease patients. Less extreme manifestations of autonomic imbalance in healthy individuals, may be associated with cardiovascular mortality as well. In the present study RR-interval length (heart rate) and PQ-interval length and their reaction to mild exercise are regarded as possible indicators of the first type of imbalance, prolonged QT interval is considered as a manifestation of the second type. Apart from possibly being a consequence of myocardial ischemia, minor ST-T abnormalities may be involved in either form of imbalance.

The case-cohort design

In an epidemiologic cohort study, all cases of a disease that arise in the cohort, are compared with the total number of members of the cohort, cases and non cases together (full-cohort approach). However, if exposure assessment is relatively expensive, ascertainment of exposure for all subjects in full-cohort design may not be feasible. Alternatives that need exposure information of only a part of all subjects are: the (nested) case-control design and the case-cohort design.

In the (nested) case-control design, exposure information of all cases, or a random sample of these, is compared with information of a sample of the non cases. The measure of association estimated in this design is the odds ratio, a valid estimate of the relative risk in the cohort only when the rare disease assumption holds. In the more recently developed case-cohort design, information of all cases is compared with a random sample of the cohort in stead of only the non cases. In this approach relative risk, rate ratio or even absolute risk and absolute incidence density can be estimated. Especially when the disease in question is rare, both designs are efficient, because exposure information needs to be collected in a small fraction of the cohort only.

In the present study, the case-cohort design (21,22) was used, because the measurement and coding of the electrocardiograms was very time-consuming and tedious. The electrocardiograms of all cases (deceased) and of a random sample from the cohort were evaluated.

The case-cohort design requires special methods of estimation and assessing precision. For crude and stratified analysis such methods have been proposed in the literature (20,21). For

multivariate adjustment, until now, no routinely applicable methods are available. This thesis addresses the case-cohort sampling design, explores the methodology and proposes modifications of standard case-control and full-cohort methods for estimation under case-cohort sampling.

1.2 Aim of the present study

The aim of the study reported in this thesis is, to investigate in a population of apparently healthy middle-aged civil servants, the predictive value for cardiovascular mortality of presumed electrocardiographic indicators of autonomic imbalance. For the sympathetic/parasympathetic balance RR- and PQ-interval lengths were considered as indicators. QT-interval length was taken as a manifestation of the balance between left and right sympathetic innervation. Minor abnormalities in ST-segment level and T-wave amplitude may reflect both kinds of imbalance, however, may also be a consequence of myocardial or epicardial disease.
The following questions were studied in relation to these electrocardiographic parameters:

- Are these parameters separately, at rest or after exercise, associated with the risk of all-cause, cardiovascular and coronary heart disease mortality?
- Are the observed associations between these parameters and mortality risk independent of established cardiovascular risk factors?
- To what extent do these electrocardiographic parameters combined predict coronary heart disease mortality risk?

In addition to the electrocardiographic subject matter, this thesis also contains a methodological digression. Its purpose is to evaluate the performance of the case-cohort sampling design relative to other cost-efficient designs and to extend methods of data analysis for this design.

1.3 Structure of the thesis

The second chapter describes the study population and data collection from the original health examination in 1953, the measurement and coding of the electrocardiograms and the

mortality follow-up. Chapter 3 elaborates on the case-cohort approach and its methodology. An empirical comparison between results from case-cohort, case-control and full-cohort approaches is reported in chapter 4. In this chapter, a new pseudo-likelihood method for relative-risk estimation in case-cohort approach is presented. Chapter 5 reports the associations observed for RR-interval length (heart rate) with all-cause, cardiovascular and coronary heart disease mortality. Chapters 6-8 address these associations for the different segments of the electrocardiogram, in their order of occurrence in the cardiac cycle: PQ- and QT-interval length and ST-T abnormalities, respectively. Since the separate effects of the electrocardiographic parameters may be mutually dependent, their joint predictive value was investigated and is presented in chapter 9. In the General discussion, chapter 10, the discussion sections of the previous chapters are integrated, the strengths and weaknesses of the methods of data acquisition and data analysis as well as the validity and implications of the findings are discussed.

REFERENCES

1. Bayes de Luna A, Coumel P, Leclercq JF: Ambulatory sudden cardiac death; Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J 1989; 117(1):151-159.
2. Fioretti P, Tijssen JPG, Azar AJ, Lazzeroni E, Brower RW, ten Katen HJ, Lubsen J, Jugenholz PG: Prognostic value of predischarge 12 lead electrocardiogram after myocardial infarction compared with other routine clinical variables. Br Heart J 1987;57:306-312.
3. Schwartz PJ, Wolf S: QT-interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074-1077.
4. Rose G, Baxter PJ, Reid DD, McCartney P: Prevalence and prognosis of electrocardiographic findings in middle-aged men. Br Heart J 1978;40:636-643.
5. Kreger BE, Cupples LA, Kannel WB: The electrocardiogram in prediction of sudden death: Framingham study experience. Am Heart J 1987;113:377-382.
6. Prineas RJ, Crow RS, Blackburn H: The minnesota code manual of electrographic findings. Standards and procedures for measurement and classification. Boston, Bristol, London: John Wright, PSG Inc, 1982.

7. Verrier RL: Neural factors and ventricular electrical instability. in: Wellens HJJ, Kulbertus HE. Sudden death. The Hague: M Nijhof, 1980.
8. Schwartz PJ, Stone HL: The role of the autonomic system in sudden cardiac death. Ann NY Acad Sci 1982:162-180.
9. Lown B, Verrier RL: Neural activity and ventricular fibrillation. New Engl J Med 1976;294:1165-1170.
10. Malliani A, Schwartz PJ, Zanchetti A: Neural mechanisms in life-threatening arrhythmias. Am Heart J 1980;100:705-715.
11. Yanowitz F, Preston JB, Abildskov JA: Functional distribution of right and left stellate innervation to the ventricles. Circ Res 1966;18:416-428.
12. Armour JA, Hageman GR, Randall WC: Arrhythmias induced by local cardiac nerve stimulation. Am J Physiol 1972;223:1068-1075.
13. Randall WC, Kaye MP, Hageman GR, Jacobs HK, Euler DE, Wehrmacher WH: Cardiac dysrhythmias in the conscious dog following surgically induced autonomic imbalance. Am J Cardiol 1976;38:178-83.
14. Schwartz PJ, Periti M, Malliani A: The long QT-syndrome. Am Heart J 1975;89:378-390.
15. Schwartz PJ: Idiopathic long QT-syndrome: progress and questions. Am Heart J 1985; 109:399-410.
16. Jervell A, Lange-Nielsen F: Congenital deaf-mutism, functional heart disease with prolongation of the QT-interval and sudden death. Am Heart J 1957;54:59-68.
17. Romano C, Gemme G, Pongiglione R: Aritmie cardiache rare dell'eta pedjatrica. Clin Pediatr 1964;45:656-683.
18. Ward OC: New familial cardiac syndrome in children. J Ir Med Assoc 1964;54:103-106.
19. Schwartz PJ, Wolf S: QT-interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074-1077.
20. Peters RW, Barker A Byington R, and the BHAT study group: Prognostic value of QTc prolongation: the BHAT experience (abstr). Circulation 1984;70:suppl II:II-6.
21. Miettinen OS: Design options in epidemiologic research. An update. Scand J Work Environ Health 1982;8 suppl 1:7-14.
22. Prentice RL: A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika 1986;73:1-11.
23. Greenland S: Adjustment of risk ratios in case-base studies (hybrid epidemiologic designs). Stat in Med 1986;5:579-584.

24. Nurminen M: Analysis of epidemiologic case-base studies for binary data. Stat in Med 1989;8:1241-1254.

2. POPULATION AND DATA ACQUISITION

2.1 Original population and baseline data

The original health examination, providing the baseline data for the present study, was carried out in 1953 and 1954 among civil servants of the city of Amsterdam. The aim was detection of disease at an early subclinical stage, when treatment might have better prospects. The examination was suggested by physicians interested in public health and approved by the municipal council of Amsterdam. The purpose was to study the feasibility of screening large numbers of healthy middle-aged persons both in terms of process and yield of subclinical disease. The examination was carried out by the physicians R.M. van de Heide and H.G. Frenkel-Tietz, the first of whom published the results in a PhD thesis in 1959 (1).

Original population

At the start of the health examination in 1953, all 11,700 Amsterdam civil servants on active duty aged 40 years and over, and their spouses were invited to be examined. The project was announced as a feasibility study, intended for healthy persons. About 54% of the eligible civil servants volunteered, with or without their spouses. From these volunteers an age- and sex-stratified random sample was chosen with the purpose of obtaining about equal numbers in each 5-year age and sex category. This way a cohort of 3,091 persons were examined: 1,583 men, nine of whom were husbands of female civil servants, and 1,508 women, 1,074 of whom were wives of male civil servants.

The baseline data

The original examination consisted of a detailed medical history obtained by a structured interview, a physical examination, an electrocardiogram, a chest X-ray micrograph and some laboratory examinations. The interview addressed age, sex, marital status, number and health of children, occupation, medical history, serious diseases and longevity of the parents. Consumption of coffee, tea, alcohol and tobacco was asked for and a short food frequency questionnaire, assessing the usual intake, was filled out. A full physical examination was carried out, covering all tracts, including retinoscopy, rectal examination and cervical smear. The laboratory investigations included urine testing on reduction, protein and cells, blood testing on hemoglobin, sedimentation rate and total serum cholesterol.

The measurements of special interest for the present study are described in more detail below.

Participants were inquired about precordial pain which was recorded as none, atypical, and of typical anginal character. Precordial pain was regarded as anginal if it was described as tightness in the chest, was accompanied by fear, and if it occurred in conjunction with emotion and exercise.

A 12-lead electrocardiogram was recorded on an Elema one-channel, ink-jet electrocardiographic recorder, type Mingograph. A second, five-lead recording was made after the Master Two Step Test (2). This second recording was intended to take place within one minute after completing light exercise, standardized for age and sex. This period may regularly have been longer, since the participant had to lie down and the electrodes had to be re-attached.

Blood-pressure readings were taken in supine position on the right arm, using a standard mercury sphygmomanometer with a 12 cm cuff. These readings were in multiples of five millimeters of mercury. Total serum cholesterol was measured according to Saifer and Kammerer's modification of the Liebermann-Burchard reaction expressed in mg/100 ml (3). Body weight was measured wearing only underwear, and height without shoes. From these measurements body-mass index (Quetelet Index) was calculated in kg/m^2 (4). Smoking habits were asked for during the interview and recorded as usual number of cigarettes, cigars or pipes per week.

Except for the electrocardiograms, the baseline data used in the present study had been entered into a computer database in 1980.

2.2 Mortality follow-up

For the assessment of survival and the follow up of the causes of death two different methods have been used. Survival until 1981 was assessed for the aim of previous studies (5-10) and the causes of death of those who died until 1981 were established in 1989, for the purpose of the present study.

Survival

The health examination providing the data of the present study was directed at civil servants and their spouses, who were at that time between 40 and 65 years of age. In 1981 all of them could be expected to receive their old age pension or to have been deceased. For finan-

cial reasons, survival of these civil servants and their spouses is monitored almost perfectly by the Civil Servants Pension Fund (A.B.P.). The follow up of survival of the Amsterdam civil servants and their spouses was therefore carried out through the records of this pension fund. Survivors were documented as still receiving their pensions in 1981. For a small number of persons, survival was determined with the help of the management of the municipal services that used to employ them. In the end survival could not be established for one man and two women.

Since 1981, associations between baseline variables and survival were investigated in several epidemiologic analyses (5-10). As the predictive power of baseline variables inevitably diminishes with increasing period of follow up, it was decided not to extend the follow-up period until 1989 for the present study.

Causes of death

In the Netherlands a copy of the municipal registration card of every citizen is sent after his death to the Central Bureau of Genealogy. The Dutch Central Bureau of Genealogy was able to produce this municipal registration card for 98.3% of the persons known to have died. The information that was used for this purpose was: name, initials, birth date, name of spouse, (only available if also participating in the study), and date of death. Additional information, for instance full first names and last address would have been convenient, but was not available. Most of the missing cases were tracked down by means of municipal population registries. From the registration cards, the place of death and the municipal death registration number were extracted.

With this information and with the date of death, the cause of death, coded according to the International Classification of Diseases (ICD), registered anonymously by the Central Bureau of Statistics (C.B.S.), could be linked to the data from the health examination in 1953-1954 by computer. For 18 men and 10 women the cause of death could not be established, in majority due to emigration.

In general, there are a number of threats to the accuracy of these registered causes of death because of problems on several levels (11):

- problems in the accuracy of the diagnosis made by the certifying clinician;
- problems in the completion of the death certificate by the certifying clinician;
- problems in classification of the underlying cause of death and its coding.

The first two sources of error were beyond correction, since it was impossible to return to the

certifying physicians or to the clinical information the diagnosis relied upon.
Inaccuracy resulting from classification and coding is inherent to the use of any register. Periodic revision of International Classification of Diseases and coding procedures complicates things further. The causes of death were registered according to four different revisions of the ICD classification system: the revisions 6, 7, 8 and 9 (12). The present study was mainly concerned with the categories of cardiovascular (ICD 9, codes 390-460) and coronary heart disease mortality (ICD 9, codes 410-414). From duplicate coding of deaths, under the eighth and ninth revision of the ICD performed by the C.B.S. in the past, it was decided that for the causes of death from 1969 on, originally coded under these two revisions, similar categories of cardiovascular and coronary heart disease mortality could be composed. The causes of death originally coded under the sixth and seventh revisions, recently were recoded to the ninth, by coding officers of the C.B.S., using the diagnosis on the original notification form.

2.3 Case-cohort study population

In the present study, associations between electrocardiographic characteristics and cardiovascular mortality are studied. For this purpose, the original electrocardiograms, recorded at baseline in 1953-1954, had to be measured and coded, a very cumbersome and time-consuming procedure. For efficiency reasons it was decided not to use all electrocardiograms, but to evaluate only a part of them, by applying case-cohort sampling (13). Under this sampling scheme valid estimation of associations is possible, using the information of all cases (deaths), and relate these to a random sample from the cohort.

Cases and cohort sample

Since the measurement and coding of electrocardiograms had to start at a moment when information on the cause of death was not yet available, electrocardiograms of all deaths from any cause had to be evaluated (914 men and 531 women), to make sure that in the end all cardiovascular deaths would have been included. To represent the cohort in the case-cohort approach, a random sample of 730 men and 502 women was drawn from the cohort. It was intended to be twice the expected number of cardiovascular deaths, estimated as 40% of the total number of deaths.

After exclusion of subjects for whom the information on survival, cause of death or the

entire electrocardiogram was missing, the study population consisted of 1,219 male and 848 female participants. The random sample counted 723 men and 498 women. Table 2.1 shows the way the case-cohort study population was derived from the original cohort.

Table 2.1 Case-cohort study population and sample as derived from the original cohort.

	men N=1,583		women N=1,508	
	ORIGINAL COHORT			
Deaths in 28 years	894		521	
Survivors	668		975	
Missing information	21		12	
on: Survival		1		2
Cause of death		18		10
ECG		2		--
	COHORT SAMPLE			
	N=730		N=502	
Deaths in 28 years	398		171	
Survivors	325		327	
Missing information		7		4
on: Cause of death		6		4
ECG		1		-
	CASE-COHORT STUDY POPULATION			
Deaths in original cohort	894		521	
Survivors in cohort sample	325		327	
	1,219		848	

In table 2.2 baseline characteristics of the individuals in the sample are compared with those in the cohort. No major or statistically significant differences ($p < 0.05$) were observed.

The random sample obviously contains only part of the deaths. As has been mentioned before, all subjects who died in the full 28 years of follow up, were taken in the study population. Therefore the total number of subjects in the case-cohort study population is the sum of the number in the sample and the extra deaths that occurred in the rest of the cohort. To put it in other words: the study population consists of all deaths in the entire cohort and only those survivors who were drawn in the sample.

Table 2.2 Mean (sd) of baseline characteristics and mortality percentages in cohort and sample, men and women separately.

MEN	COHORT N=1,562*		SAMPLE N=723*	
	mean	(sd)	mean	(sd)
Cholesterol (mmol/l)	6.7	(1.3)	6.6	(1.3)
Diastolic BP (mm Hg)	79.4	(10.5)	79.1	(10.6)
Age (yrs)	52.8	(7.4)	52.7	(7.6)
Body-mass index (kg/m^2)	24.7	(2.7)	24.6	(2.7)
Smokers (%)	63.6		62.8	
Cigarettes (n/week)	70.1	(51.3)	72.6	(53.1)
Mortality 28 yrs (%)				
Total	57.3		55.1	
CVD	27.2		25.1	
CHD	15.2		13.0	
Mortality 15 yrs (%)				
Total	22.3		22.2	
CVD	11.1		10.9	
CHD	6.6		6.6	
WOMEN	COHORT N=1,496*		SAMPLE N=498*	
	mean	(sd)	mean	(sd)
Cholesterol (mmol/l)	7.1	(1.4)	7.2	(1.6)
Diastolic BP (mm Hg)	87.0	(13.3)	87.8	(13.7)
Age (yrs)	51.8	(7.1)	52.0	(7.4)
Body-mass index (kg/m^2)	26.5	(3.8)	26.4	(3.5)
Smokers (%)	37.2		37.2	
Cigarettes (n/week)	21.8	(30.5)	18.2	(24.7)
Mortality 28 yrs (%)				
Total	34.8		34.3	
CVD	15.3		14.5	
CHD	6.4		6.4	
Mortality 15 yrs (%)				
Total	10.0		10.8	
CVD	4.1		4.4	
CHD	1.4		2.4	

* Individuals with missing information on survival or cause of death were excluded; individual parameters may have missing data.

The sample representing the cohort is the same in all analyses. The number of extra deaths in the rest of the cohort, however, depends on mortality category and on the follow-up period of a particular analysis. Whenever cardiovascular or coronary heart disease mortality is studied, or whenever a follow-up period of less than the full 28 years is considered, the case-cohort study population is somewhat smaller.

2.4 Measurement and coding of the electrocardiograms

Although more than 35 years old, the quality of the electrocardiograms recorded at baseline in general was sufficient to enable measurement and coding. Only one electrocardiogram was available, per participant at baseline.

Electrocardiographic characteristics

The electrocardiograms were measured and coded on a large number of items at rest and after exercise. These items were chosen, because they are possible indicators of the autonomic nervous system balance, important for comparison with other studies or play a role in exclusion of subjects with manifest heart disease at baseline.

The following items are important for the present study;

- **heart rate**, which at rest is mainly under parasympathetic autonomic influence.
- the **Cardiac Infarction Injury Score** (CIIS) (14), a twelve-item, mainly quantitative scoring system, designed to measure myocardial damage by infarction. This CIIS score was used to be able to exclude persons with manifest heart disease from certain analyses.
- the **Minnesota Code** (15,16), a 16 item qualitative classification system, that uses mainly clinical criteria. Reasons for applying it in the present study were, that it enables exclusion of persons with heart disease and, since it is the most frequently used electrocardiographic classification for epidemiologic studies, it would make comparison with other epidemiological studies possible.
- **PQ-interval length** measured in units of 10 msec, the longest in standard lead I, II or III. AV-node conduction, is thought to be equally under the influence of the sympathetic and the parasympathetic parts of the autonomic nervous system. Therefore PQ-interval length may be an indicator of the balance between these two systems. The longest interval was used, since the earliest manifestation of atrial depolarization was assumed to provide the best measure of

the duration of atrioventricular conduction.

- **QT-interval length**, the longest in standard lead I, II or III, together with the preceding RR interval, in multiples of ten milliseconds. The QT interval was adjusted for the preceding RR interval according to the method of Bazett (17) and was regarded as a measure of autonomic balance.
- **T-wave amplitude** was measured in mm (0.1 mV) and **ST-segment level** in quarters of millimeters (0.025 mV), all in standard lead I. These parameters may, when meeting certain criteria, be indicative of coronary heart disease. More subtle abnormalities may indicate autonomic imbalance. Standard lead I was chosen, because most abnormalities of left ventricle depolarization and repolarization are represented in this lead, and because this lead was recorded after exercise as well.

  PQ and QT interval, ST segment and T wave all were measured in the resting as well as the post-exercise electrocardiogram.

Procedure

The strips from the one-channel recordings that were made in the health examination in 1953-1954, at that time were glued onto a sheet of paper and stored. In 1989 these recordings were measured and coded by four coders who were blinded for survival and for baseline status. Three of the coders were medical doctors, one was an epidemiologist. PQ interval was added later and was measured in all electrocardiograms by a single coder. The cohort design allowed limitation of the number of electrocardiograms that had to be processed, from more than 3,000 to about 2,000.

Since one of the coders, an assistant cardiologist, systematically ignored minor ST-segment abnormalities, his part of the ST-segment coding had to be recoded by the same coder who performed the PQ measurements.

About 10 % of the electrocardiograms were coded for a second time by an independent coder, for quality control. Most differences in these duplo measurements for the key electrocardiographic variables were small and distributed around zero, indicating no major systematic measurement error (Appendix 1). The measurements and coding were carried out using a magnifying glass and took on average about 15 minutes per electrocardiogram. For data input in a computer database, a special optically readable form was developed. To eliminate coding errors, ranges of variables and inconsistencies were checked by a computer program.

REFERENCES

1. Heide van der RF: Resultaten van een geneeskundig onderzoek van 3091 gezonde mannen en vrouwen, 40-65 jaar oud. PhD thesis, Amsterdam: University of Amsterdam, 1959.
2. Master AM, Friedman T, Dack S: The electrocardiogram after standard exercise as a functional test of the heart. Am Heart J 1942;777-793.
3. Saifer A, Kammerer DF: Photometric determination of total cholesterol in plasma or serum by a modified Liebermann-Burchard reaction. J Prot Chem 1946;164-167.
4. Quetelet A: Anthropométrie, ou mésure des différentes facultés de l'homme. Brussels: Muqardt, 1870.
5. Vandenbroucke JP, Mauritz BJ, de Bruin A, Verheesen JHH, van der Heide-Wessel C, van der Heide RM: Weight, smoking, and mortality. JAMA 1984;252:2859-2860.
6. Vandenbroucke JP, Matroos AW, van der Heide-Wessel C, van der Heide RM: Parental survival, an independent predictor of longevity in middle-aged persons. Am J Epidemiol 1984;119:742-750.
7. Vandenbroucke JP, Verheesen JHH, de Bruin A, Mauritz BJ, van der Heide-Wessel C, van der Heide RM: Active and passive smoking in married couples: results of 25 year follow up. Br Med J 1984;288:1801-1802.
8. Schouten EG, Vandenbroucke JP, Van der Heide-Wessel C, van der Heide RM: Retinopathy as an independent indicator of all-causes mortality. Int J Epidemiol 1986;15:234-236.
9. Kok FJ, Vandenbroucke JP, van der Heide-Wessel C, van der Heide RM: Dietary sodium, calcium, and potassium, and blood pressure. Am J Epidemiol 1986;123:1043-1048.
10. Van den Ban GC, Kampman E, Schouten EG, Kok FJ, van der Heide RM, van der Heide-Wessel C: Isolated systolic hypertension in Dutch middle aged and all-cause mortality: A 25-year prospective study. Int J Epidemiol 1989;18:95-99.
11. Alderson M: Mortality, morbidity and health statistics. New York: Stockton Press, 1988.
12. Manual of the international statistical classification of diseases, injuries, and causes of death, 9th ed, vol 1. Geneva: World Health Organisation, 1977.
13. Miettinen OS: Theoretical epidemiology. Principles of occurrence research in medicine. New York, Chichester, Brisbane, Toronto, Singapore, John Wiley & Sons, 1985.

14. Rautaharju PM, Warren JW, Jain U, Wolf HK, Nielsen CL: Cardiac Infarction Injury Score: an electrocardiographic coding scheme for ischaemic heart disease. Circulation 1981;64:249-256.
15. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S: The electrocardiogram in population studies. A classification system. Circulation 1960;vol XXI:1160-1175.
16. Prineas RJ, Crow RS, Blackburn H: The Minnesota Code manual of electrocardiographic findings. Boston: John Wright PSG Inc., 1982.
17. Bazett HC: An analysis of the time relations of electrocardiograms. Heart 1920;7:353-370.

3. THE CASE-COHORT APPROACH: METHODS AND ANALYSIS

3.1 Introduction

The data from the study described in this thesis originally were collected in a survey, carried out with the purpose of testing the feasibility and usefulness of a general medical screening in an apparently healthy middle-aged population. The present study, however, is a follow-up study, investigating the association between electrocardiographic characteristics and cardiovascular mortality. The usual strategy of data analysis in this type of study is to stratify the cohort in groups according to some electrocardiographic characteristic and compare these groups with respect to a measure of mortality incidence, e.g. cumulative incidence ("risk") or incidence density ("rate"). In the analysis, all members of the cohort would contribute information on survival and on covariates (electrocardiographic variables, confounders). In this chapter this approach will be called the "full-cohort design".

Because of the hand measurement and coding of electrocardiograms that had to be carried out in the study, the full-cohort design, using all electrocardiograms, was not feasible. Hence, alternative designs were considered in which evaluation of a smaller number of electrocardiograms would suffice, without losing much precision in the measures of association.

This chapter addresses the structure of the analysis, as used throughout the thesis. It is a structure in which all cases are studied, while the cohort is approximated by a random sample. This "case-cohort sampling procedure" is described in chapters 2 and 3. Paragraph 3.2 describes different design options for cohort studies, with special attention to the case-cohort design. In paragraph 3.3 the merits of the various options and the rationale of choosing for the case-cohort design are discussed.

3.2 Design options

Prospective cohort studies of rare diseases in the general population often require follow up of very large numbers of persons initially free of the disease. Frequently these persons have to be followed for a long period, to ensure a sufficient yield of the rare disease end-points. Financial and other resources needed for recruitment, exposure assessment and follow up are large and may easily preclude performing such studies. Examples of very large-scale studies are the Nurses Health study (1) in the USA and the prospective cohort study on diet and cancer (2)

in the Netherlands, among more than 120,000 subjects.

Even in case of less rare diseases and less numerous populations, like in the present investigation, a prospective cohort study in the general population may not be feasible for several reasons:

- Collection of exposure information on a large number of healthy persons may be too expensive in terms of money and/or cooperation required.
- The costs of processing of collected material containing exposure information may be prohibitive. Examples of this are blood or tissue samples requiring complicated biochemical analysis, and the hand measurement and coding of electrocardiograms.

In these circumstances, strategies more cost-efficient than the full-cohort design are needed, allowing reduction of the number of cohort members for whom collection and/or processing of covariate information has to be carried out. With this purpose in mind, several outcome-selective sampling designs have been developed, which are efficient in that they do not require evaluation of covariate data on all members of a population, but only on a fraction of them. These designs are the case-control study, the nested case-control study (case-control within cohort) and the case-cohort (or case-base) study. Some authors discussing these designs, use the term "nested case-control design" for both case-control within cohort and case-cohort designs.

The remaining part of this paragraph deals with these design options for investigating the association between a dichotomous exposure and a dichotomous outcome in a large cohort study. First a description is given of how this would be handled in the normal full-cohort approach, followed by more cost-efficient approaches for estimating the association in the cohort. To point out the differences between the designs, the data layout of table 3.1 is used. Figure 3.1 provides a diagram of the different sampling designs. In chapter 4 the results obtained by application of some of these strategies are empirically compared.

Full-cohort design

In the upper part of table 3.1, the data layout for the present cohort study on coronary heart disease (CHD) death is given. The symbols used for the cell frequencies are capitals, to represent all members of the cohort. Using the counts of exposed and unexposed cases and non-cases of CHD death, with and without some electrocardiographic characteristic, absolute risk among exposed, [A/(A+B)], and non-exposed, [C/(C+D)], and their ratio can be calculated. The ratio is called the relative risk, a measure of the association between exposure and CHD

death. A related measure of association, although not usually calculated in a cohort study, is the disease odds ratio [AD/BC]. It is evident, that when [A] and [C] are small, in other words, when the disease is rare, the odds ratio and the relative risk are practically equal (3). When this so-called "rare disease assumption" is not satisfied, the odds ratio overestimates relative risk. Using person-time data, if available, the corresponding incidence densities [A/PY_1] and [C/PY_0] for exposed and unexposed, respectively, and their ratio can be calculated. This incidence density ratio is sensitive for differences in person-time at risk and therefore may be a more valid measure of the exposure-disease association in case of a long period of follow up or in the presence of competing mortality. If for instance persons with a certain electrocardiographic characteristic would die shortly after the start of the study, while persons without that characteristic would die mainly at the end of the period of observation, the cumulative incidence ratio over that period would underestimate the relative risk.

Both relative risk and incidence density ratio obtained from observational studies, often have to be adjusted for confounding variables. Several methods of pooling over confounder strata in stratified analysis are available (4,5). For multivariate adjustment of relative risk, until now (see chapter 4), there are no generally available methods. Usually, therefore, logistic regression analysis (6) is carried out. This, however, produces a logistic coefficient that has an odds-ratio and not a relative-risk interpretation. For multivariate adjustment of the incidence density ratio, Cox' proportional hazards model (7) is the commonly used method.

Case-control design

The second part of table 3.1 represents a case-control study that might be undertaken afterwards, to estimate the association between exposure and disease, without following up the cohort of the upper panel. A sample of cases of the disease under study are identified and their exposure is compared with a sample of non-cases. The exposure is assessed retrospectively for the case and non-case sample. Typically the number of controls is chosen to be equal to the number of cases, or a small multiple of it. This approach is in fact the classical case-control approach (3), except that the source population is exactly defined.

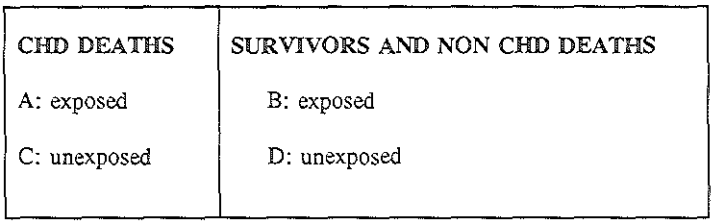
Since [a+b] and [c+d] do not represent any meaningful quantity, relative risk can not be estimated. The ratio of exposed [a] and unexposed [c] cases (odds of exposure among the cases), is compared with the ratio of exposed [b] and unexposed [d] non-cases out of the non-case sample (odds of exposure among the non-cases). The ratio of these two exposure odds, the odds ratio [ad/bc], is the measure of association calculated from this kind of study. It estimates

the exposure odds ratio [AD/BC] in the cohort. As explained before, the exposure odds ratio in the cohort is identical to the disease odds ratio, which has relative risk interpretation, provided that the disease in question is rare.

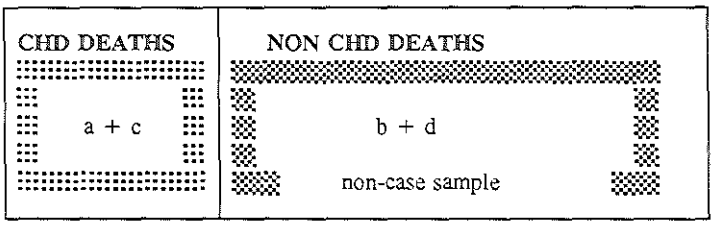
Table 3.1 Data layout of full-cohort, case-control, nested case-control and case-cohort design.

Exposure	CHD deaths	survivors and non CHD deaths	total number	person-years
Full-cohort design				
Exposed	A	B	A + B	PY_1
Not exposed	C	D	C + D	PY_0
Total	A + C	B + D	N	PY
case-control design				
Exposed	a	b	?	?
Not exposed	c	d	?	?
Total	a+c	b+d	?	?
nested case-control design				
Exposed	A	b	?	?
Not exposed	C	d	?	?
Total	A + C	b + d	?	?
Case-cohort design				
			Sample	
Exposed	A	b'	a' + b'	py_1
Not exposed	C	d'	c' + d'	py_0
Total	A + C	b' + d'	n	py

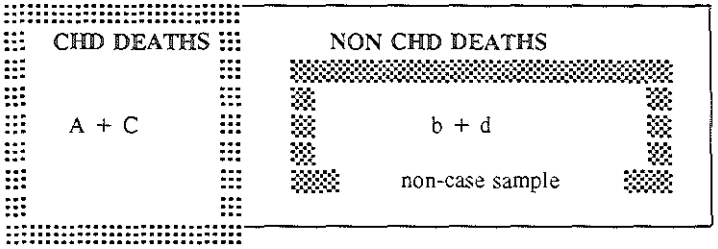
Capitals: numbers in the cohort
Small print: samples from the full cohort



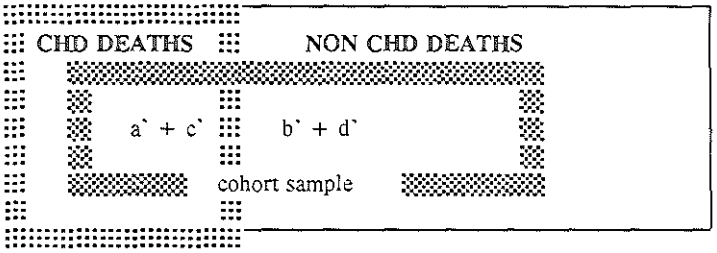
I Full-cohort



II Case-control design



III Nested case-control design



IV Case-cohort design

Legends: cases taken in the analysis

referents taken in the analysis

Figure 3.1 Diagram of the different sampling designs

Case-cohort approach

Because under the case-control sampling design, the person-years at risk that gave rise to the cases are unknown, incidence densities nor their ratio can be estimated. Adjustment of the odds ratio by pooling over strata of confounders is usually carried out by the method of Mantel Haenszel (8), multivariate adjustment by logistic regression analysis (6).

Nested case-control design

In this section two types of nested case-control (or case-control within cohort) design are distinguished: 1. a type using cumulative incidence sampling, and 2. a type using density sampling, also called "synthetic case-control study" (9).

In a nested case-control study with cumulative incidence sampling, like in the full cohort design, the whole cohort is followed with respect to disease occurrence and all cases [A+C] are enrolled (table 3.1, third part). Material containing exposure information like records or biological specimens is collected on all cohort members at baseline, like in the full-cohort approach and is stored. The processing of this material (coding, chemical analysis etc.), however, is postponed and carried out later, after disease occurrence, on all cases and on a random sample of the non-cases, that in size usually is equal to or a small multiple of the number of cases. The exposure odds ratio [Ad/bC] is the measure of association that is calculated from this study, estimating the disease odds ratio [AD/BC] in the cohort. The total number of exposed and unexposed subjects and the number of person-years at risk accumulated among them are unknown. Consequently, relative (and absolute) risk and incidence density cannot be calculated. Stratified and multivariate analysis are carried out with the methods described under case-control design.

The nested case-control study with density sampling or **synthetic case-control study** (10-12) is in fact a time-matched nested case-control study: processing of exposure information is postponed until after case occurrence, and performed on all cases and a sample of the non-cases. Each case, however, is matched to one or more non-cases drawn from those subjects who still were candidates of the disease at the time of occurrence of that particular case. A matched analysis of these sets yields an estimate of the incidence density ratio. Multivariate adjustment can be carried out with Cox` proportional hazards model, using conditional maximum likelihood estimation (13).

Case-cohort design

In a case-cohort study (table 3.1, lower panel), like in the nested case-control and full-cohort designs, covariate information is collected at baseline for all cohort members. The information is processed and studied after completion of follow up, using the following sampling scheme: a random sample is drawn (a subset of cases and non-cases, size n) from the cohort, and all remaining cases that were not drawn as a member of the sample, are added (11,13-17). In other words, the case-cohort population consists of all cases that occurred during the follow up period and the non-cases of a random sample from the cohort. The cohort sample is the source of information about the cohort. Miettinen summarizes the case-control, nested case-control and case-cohort designs all under the name "case-referent designs" and uses the term "case-base design" instead of "case-cohort design", in order to include a study base that consists of the experience of a dynamic population (17).

A case-cohort study can be looked at from two different perspectives: 1. as a peculiar type of cohort study; 2. as a nested case-control study.

1. Viewed as a type of cohort study, the distinction with a normal cohort study is, that in the analysis the cohort is represented by the random sample: the number of persons or person-years at risk in the cohort, needed for the denominators of the incidence measures, is substituted by the corresponding number in the sample. Evidently, the relative risk (cumulative incidence ratio) [A/(A+B):C/(C+D)] in the full cohort is estimated by [A/(a'+b'):C/(c'+d')], since ϵ[a'+b'], the expectation of [a'+b'], is f(A+B) and ϵ[c'+d'] = f(C+D), where f = n/N is the sampling fraction that is divided out in the ratio measure. If person-time data are available, the incidence density ratio [A/PY_1:C/PY_0] can be estimated similarly, since $\epsilon py_1 = fPY_1$ and $\epsilon py_0 = fPY_0$.

   The relative risk and the incidence density ratio estimation do not require knowledge of the sampling fraction. If the sampling fraction nevertheless is known, the corresponding numbers (or person-years) in the cohort can be estimated, and using these, absolute cumulative incidence and incidence density. The precision of these estimates depends both on the size of the cohort sample and on the sampling fraction.

2. A case-cohort study can be looked at as a nested case-control study, if relative risk (cumulative incidence ratio) is the measure of interest. The cohort sample then is the referent group, instead of a sample of the non-cases, (15). The cohort sample essentially is a sample of the non-cases [b'+d'], supplemented with a proportional sample of the cases

[a'+c']. Substitution of the cohort sample in the formula of the nested case-control odds ratio [A/b:C/d] (=Ad/bC) gives [A/(a'+b'):C/(c'+d')], which is an estimate of the relative risk in the cohort [A/(A+B):C/(C+D)], whether the outcome is rare or not, since ϵ[a'+b'] = f(A+B) and ϵ[c'+d'] = f(C+D). The sampling fraction f=n/N again is divided out in the ratio. In conclusion, the true relative risk in the cohort is estimated by the "case-cohort odds ratio", without invoking the rare disease assumption.

As demonstrated above, analysis of crude case-cohort data is rather straightforward. Standard methods for stratified analysis in case-cohort design, however, are partly, standard methods for multivariate analysis completely absent. The few epidemiology text books that mention the case-cohort sampling design at all (4,18), implicitly seem to suggest application of odds ratio methods. This may yield valid crude estimates, but the standard error is invalid because of the dependency in the data, existing between the case-group and the referent group. Miettinen (16,17) proposes to remove this dependency in significance testing, by omitting the cases from the referent group. This implies testing the corresponding case-control odds ratio and accepting inability to produce a confidence interval for the relative risk. For a more valid standard error of the crude case-cohort odds ratio, Miettinen also provides a formula that is a modification of Woolfs method (16). Greenland (19) and Nurminen (20) provide special methods for pooled case-cohort odds ratio estimates and their standard error.

In order to force the multivariate logistic regression model, to treat both the cases and the non-cases from the cohort sample as the referent group, some manipulation is necessary. It means, that the non-case referents, coming from the cohort sample, have to be supplemented with case referents from the same cohort sample. These cases have to play a double role in the logistic regression analysis: they have to be the case which they really are and to play simultaneously a non-case in contribution to the referent group. Therefore, the cases from the cohort sample are brought in the analysis a second time, recoded as non-case. Le Cessie et al. (21) have argued that this mathematically comes down to maximizing a pseudo likelihood function and that the logistic model produces valid parameter estimates. Moreover, they propose methods of estimation of the standard error that are easily performed with standard software for logistic regression. An empirical comparison of the results of different approaches used in the same dataset, is presented in Chapter 4.

Case-cohort approach

For adjustment of case-cohort incidence density ratios (or rate ratios), Prentice (11) has proposed a modification of the Cox Proportional Hazards model. For parameter estimation in this model, however, no standard statistical software is available. The use of the commonly available software for estimation of parameters in the proportional hazards model, produces biased results.

A way out of this, however, is the use of Poisson regression for estimation of the case-cohort incidence density ratio. Le Cessie et al. (21) demonstrated that this yields valid parameter estimates, while standard errors can easily be estimated with generally available statistical software. In chapter 4 the results of this procedure are also compared with the results of the other sampling designs.

3.3 Choice for the case-cohort design

From the design options in the preceding paragraph, the case-cohort design was chosen as the preferred cost efficient sampling design for the present study. Relevant characteristics of the different options are summarized in table 3.2.

The rationale of the choice for the case-cohort design is given in this paragraph, by discussing the strengths and weaknesses of the alternative design options addressed in 3.1.

Since the special methods for estimation of the variance in the case-cohort approach came available, when some of the analyses in this thesis had already been performed, the results reported in the following chapters concentrate on the relative risk, while significance testing in the chapters 6 and 7 was carried out by omitting the cases from the referent group.

Covariate assessment

All three alternative strategies are efficient in that processing of covariate data on non-cases is limited to a sample of the cohort. An additional advantage of the case-control design is, that it is the only design that does not require collection of covariate data on all cohort members. In the present study, however, covariate information had already been collected on all cohort members in the past.

The case-cohort design has the advantage, that the sampling strategy to obtain the referent group is very simple and can be carried out at the start of the study. Data processing for the sample can start immediately after data collection, if required. Only in the case-cohort design,

a source of information about the total cohort is available, since the referent group is a random sample from the cohort.

Estimation

In the case-control and nested case-control designs, the odds ratio is the estimated measure of association. It can be interpreted as a relative risk only if the rare disease assumption holds.

The odds ratio calculated in a synthetic case-control study estimates the incidence density ratio. This, however, requires a matched analysis.

In the case-cohort design a variety of epidemiologic measures can be estimated: If count data are available, true relative risk can be calculated. If person-time data have been collected, the incidence density ratio can be estimated as well. Using the methods proposed in 3.1 and in chapter 4, adjusted estimates of these measures can easily be calculated. Knowledge of the sampling fraction enables calculation of the absolute risk and absolute incidence density.

Taking the arguments together, if the disease outcome is not rare (cumulative incidence $> 10\%$), like cardiovascular and coronary heart disease mortality in the present study, the synthetic case-control and case-cohort designs are preferable, because they do not need a rare disease assumption. When the disease is very frequent, none of the alternative designs is advantageous over the full-cohort design. Because of the number of epidemiologic measures that can potentially be estimated in the case-cohort design, in the present study this was preferred over the synthetic case-control design.

Precision

For the case-control and nested case-control designs standard errors of the calculated odds ratios are provided without any trouble by the case-control methods described in 3.1.

In the synthetic case-control study, the standard error of the incidence density ratio follows from matched analysis of the case-control subsets.

Although the case-cohort sampling design conceptually is very attractive, methods for assessing the precision of the relative risk and the incidence density ratio until now were incomplete. The adaptation of logistic regression and the poisson regression described in 3.1 and in chapter 4, however, provide simple ways to estimate standard errors and remove this drawback.

Bias

In the case-control approach, exposure is assessed retrospectively for a sample of the cases and non-cases from the cohort. By performing a case-control study in a well-defined cohort, the requirement that the controls have to be recruited from the source population that gave rise to the cases is evidently fulfilled. The case-control design, however, is subject to the well known recall and selection bias (3).

In both nested case-control and case-cohort designs, exposure is measured on all subjects at baseline. Therefore, recall bias is either impossible, because exposure assessment is not depending on the memory of the study subjects, or even if it is, recall bias is unlikely, because disease has not yet occurred when the information is collected. Protopathic bias in these designs is largely prevented, since exposure is measured at baseline in disease-free individuals. To be even more confident about this, the cases occurring in the first years of follow up may be omitted.

Bias existing in the cohort, as a result of non-response and loss to follow up related to exposure and, independent of exposure, to outcome, are reflected in the estimates produced by all alternative approaches (5).

Rationale

In conclusion, in the present study on electrocardiographic determinants of cardiovascular mortality, the case-cohort approach was the preferred sampling design for the following reasons:

1. With newly developed methods, a variety of epidemiologic measures and their precision can be estimated in case-cohort design, i.e. cumulative incidence, incidence density, relative risk and incidence density ratio.
2. The distribution of electrocardiographic and other variables in the cohort can be estimated from the sample.
3. Since cardiovascular mortality was not exactly rare: 27% among men and 15% among women in 28 years of follow up, the rare disease assumption was not satisfied and consequently the case-control odds ratio was not expected to be a good approximation of the relative risk.
4. In a long period of follow up the cumulative incidence ratio may not estimate relative risk accurately, since it does not account for differences in person-time at risk between exposure

groups, that may be considerable. The case-cohort design enables calculation of the incidence density ratio, if necessary.

5. Since the main end points in the present study are cardiovascular disease mortality and coronary heart disease mortality, differences in competing mortality by other causes of death may exist between the exposure groups. The case-cohort design enables verification of the relative risk estimates through calculation of the incidence density ratio, to evaluate the effect of competing mortality.

Table 3.2 Characteristics of cost efficient sampling designs as an alternative for a cohort study in a large population.

	case-control			case-cohort	Full-cohort
	classical	nested	synthetic		
Cases	sample	all	all	all	all
Referents					
type	non-case sample	non-case sample	matched non-cases	cohort sample	full cohort
time of identification	end of follow up	end of follow up	during follow up	at start	at start
Data Collection	samples of (non-)cases	whole cohort	whole cohort	whole cohort	whole cohort
Data processing on	samples of (non-)cases	cases and non-case sample	cases and non-case sample	sample and cases*	whole cohort
Estimation	OR	OR	IDR	CIR, IDR, CI, ID	CIR, IDR, CI, ID
Likelihood of bias	+	-	-	-	-
Cohort information	-	-	-	+	+

Abbreviations: OR: Odds ratio; CIR: Cumulative incidence ratio; IDR: Incidence density ratio; CI: Cumulative incidence; ID: Incidence density.

* joint set of sample and cases, partly overlapping

REFERENCES

1. Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, Hennekens CH: A prospective study of postmenopausal estrogen therapy and coronary heart disease. N Engl J Med 1985;313:1044-1049.
2. Brandt PA van den, Goldbohm RA, Veer P van 't, Volovics A, Hermus RJJ, Sturmans F: A large scale prospective study on diet and cancer in the Netherlands. J Clin Epidemiol 1990;43:285-295.
3. Schlesselman JJ: Case-control studies. Design, conduct, analysis. New York: Oxford University Press, 1982.
4. Rothman KJ: Modern Epidemiology. Boston/Toronto: Little, Brown and Company, 1986.
5. Hennekens CH, Buring JE: Epidemiology in medicine. Boston Toronto: Little Brown and Company, 1987.
6. Kleinbaum DG, Kupper LL, Morgenstern H: Epidemiologic research. Principles and quantitative methods. New York: Van Nostrand Reinhold Company Inc., 1982.
7. Cox DR: Regression models and life tables. J Royal Stat Soc (B) 1972;34:187-220.
8. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-748.
9. Flanders WD, Louv WC: The exposure odds ratio in nested case-control studies with competing risks. Am J Epidemiol 1986;124:684-692.
10. Liddell FDK, McDonald JC, Thomas DC: Methods of cohort analysis appraisal by application to asbestos mining. J R Stat Soc (A) 1977;140:469-491.
11. Prentice RL: A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika 1986:73:1-11.
12. Mantel N: Synthetic retrospective studies and related topics. Biometrics 1973;29:479-486.
13. Prentice RL, Self SG, Mason MW: Design options for sampling within a cohort. In: Prentice RL, Moolgavkar SH, eds. Modern statistical methods in chronic disease epidemiology. New York: John Wiley and Sons, 1986:50-62.
14. Kupper LL, Mc Michael AJ, Spirtas R: A hybrid epidemiologic study design useful in estimating relative risk. J Am Stat Ass 1975;70:524-528.
15. Miettinen OS: The "case-control" study: valid selection of subjects. J Chron Dis 1985;38:543-548.

16. Miettinen OS: Design options in epidemiologic research. An update. Scand J Work Environ Health 1982;8 suppl 1:7-14.
17. Miettinen OS: Theoretical epidemiology. Principles of occurrence research in medicine. New York: John Wiley and Sons, 1985.
18. Kahn HA, Sempos CT: Statistical methods in epidemiology. New York: Oxford University Press, 1989.
19. Greenland S: Adjustment of risk ratios in case-base studies (hybrid epidemiologic designs). Stat in Med 1986;5:579-584.
20. Nurminen M: Analysis of epidemiologic case-base studies for binary data. Stat in Med 1989;8:1241-1254.
21. Le Cessie S, Van Houwelingen HC, Dekker JM, Schouten EG: Maximum likelihood and pseudo-likelihood estimates in the case-base design (submitted).

4. A RISK-RATIO MODEL EMERGING FROM EMPIRICAL COMPARISON OF CASE-REFERENT SAMPLING DESIGNS[1]

Evert G. Schouten MD, Jacqueline M. Dekker MSc, Frans J. Kok PhD, Saskia le Cessie MSc, Hans C. van Houwelingen PhD, Jan Pool MD PhD, Jan P. Vandenbroucke MD PhD

4.1 Abstract

The nested case-control and case-cohort sampling designs are cost-efficient alternatives for full-cohort analysis. In principle, the latter would be preferred, since it enables estimation of risk ratio, rate ratio and absolute incidence without requiring the rare disease assumption. A drawback, however, is that multivariate analysis in case-cohort design until now depends on approximate methods. In our study, nested case-control, case-cohort and full-cohort analysis were compared for estimation of the association between hypertension and cardiovascular mortality, in a single cohort. To overcome the analytical drawback, we applied newly developed pseudo-likelihood methods for estimation of case-cohort risk ratio and rate ratio, by logistic regression and Poisson regression. To investigate the validity of the rather unconventional logistic estimate, repeated sampling was applied, with fixed sampling fractions of 25 and 50 per cent of the cohort.

Comparison of the results shows that the new multivariate methods of estimation under case-cohort sampling, which use widely available software, are valid. An attractive implication is, that a multivariate model for estimation of the true risk ratio, is now at every investigators disposal. This model can be generalized for use in the full cohort, representing an advance in risk-ratio methods.

4.2 Introduction

Two increasingly popular cost-efficient alternatives for studying exposure-disease associations in a large cohort are the nested case-control design and the case-cohort or case-

---

[1] Submitted.
Supported by the Netherlands Heart Foundation (grant 86.060)

base design (1-9). In both designs, ascertainment of exposure and other covariates is confined to a subset of the individuals in the cohort. The case-cohort approach involves comparison of all incident cases with a representative sample of the cohort in which they arose. In the nested case-control study, the cases are compared with a sample of exclusively the non-cases. The advantage of the former is, that the estimated case-cohort "exposure odds ratio" has true risk-ratio interpretation, even if the outcome is not rare (1,2,4-6). Besides, the case-cohort approach enables rate-ratio estimation as well, provided that person-time information is available on the sample of the cohort.

Miettinen has proposed a formula for calculation of the standard error of crude case-cohort risk ratio (5); Greenland (10) and Nurminen (11) developed methods for stratified analysis. There are, however, no generally available multivariate case-cohort methods for risk-ratio or rate-ratio estimation. With respect to the risk ratio, most of the available literature implicitly seems to suggest to rely on case-control methods (1,2), but does not address the definite problems of assessing the precision of the estimates. Because of these problems, Miettinen proposed to restrict precision assessment to a significance test, after having removed the cases from the control group (6,7). For the case-cohort rate ratio Prentice developed a modification of Cox's proportional hazards model (8). However, no standard statistical software is available for parameter estimation in this model.

Pursuing the analogy between the case-cohort and the case-control design, multivariate risk-ratio estimation in the former may be carried out by a modification of the logistic regression model. In this modification, the usual non-case referent group is replaced by a random sample from the cohort. Le Cessie et al. (12), argue that in this procedure a pseudo likelihood function is maximized, yielding valid risk ratio estimates, and that standard errors of the parameter estimates are obtained with little extra effort.

For multivariate rate-ratio estimation, Poisson regression could be applied, using all cases and the person-time at risk of the sample. Calculation of the standard error requires a special, however easily performed method. This method and its mathematical underpinnings are also given by Le Cessie et al. (12).

To illustrate the performance of the mentioned procedures, we investigated the association between hypertension and 15-year cardiovascular mortality in a population of 1,583 Dutch civil servants. The results obtained in case-cohort approach were compared with those from the normal full-cohort and the nested case-control approach, using different sampling fractions, including the ultimate fraction 100%.

4.3 Subjects and methods

Details about the study population and data collection were published previously (13). For the purpose of the present study the information is briefly summarized.

Study population

In 1953-1954, a cohort of 1,583 men and 1,508 women, civil servants of the city of Amsterdam, aged between 40 and 65 years, participated in a general health survey. They were an age- and sex-stratified sample from 54 percent volunteers out of 11,700 eligible civil servants and their spouses. The present study was confined to the male participants. Information on serum cholesterol, survival or cause of death was missing for 107 men. Thus the study population finally consisted of 1,476 participants.

Data collection

The general health survey in 1953-1954 included a detailed medical history obtained by interview, a physical examination, an electrocardiogram, a chest X-ray and some laboratory examinations. All results were published by Van der Heide (14), one of two physicians who performed the examinations.

Blood pressure was measured in multiples of 5 mm Hg, in supine position on the right arm, using a standard mercury sphygmomanometer with a 12 cm cuff. Total serum cholesterol concentration was measured and body-mass index was calculated from body weight and length.

Survival until 1981 was assessed for 99.9 percent of the total population using the records of the Civil Servants Pension Fund (A.B.P.). The cause of death was established for 98.0 percent of the deceased men using the registers of the Dutch Central Bureau of Statistics. The classification of causes of death was based on the International Classification of Diseases, 9th revision (15). For the analysis, 15-year cardiovascular mortality (ICD-9 390-460) was selected.

Data analysis

The association between hypertension and cardiovascular mortality, as present in the cohort, was estimated in case-cohort approach with newly developed multivariate methods, and in nested case-control approach, using samples of 25, 50, 75 and 100% from the cohort

and from the non-cases, respectively. Estimation in case-cohort design using a 100% sample, means application of the case-cohort methodology to the complete cohort.

Participants were classified in 2 categories of systolic blood pressure: $<$ 160 mm Hg and $\geq$ 160 mm Hg. Age, total serum cholesterol and body-mass index were regarded as confounders. For the analysis, they were each divided in 3 categories: cut off points for cholesterol, 5.9 and 7.0 mmol/l, and body-mass index, 23.4 and 25.6 kg/m^2, were based on approximate tertiles; for age, 50 and 60 years were chosen as cut off points. In all multivariate models categories of confounders were entered as indicator variables.

Risk ratios (cumulative incidence ratios) and their 95% confidence intervals were calculated in both full-cohort and case-cohort approach. The standard error of the crude case-cohort estimate was calculated according to Miettinen (7), age-adjustment was carried out by the direct-pooling method in the full-cohort (1) and by pooling according to Greenland in the case-cohort approach (10). Multivariate case-cohort risk ratio estimates were obtained by a modification of logistic regression analysis. In this procedure, the cohort sample instead of the usual sample of non-cases, was included in the model. This was achieved by introducing the subset of the cases drawn in the sample, twice into the analysis: once as the cases which they really were, the second time recoded as non-cases, to serve in the referent group. The antilogarithm of the parameters from this procedure is an estimator of the true risk ratio. Two confidence intervals were calculated for these multivariate estimates: one as produced by the logistic model, which is regarded as too conservative (too wide) and the other, more appropriate, calculated from the covariance matrix as proposed by Le Cessie et al., elsewhere in this issue (12). To assess the validity and the variability of these logistic estimates of risk ratio empirically, the 25 and 50% samples were each drawn 10 times.

The adjusted rate-ratios and their 95% confidence intervals were estimated both in the full-cohort and the case-cohort approach by means of direct pooling over confounder strata (1) and Poisson regression (16). Since in case-cohort approach the 95% confidence interval of the rate ratio calculated in the usual manner, is expected to be too narrow, a second, more appropriate interval was calculated according to Le Cessie (12), using the covariance matrix.

The odds ratio and its 95% confidence interval were estimated in the full-cohort and the nested case-control design by standard methods: pooled according to Mantel and Haenszel and multivariately adjusted by logistic regression. The nested case-control approach using 100% of the non-cases in fact is exactly the same as calculating the odds ratios in the full

cohort. Analyses were performed using the statistical package SAS (17), except for the Poisson regression which was carried out by means of GLIM (18). Personyears of observation were calculated using a Fortran computer program (19).

4.4 Results

Fifteen-year cardiovascular mortality in the study population was 0.09 among normotensive and 0.24 among hypertensive persons. Incidence density over the same period was 0.006 and 0.019 yr^{-1} (table 4.1).

Table 4.1 Fifteen-year cardiovascular mortality of 1,476 male Amsterdam civil servants.

	Blood pressure	
	< 160 mm Hg	≥ 160 mm Hg
Cases (n)	112	59
Population (n)	1,235	241
Observation (pers.yrs.)	18,376	3,147
Cumulative incidence (%)	9	24
Incidence density (yr^{-1})	0.006	0.019

Full-cohort design

The results presented in table 4.2 represent the association in the total study population, expressed as risk ratio (cumulative incidence ratio), rate ratio (incidence density ratio) and odds ratio and their 95-percent confidence intervals (CI). The crude risk ratio of hypertension in relation to cardiovascular mortality is 2.70 (CI: 2.03-3.58), the rate ratio 3.08 (CI: 2.24-4.22) and the odds ratio 3.25 (CI: 2.29-4.62). As expected, the risk ratio underestimates the rate ratio, while the odds ratio overestimates both. Age-adjusted estimates are lower: 2.02 (CI: 1.50-2.70), 2.25 (CI: 1.62-3.13) and 2.37 (CI: 1.64-3.42), respectively. Multivariate estimates, adjusted for age, serum cholesterol and body-mass index, are slightly lower than the age-adjusted ones.

Table 4.2 The association between hypertension and cardiovascular mortality in a cohort of 1,476 male Amsterdam civil servants.

	RISK RATIO[a]	RATE RATIO[b]	ODDS RADIO
Crude	2.70 (2.03-3.58)	3.08 (2.24-4.22)	3.25 (2.29-4.62)
Age-adjusted by direct pooling	2.02 (1.50-2.70)	2.25 (1.62-3.13)	2.37 (1.64-3.42)
regression	-[c]	2.24[d] (1.61-3.11)	2.37[e] (1.64-3.42)
Multivariate	-[c]	2.18[d] (1.57-3.03)	2.30[e] (1.59-3.34)

[a] Ratio of two cumulative incidences
[b] Ratio of two incidence densities
[c] No estimation possible, until now
[d] Estimated by Poisson regression
[e] Estimated by logistic regression

Nested case-control design

Necessarily, the odds ratios from the nested case-control approach (table 4.3) using all cases and all non-cases, are exactly identical to the full-cohort odds ratios. The odds ratios comparing the cases with 75 and 50 percent of the non-cases, are similar, while those observed using the 25-percent sample are lower. Age-adjusted estimates are lower than the crude ones, multivariate estimates slightly lower than their age-adjusted counterparts.

Table 4.3 The odds ratio and 95% confidence interval of hypertension and cardiovascular mortality in nested case-control approach.

	Crude	Age-adjusted pooled	Multivariate	
			LR*	LR*
Non-cases	Nested case-control OR*			
100%[a]	3.25 (2.29-4.62)[b]	2.37 (1.64-3.42)[c]	2.37 (1.64-3.42)	2.30 (1.59-3.34)
75%	3.43 (2.34-5.02)	2.48 (1.69-3.65)	2.48 (1.69-3.63)	2.41 (1.64-3.54)
50%	3.25 (2.17-4.88)	2.36 (1.56-3.56)	2.36 (1.57-3.54)	2.31 (1.53-3.49)
25%	2.41 (1.54-3.78)	1.75 (1.09-2.83)	1.75 (1.11-2.76)	1.61 (1.01-2.57)

* LR: Logistic regression; OR: Odds ratio
[a] Cases/non-cases: normotensives: 112/1123; hypertensives: 59/182
[b] 95% confidence interval according to Woolf
[c] 95% confidence interval according to Mantel-Haenszel

Case-cohort design

Using case-cohort methods on all cases and the complete cohort instead of a sample from it (sampling fraction of 100 %), crude (2.70, CI: 2.03-3.58) and pooled risk ratio (2.03, CI: 1.51-2.73) and their confidence intervals (table 4.4) are nearly equal to those from the normal full-cohort approach. The results from the case-cohort analysis with 75 and 50 percent of the cohort as referents, are quite similar. Estimates based on the 25-percent sample are lower.

Table 4.4 The risk ratio (CIR*) and 95% confidence interval of hypertension and cardiovascular mortality in case-cohort approach.

	Crude	Age-adjusted pooled	Multivariate	
			LR*	LR*
single sampling		Case-cohort risk ratio		
100%[a]	2.70	2.03[b]	2.02	1.96
	(2.03-3.58)	(1.51-2.73)	(1.41-2.89)[c]	(1.36-2.82)[c]
			(1.51-2.70)[d]	(1.46-2.62)[d]
75%	2.80	2.04	2.05	1.98
	(2.08-3.77)	(1.52-2.86)	(1.41-2.96)	(1.36-2.89)
			(1.51-2.78)	(1.46-2.69)
50%	2.75	2.05	2.04	2.01
	(2.01-3.70)	(1.47-2.86)	(1.38-3.02)	(1.36-2.98)
			(1.47-2.83)	(1.45-2.80)
25%	1.97	1.48	1.49	1.36
	(1.39-2.80)	(1.08-2.03)	(0.97-2.28)	(0.88-2.11)
			(1.03-2.16)	(0.93-2.00)
repeated sampling				
50%	2.64[e]	1.97[e]	1.91[e]	
	(2.43-2.91)	(1.78-2.14)	(1.70-2.07)	
25%	2.65	2.03	1.98	
	(2.18-3.08)	(1.67-2.43)	(1.65-2.34)	

* CIR: Cumulative incidence ratio; LR: Logistic regression, case-cohort modification
[a] Cases/population: normotensives: 112/1235; hypertensives: 59/241
[b] Pooled according to Greenlands modification of the Mantel-Haenszel formula
[c] Standard confidence interval produced by logistic model
[d] Special confidence interval for case-cohort design
[e] Mean (range) of 10 observations

The age-adjusted logistic point estimates are very close to the pooled estimates, the multivariately adjusted estimates are a little lower. The 95% confidence intervals calculated from the standard logistic output, are larger than their pooled counterparts. The confidence intervals calculated as proposed by Le Cessie (12) are narrower, also in the multivariate case. Means of 10 risk ratios, calculated by drawing 10 different 25- and 50-percent samples (table 4.4) are almost perfect estimates of the full-cohort values, although it must be remembered that the samples are necessarily correlated.

The rate ratios in case-cohort approach and the 95-percent confidence intervals from standard Poisson regression, are virtually identical to those observed in the complete cohort,

except for those based on the 25% sample (table 4.5). The more appropriate specially adapted confidence intervals are slightly wider than the standard confidence intervals, particularly for the smaller sampling fractions.

Table 4.5 The rate ratio (IDR*) and 95% confidence interval of hypertension and cardiovascular mortality in case-cohort approach.

	Crude	Age-adjusted pooled	Multivariate	
			PR*	PR*
cohort sample	Case-cohort rate ratio			
100%[a]	3.08	2.25	2.24	2.18
	(2.24-4.22)	(1.62-3.13)	(1.61-3.11)[b]	(1.57-3.03)[b]
			(1.64-3.06)[c]	(1.59-2.98)[c]
75%	3.22	2.30	2.29	2.23
	(2.35-4.17)	(1.65-3.20)	(1.65-3.18)	(1.60-3.09)
			(1.65-3.18)	(1.60-3.09)
50%	3.06	2.23	2.21	2.19
	(2.23-4.19)	(1.60-3.10)	(1.59-3.06)	(1.58-3.04)
			(1.56-3.12)	(1.54-3.11)
25%	2.28	1.67	1.67	1.50
	(1.66-3.12)	(1.20-2.32)	(1.20-2.32)	(1.07-2.10)
			(1.13-2.46)	(1.00-2.24)

* IDR; Incidence density ratio; PR: Poisson regression
[a] Cases/personyears: BP < 160: 112/18,376; BP ≥ 160: 59/3,147
[b] Standard confidence interval from Poisson regression
[c] Special confidence interval for case-cohort design

4.5 Discussion

The case-cohort and nested case-control estimates based on the 100, 75 and 50% samples from the cohort, are almost equal to the corresponding ratios calculated in the conventional full-cohort design. The results from the 25% sample are most probably an extreme chance finding, considering the distribution of the repeated observations of the risk ratio in table 4.4. The impact of multivariate adjustment on the case-cohort risk-ratio estimates (table 4.4) has to be compared with the impact of multivariate adjustment on the odds ratio in full-cohort design (table 4.2), and seems to be valid.

The confidence intervals of the logistic case-cohort estimates, calculated according to Le

Cessie, are somewhat narrower, those of the Poisson estimates somewhat wider than the usual intervals calculated from the normal output of these procedures. In the case-cohort situation, the variance given in the logistic regression output is in expectation always equal to or larger than the real asymptotic variance, depending on sampling fraction and disease probability (12). The usual variance calculations based on the assumption of Poisson distribution, are inappropriate, since they do not account for the fact that the person-time distribution of the cohort is not known exactly, but approximated by the sample.

Comparison of the average risk ratio, calculated from the ten 25- and 50-percent samples, with the full-cohort values they estimate, also demonstrates the validity of the applied method. There are two components of random error in the case-cohort estimates: the first component is the error in the full-cohort estimate itself, the second is the surplus error resulting from case-cohort sampling. Provided that all cases are studied, the second component depends exclusively on the size of the cohort sample. To get an idea of this part of the variance, due to case-cohort estimation only, the range of the results of the repeated sampling was given. Although the samples were not independent, these results seem to be in agreement with Miettinen (6), who argues, that even in the context of much lower sampling fractions, a sample that is a five-fold of the number of cases, gives rise to only a small increase in variance. In the present study a sample of 50 percent corresponds to a sample/case ratio of about 4, and a sample of 25% to a ratio of about 2. The remarkably low risk ratios and rate ratios calculated using the single 25% sample may illustrate the fact that a sample/case ratio of 2 may be less adequate.

In summary, the pattern of results of the different sampling designs gives credit to the applied methods.

Apart from its value for estimation in the case-cohort design, the proposed modification of logistic regression extends epidemiologic methods with something new: a multivariate model for estimation of the true risk ratio, i.e. not the odds ratio.

The risk ratios, as expected, are systematically lower than the corresponding odds ratios, because the rare disease assumption is not satisfied. They are lower than the rate ratios as well, because the person-time distributions of exposed and non-exposed are different.

The case-cohort and nested case-control designs as methods of improving cost efficiency in an epidemiologic study, differ in several ways:

1. In the case-cohort design in addition to the risk ratio, the rate ratio can be estimated, when

person-time information is available. In a nested case-control study in a fixed cohort this is not possible. It is possible, however, in a time-matched or synthetic case-control study (20). When the follow-up period is long, like in our study, the risk ratio as estimated by the ratio of cumulative incidences may be biased because of competing mortality by other causes (21). Under such circumstances the rate ratio is a more valid measure of the strength of the association between exposure and endpoint.

2. For estimation of the risk ratio in the case-cohort design, contrary to the case-control design, no rare disease assumption is required. In case of a truly rare disease, the risk ratio may well be estimated by a case-control odds ratio. Even then, however, competing mortality may still render the rate ratio the preferred measure, and therefore the case-cohort approach the preferred design.
3. If in case-cohort design the sampling fraction of the cohort sample is known, absolute cumulative incidence and incidence density among exposed and unexposed can easily be estimated in addition to their ratios.
4. For estimation in case-control design, standard methodology has been developed in the past. For case-cohort design the situation was more complicated. Methods for estimation of the crude and stratified case-cohort risk ratio have been proposed in the literature. For multivariate risk-ratio and for rate-ratio estimation methods have been lacking, until now.

In conclusion, in case-cohort design valid estimation is possible of a number of epidemiologic measures that can not be estimated in nested case-control design. The available methods, however, so far were rather incomplete. In the present study these methods were explored further. In this exploration, a modification of logistic regression for case-cohort data was developed that can as well be applied to the cohort as a whole, using a "sample" of 100%. This manoeuvre gives epidemiologists a multivariate true risk-ratio model, requiring nothing but widely available statistical software for parameter estimation.

The case-cohort design is especially useful in studying an outcome that is not rare, over a long period of follow up, since true risk ratio and rate ratio can be estimated. If the number of referents is a four-fold or more of the number of cases, the loss of precision is very limited, unless the distribution over strata of covariates is extremely unbalanced.

If the outcome is rare and competing mortality low, the nested case-control design may be a reasonable alternative. If the outcome is very frequent, using the case-cohort nor the case-control design will be more efficient than studying the whole cohort.

REFERENCES

1. Rothman KJ: Modern Epidemiology. Boston/Toronto: Little, Brown and Company, 1986.
2. Kahn HA, Sempos CT: Statistical methods in epidemiology. New York/ Oxford: Oxford University Press, 1989.
3. Kupper LL, Mc Michael AJ, Spirtas R: A hybrid epidemiologic study design useful in estimating relative risk. J Am Stat Ass 1975;70:524-528.
4. Miettinen OS: Estimability and estimation in case-referent studies. Am J Epidemiol 1976;103:226-235.
5. Miettinen OS: The "case-control" study: valid selection of subjects. J Chron Dis 1985;38:543-548.
6. Miettinen OS: Theoretical epidemiology. Principles of occurrence research in medicine. New York: John Wiley and Sons, 1985.
7. Miettinen OS: Design options in epidemiologic research. An update. Scand J Work Environ Health 1982;8 suppl 1:7-14.
8. Prentice RL: A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika 1986;73:1-11.
9. Wacholder S, Boivin J-F: External comparisons with the case-cohort design. Am J Epidemiol 1987;126:1198-1209.
10. Greenland S: Adjustment of risk ratios in case-base studies (hybrid epidemiologic designs). Stat in Med 1986;5:579-584.
11. Nurminen M: Analysis of epidemiologic case-base studies for binary data. Stat in Med 1989;8:1241-1254.
12. Le Cessie S, van Houwelingen HC, Dekker JM, Schouten EG: Maximum likelihood and pseudo-likelihood in the case-base design (submitted).
13. Vandenbroucke JP, Matroos AW, Van der Heide-Wessel C, Van der Heide RM: Parental survival, an independent predictor of longevity in middle aged persons. Am J Epidemiol 1984;119:742-750.
14. Van der Heide RF: Resultaten van een geneeskundig onderzoek van 3091 gezonde mannen en vrouwen, 40-65 jaar oud. PhD thesis, Amsterdam: University of Amsterdam, 1959.
15. Manual of the international statistical classification of diseases, injuries, and causes of death, 9th ed, vol 1. Geneva: World Health Organisation, 1977.

16. Breslow NE, Day NE: Statistical methods in cancer research. Volume II. The design and analysis of cohort studies. Lyon: International Agency for the Research on Cancer, 1987.
17. SAS institute Inc. SAS User's Guide: Basics and Statistics. Cary, NC: SAS Institute Inc, 1985.
18. Payne CD, ed.: The GLIM System Release 3.77 Manual-Edition 2. Royal Statistical Society 1987.
19. Coleman M, Douglas A, Hermon C, Peto J: Cohort study analysis with a Fortran computer program. Int J Epidemiol 1986;15:134-137.
20. Prentice RL, Self SG, Mason MW: Design options for sampling within a cohort. In: Modern statistical methods in chronic disease epidemiology. Moolgavkar SH, Prentice RL eds; New york: Wiley & Sons, 1986.
21. Flanders WD, Louv WC: The exposure odds ratio in nested case-control studies with competing risks. Am J Epidemiol 1986;124:684-692.

5. HEART RATE AND CARDIOVASCULAR MORTALITY: A FOLLOW UP OF MIDDLE-AGED MEN AND WOMEN[1]

Evert G Schouten MD, Jacqueline M Dekker MSc, Irene EM Bosselaers, Regina MC in 't Veld, Frans J Kok PhD, Jan Pool MD PhD, Jan P Vandenbroucke MD PhD

5.1 Abstract

Sympathetic overactivity unopposed by parasympathetic activity after myocardial infarction, is associated with arrhythmia and sudden death. In apparently healthy individuals this autonomic imbalance might also be a risk factor for mortality. We investigated the association of heart rate at rest and after a light exercise test, measures of parasympathetic function, with all-cause, cardiovascular and coronary heart disease mortality in 3,091 middle-aged men and women.

Among men, adjusted relative risks of mortality during 15 years, ranged from 1.2 to 1.4 per 20 beats per minute increment, all significant, except for heart rate at rest in relation to cardiovascular mortality. Among women they ranged from 1.3 to 1.5, only significant for all-cause mortality. The associations are unspecific with respect to cause of death, not due to existing heart disease, and are weaker for 28-year mortality.

The observed associations may result from autonomic imbalance combined with unfavorable cardiovascular risk factors. Heart rate after more strenuous exercise or heart-rate variability might be a better indicator of parasympathetic function and show the association more clearly.

5.2 Introduction

Sympathetic nervous system activity in the heart, unopposed by adequate parasympathetic activity may modulate risk of fatal arrhythmias, particularly in the presence of a

---

[1] Submitted.
Supported by the Netherlands Heart Foundation (grant 86.060)

substrate of damaged myocardium, and of triggering premature ventricular complexes. Under special circumstances, like extreme stress or myocardial ischemia, impaired sympathetic activity may lead to sudden death because of ventricular fibrillation (1,2). Increased resting heart rate, decreased baroreflex sensitivity and decreased heart rate variability are frequently observed after myocardial infarction and indicate reduced parasympathetic activity and increased risk of arrhythmias and sudden death (3-5).

Milder forms of imbalance between sympathetic and parasympathetic activity in apparently healthy individuals, manifest in a fast heart rate, might be a risk factor for cardiovascular death as well. Therefore, resting heart rate was investigated in relation to morbidity and mortality in apparently healthy populations (6-8). These studies report an association between heart rate and total mortality, however, do not agree on the specificity of the association with respect to cardiovascular and coronary heart disease mortality, with the exception of sudden death, nor on its dependence of cardiovascular riskfactors (6-9). These associations and those observed between physical fitness, and cardiovascular disease mortality (10,11) may be the result of autonomic imbalance, of an unfavorable cardiovascular risk profile, or of both.

In the present study on electrocardiographic indicators of autonomic function, the relation between resting heart rate as a measure of parasympathetic function and 28-year mortality from all causes, cardiovascular disease and coronary heart disease has been investigated in 3,091 middle-aged men and women. In addition we studied these associations for heart rate after a light exercise test and for the difference between the heart rates after and before the exercise test.

5.3 Population and methods

Study population

In 1953-1954, a cohort of 1,583 men and 1,508 women, apparently healthy civil servants and spouses of civil servants of the city of Amsterdam, aged between 40 and 65 years, participated in a general health survey. About 54% of the 11,700 eligible civil servants volunteered, with or without their spouses. The cohort consisted of an age- and sex-stratified sample with about equal numbers in five-year age and sex categories. Information on survival or cause of death was missing for 19 men and 12 women, leaving 1,564 men and 1,496

women (896 and 521 deceased in the total follow-up period, respectively).

Since coding of all electrocardiograms was not feasible, we used the case-cohort sampling design (12-14). According to this approach all deaths were identified and studied, while random samples of men and women, drawn from the cohort, provided the information about the cohort. The samples consisted of 730 men and 502 women, being about twice the expected number of cardiovascular deaths (expected: 40% of all deaths). This resulted in a population of 1,219 men and 848 women, comprising all individuals in the respective samples, supplemented with the deaths in the rest of the cohort. Exclusion of 14 men and 9 women, for missing information on heart rate, left a study population of 1,205 men and 839 women (883 and 512 deaths in 28 years, respectively).

Data collection

The general health survey in 1953-1954 consisted of a detailed medical history obtained by a structured interview, a physical examination, and some laboratory examinations. All results were published by Van der Heide (15), who was one of two physicians who performed the examinations. At baseline in 1953-1954 a 12-lead electrocardiogram was recorded on an Elema one-channel, ink-jet electrocardiographic recorder, type Mingograph. A second recording was made after the Master Two Step Test (16). Recently the electrocardiograms were classified and coded according to the Minnesota Code (17) and according to the Cardiac Infarction Injury Score (CIIS) (18), without knowledge of outcome or other baseline variables. Furthermore the longest RR interval in lead I, II or III was measured in 10 msec. units. The standard leads were chosen, because these leads were recorded after the exercise test as well.

In 1981 survival of 99.9% of the original population was established by means of the records of the Civil Servants Pension Fund (A.B.P.). Details of this follow-up procedure were published elsewhere (19). The cause of death until 1981 was established in 1989 for 98.0% of the deceased men and 98.1% of the women using the registers of the Dutch Central Bureau of Statistics (C.B.S.).

The classification of causes of death was based on the International Classification of Diseases, 9th revision (20). For the analysis total mortality, cardiovascular (ICD-9 codes 390-460) and coronary heart disease mortality (ICD-9 codes 410-414) were selected.

Data analysis

Participants were classified in 5 categories of resting heart rate, heart rate after exercise and the difference between these two, based on approximate quintile limits. Cut points for men were 60, 66, 71 and 79 beats per minute (bpm) for resting heart rate, 62, 68, 74 and 82 bpm for heart rate after exercise and -3, 1, 4 and 9 bpm for delta heart rate (rate after exercise minus resting rate). For women cut points were 66, 73, 79 and 88 bpm for resting heart rate, 69, 76, 83 and 94 bpm for heart rate after exercise, and -3, 1, 5 and 12 bpm for delta heart rate. Differences in means and percentages of relevant characteristics between categories of resting heart rate in the sample of the cohort, were tested by two-sample t-tests.

To evaluate the effect of the cardiovascular risk factors blood pressure, serum cholesterol, body-mass index and smoking as potential confounders, a stratified analysis was performed. For this purpose we used age strata with cut points 50 and 60 years and strata based on approximate tertiles for the other confounders.

Case-cohort relative risks (cumulative incidence ratios) adjusted for age only and for age and the other potential confounding variables combined and their 95% confidence intervals were estimated using logistic regression analysis. Categories of potential confounders were entered into the model as indicator variables. In the case-cohort analysis, the "odds ratio" estimates true relative risk (cumulative incidence ratio) without having to satisfy the "rare disease assumption" (12). Multivariate analysis was also carried out with heart rate brought into the logistic model as a continuous variable.

In all analyses, the sample representing the cohort is identical. The number of deaths in the rest of the cohort and therefore the size of the population studied, depends upon the period of follow up and cause of death category.

To account for the possibility that an eventual association might be a consequence of already manifest heart- or other disease, we studied the associations for 15-year mortality in a subpopulation without signs of such disease at baseline as well. Therefore subjects who reported typical angina, or with electrocardiographic infarction patterns, ST-segment and T-wave changes meeting Minnesota criteria, ventricular hypertrophy, intraventricular conduction disturbances or with a Cardiac Infarction Injury Score (CIIS) over 20, and all deaths during the first three years of follow up, were excluded (214 men, 87 women).

5.4 Results

In table 5.1, means and standard deviations (when appropriate percentages) of study parameters and possible confounders are presented for categories of resting heart rate among males and females. Particularly among the men significant differences between quintiles in diastolic blood pressure, serum cholesterol and 15-year all-cause mortality were observed.

In tables 5.2 and 5.3 the 15-year all cause, cardiovascular and coronary heart disease mortality risk ratios are presented for the quintiles II to V relative to the first quintile of heart rate, at rest and after exercise for men and women, respectively. Among men, (table 5.2), most multivariate estimates are only slightly elevated and not statistically significant, except for the fifth quintile, particularly after exercise. The age-adjusted estimates are clearly higher. The relative risk estimates per 20 bpm of heart rate used as a continuous variable, range from 1.2 to 1.4, and are all statistically significant except for resting heart rate in relation to cardiovascular mortality.

For the women (table 5.3), only 15-year all-cause and cardiovascular mortality could be studied, because of the small number of coronary deaths. All estimates after exercise are higher than those at rest and the estimates of the fourth quintile are the highest and statistically significant for all cause mortality only. Here multivariate adjustment affects the estimates only marginally. The 20 bpm estimates for heart rate as a continuous variable range from 1.3 to 1.5 and differ significantly from 1.0 only for all-cause mortality.

The strength of the associations does not increase, going from all-cause mortality to the more specific mortality categories. The risk ratios in the subpopulation without signs of heart disease and with the first three years of follow up excluded are all very similar to the ones reported. Associations with 28-year mortality are weaker and non significant for the men For the women these estimates are similar to the 15-year estimates, but the results for the fourth quintile are less striking. Relative risks for quintiles of delta heart rate were all rather close to 1.0, except, however not statistically significant, for men in the fifth quintile, who after exercise had a heart rate exceeding resting heart rate more than 9 bpm.

Table 5.1 Baseline characteristics (mean ± sd) and mortality percentages of quintiles of resting heart rate in the sample of the cohort.

Men	I	II	III	IV	V
n†:	146	139	139	138	154
Age (years)	51.9 ± 7.3	52.8 ± 7.5	53.0 ± 7.85	1.6 ± 7.5	53.7 ± 7.9‡
Diastolic blood pressure (mg Hg)	75.2 ± 9.8	79.1 ± 11.1‡	77.9 ± 9.9‡	80.9 ± 10.6‡	82.0 ± 9.8‡
Serum cholesterol (mmol/l)	6.4 ± 1.2	6.6 ± 1.1‡	6.6 ± 1.3‡	6.8 ± 1.5‡	6.8 ± 1.4‡
Body-mass index (kg/m²)	24.4 ± 2.7	24.3 ± 2.5	24.6 ± 2.6	24.9 ± 2.8	24.8 ± 2.7
Heart rate after exercise bpm	60.4 ± 6.6	67.8 ± 7.6‡	70.8 ± 7.2‡	76.9 ± 7.2‡	88.7 ± 10.9‡
Percentage of smokers	73.3	68.3	67.6	71.7	64.3
Cigarette/week among smokers (n)	72.6 ± 47.1	68.7 ± 53.2	70.2 ± 55.2	80.6 ± 54.1	80.6 ± 52.9
Mortality 15 years (%)	11.6	21.6‡	19.4‡	22.5‡	33.1‡
CVD* (CHD*) (%)	6.8 (3.4)	7.9 (3.6)	9.4 (5.8)	11.6 (6.5)	16.9 (13.0)
Mortality 28 years (%)	47.3	52.5	56.1	54.3	64.3‡
CVD* (CHD*) (%)	19.9 (8.9)	23.0 (10.8)	25.9 (12.9)	25.4 (13.8)	29.9 (18.2)
Women	I	II	III	IV	V
n†:	103	69	79	103	96
Age (years)	51.8 ± 7.0	51.9 ± 7.6	51.7 ± 7.0	51.6 ± 7.9	52.6 ± 7.5
Diastolic blood pressure (mm Hg)	86.9 ± 13.2	87.4 ± 12.7	86.4 ± 13.3	88.6 ± 4.0	8828.0 ± 14.4
Serum cholesterol (mmol/l)	7.2 ± 1.5	7.3 ± 1.5	7.2 ± 1.7	7.0 ± 1.5	7.2 ± 1.6
Heart rate after exercise (bpm)	68.0 ± 9.3	73.9 ± 8.8‡	82.3 ± 10.5‡	85.2 ± 8.9‡	99.3 ± 11.7‡
Body mass index (kg/m²)	26.1 ± 3.2	26.9 ± 3.5	26.6 ± 3.9	26.4 ± 3.6	26.1 ± 3.4
Percentage of smokers	31.1	39.6	34.0	39.8	39.6
Cigarette/week among smokers (n)	29.4 ± 31.3	15.5 ± 19.2‡	14.4 ± 19.4‡	12.8 ± 16.1‡	20.6 ± 31.9
Mortality 15 years (%)	9.7	13.5	5.2	12.6	11.5
CVD* (CHD*) (%)	4.9 (3.9)	5.2 (4.2)	2.1 (1.0)	5.8 (2.9)	3.1 (0.0)
Mortality 28 years (%)	33.0	36.5	32.0	34.0	34.4
CVD* (CHD*) (%)	12.6 (6.8)	13.5 (6.3)	10.3 (5.2)	18.4 (9.7)	16.7 (4.2)

* CVD: cardiovascular mortality; CHD: coronary heart disease mortality.

† individual parameters have missing data.

‡ significantly different from reference category I ($p < 0.05$, Two-sided t-test).

Table 5.2 Case-cohort* relative risk (95% confidence interval) of 15-year all-cause, cardiovascular and coronary heart disease mortality for first (reference) compared to other quintiles† of momentaneous heart rate in men.

	HEART RATE AT REST					AFTER EXERCISE			
All-cause mortality	II	III	IV	V	n=898	II	III	IV	V
Age adjusted RR	1.3 (0.9-1.9)	1.3 (0.9-1.9)	1.1 (0.8-1.7)	1.7 (1.2-2.4)		1.4 (1.0-2.2)	1.5 (0.9-2.3)	1.5 (1.0-2.3)	2.1 (1.4-3.0)
Multivariate‡ RR	1.1 (0.8-1.7)	1.1 (0.8-1.7)	1.0 (0.7-1.5)	1.4 (1.0-2.0)		1.3 (0.9-2.0)	1.3 (0.9-2.0)	1.3 (0.8-1.9)	1.8 (1.2-2.6)
RR per 20 bpm§	1.2 (1.0-1.4)					1.3 (1.1-1.6)			
Cardiovascular mortality					n=806				
age adjusted RR	1.0 (0.6-1.7)	1.2 (0.7-2.0)	1.3 (0.8-2.2)	1.6 (1.0-2.1)		1.6 (0.9-2.7)	1.5 (0.8-2.7)	1.6 (0.9-2.8)	2.2 (1.3-3.7)
multivariate RR	0.9 (0.5-1.5)	1.0 (0.6-1.7)	1.0 (0.6-1.7)	1.2 (0.7-1.9)		1.4 (0.8-2.6)	1.2 (0.7-2.1)	1.3 (0.8-2.3)	1.7 (1.0-2.9)
RR per 20 bpm	1.2 (0.9-1.5)					1.3 (1.0-1.7)			
Coronary heart disease mortality					n=768				
age adjusted RR	1.2 (0.6-2.5)	1.5 (0.7-3.0)	1.5 (0.7-3.1)	2.2 (1.2-4.2)		1.3 (0.6-2.7)	1.1 (0.5-2.4)	1.3 (0.6-2.7)	2.4 (1.3-4.6)
multivariate RR	1.0 (0.5-2.2)	1.2 (0.6-2.6)	1.1 (0.5-2.3)	1.7 (0.5-2.3)		1.2 (0.6-2.5)	0.9 (0.4-2.1)	1.0 (0.5-2.1)	1.8 (1.0-3.6)
RR per 20 bpm	1.4 (1.0-2.0)					1.4 (1.0-1.9)			

* Cases compared with random sample from the cohort

† Quintile cut off points at rest: 60, 66, 71, 79; after exercise: 62, 68, 74, 82

‡ Adjusted for age, diastolic blood pressure, serum cholesterol, smoking and body mass index

§ Heart rate as a continuous variable in multivariate model

Table 5.3 Case-cohort* relative risk (95-% confidence interval) of 15-year all-cause and cardiovascular mortality for first (reference) compared to other quintiles† of momentaneous heart rate at rest and after exercise in women.

	HEART RATE AT REST					AFTER EXERCISE			
All-cause mortality	II	III	IV	V	n=591	II	III	IV	V
Age adjusted RR	1.2 (0.7-2.2)	1.4 (0.8-2.4)	2.0 (1.2-3.4)	1.4 (0.8-2.5)		1.6 (0.9-2.9)	1.6 (0.9-2.9)	2.4 (1.3-4.2)	1.8 (1.0-3.2)
Multivariate‡ RR	1.2 (0.7-2.2)	1.5 (0.8-2.8)	1.9 (1.1-3.3)	1.4 (0.8-2.9)		1.5 (0.8-2.9)	1.5 (0.8-2.9)	2.3 (1.3-4.2)	1.7 (0.9-3.2)
RR per 20 bpm§	1.3 (1.0-1.8)					1.3 (1.0-1.7)			
Cardiovascular mortality					n=534				
age adjusted RR	0.9 (0.4-2.0)	1.1 (0.5-2.7)	1.9 (0.9-4.2)	1.3 (0.6-3.0)		1.4 (0.6-3.4)	1.5 (0.6-3.7)	2.2 (1.0-5.1)	1.5 (0.6-3.6)
multivariate RR	0.9 (0.4-2.1)	1.3 (0.5-3.2)	1.8 (0.8-3.8)	1.2 (0.5-2.8)		1.4 (0.6-3.2)	1.4 (0.6-3.5)	2.1 (0.9-5.0)	1.4 (0.6-3.4)
RR per 20 bpm	1.5 (0.9-2.4)					1.3 (0.8-2.0)			

* Cases compared with random sample from the cohort

† Quintile cutoff points at rest: 66, 73, 79, 88 bpm; after exercise: 69, 76, 83, 94 bpm

‡ Adjusted for age, diastolic blood pressure, serum cholesterol, smoking and body-mass index

§ Heart rate as a continuous variable in multivariate model

5.5 Discussion

In this cohort study we observed an association between all-cause mortality and resting heart rate and, slightly more pronounced, heart rate after light exercise, among middle-aged men and women. The association appeared to be aspecific with respect to mortality category, was particularly in men, partly explained by cardiovascular risk factors, and was not secondary to heart disease or other disease at baseline. If the results for the fourth quintile of the women are considered as a chance finding, heart rate seems to be a better predictor in men than in women. Our expectation that associations for delta heart rate, a proxy measure for heart rate variability, would be stronger, since it might be a better indicator of parasympathetic potential to counter sympathetic activity, was not confirmed.

In the literature similar associations have been reported for resting heart rate, but whether these associations depend on other risk factors and whether they are specific with respect to cardiovascular mortality is not clear. Dyer et al. (7) state that heart rate possibly is an independent risk factor for sudden cardiac death, but not for other cardiovascular death or other death in general. Kannel et al. (6) conclude that the association may be nonspecific to cardiovascular death, with the exception of sudden coronary death in men. In one of the three reported Chicago Studies (7), a U-shaped relation with sudden death was observed, which has not been confirmed by others. In our study, however, unfortunately we could not separate sudden death from other cardiovascular death. In the quintile analysis, we did not find evidence of a U-shaped association. Slattery et al. (9) reported a relation between heart rate during submaximal exercise and all-cause and cardiovascular mortality, partly mediated by hypertension. The intensity of the exercise in our study, however, was much lighter and heart rate was measured after, not during the exercise test.

A number of potential methodological problems may have affected the validity of this study. Possibly measurement and coding errors of RR interval as well as diagnostic and coding errors of causes of death may have resulted in misclassification. Moreover, a single measurement may be insufficient to characterize a persons 'average' heart rate, because of short term and/or long term variability. All mentioned potential sources of error would lead to non-differential misclassification, resulting in dilution of the associations really existing.

A bias because of pharmacological effects interfering with heart rate at baseline is not likely, because at the time of the original investigation hardly any medication was used in this healthy population.

We used the case-cohort sampling design, in order to limit the number of electrocardiograms to be coded. If under this design, the cohort sample size is a small multiple of the size of the case series, loss of precision is limited (13,14). A comparison of baseline characteristics between the total cohort and the sample did not reveal substantial differences. Therefore, we consider the sample to be representative.

An association between heart rate and all-cause mortality may reflect less optimal health in general, resulting in both increased all-cause mortality risk and fast heart rate. Since exclusion of the first three years of follow up did not make a difference, the results do not appear to be a consequence of existing acute life-threatening disease. They may be a consequence of poor physical fitness of persons with a sedentary, stressful life style, resulting in an unfavorable autonomic balance and implying an unfavorable risk profile (21). The combination of unfavorable autonomic balance and cardiovascular risk profile might result in an increased incidence of coronary heart disease and coronary death. The autonomic imbalance might be responsible for an increased risk of sudden death among persons who have developed coronary heart disease.

In conclusion, resting heart rate is predictive of all-cause mortality in this middle-aged population. This predictive value partly depends on the established cardiovascular risk factors and may further be mediated by the autonomic balance. The same association was observed for heart rate after a light exercise test. It would be interesting to investigate the prognostic value of heart rate after or during a more strenuous exercise test or, of heart-rate variability in populations like ours, since this probably is a better measure of the balance between sympathetic and parasympathetic balance.

REFERENCES

1. Schwartz PJ, Billman GE, Stone HL: Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction: an experimental preparation for sudden cardiac death. Circulation 1984;69:790-800.
2. Malliani A, Schwartz PJ, Zanchetti A: Neural mechanisms in life-threatening arrhythmias. Am Heart J 1980;100:705-715.

3. Eckberg DL, Drabinsky M, Braunwald E: Defective cardiac parasympathetic control in patients with heart disease. New Engl J Med 1971;285:877-883.
4. Kleiger RE, Miller JP, Bigger JT, Moss AJ, The Multicenter Post Infarction Research Group: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256-262.
5. Bigger JT, Kleiger RE, Fleiss JL, Rolnitzky LM, Steinman RC, Miller JP, The Multicenter Post-Infarction Research Group: Components of heart rate variability measured during healing of acute myocardial infarction. Am J Cardiol 1988;61:208-215.
6. Kannel WB, Kannel C, Paffenbarger RS, Cupples LA: Heart rate and cardiovascular mortality: The Framingham Study. Am Heart J 1987;113:1489-1494.
7. Dyer AR, Persky V, Stamler J et al.: Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. Am J Epidemiol 1980;112:736-749.
8. Kannel WB, Wilson P, Blaire SN: Epidemiologic assessment of the role of physical activity and physical fitness in development of cardiovascular disease. Am Heart J 1985;109:876-885.
9. Gillum RF: The epidemiology of resting heart rate in a national sample of men and women: Associations with hypertension, coronary heart disease, blood pressure and other cardiovascular risk factors. Am Heart J 1988;116:163-174.
10. Slattery ML, Jacobs DR: Physical fitness and cardiovascular disease mortality: the US Railroad Study. Am J Epidemiol 1988;27:571-580.
11. Leon AS, Blackburn HW: The relationship of physical activity to coronary heart disease and life expectancy. Ann NY Acad Sci 1977;301: 561-578.
12. Miettinen, OS: The "case-control" study: valid selection of subjects. J Chron Dis 1985;38:543-548.
13. Miettinen, OS: Theoretical epidemiology: principles of occurrence research in medicine. New York: John Wiley & Sons, 1985.
14. Miettinen OS: Design options in epidemiologic research. An update. Scan J Work Environ Health 1982;8:suppl 1,1-14.
15. Heide RM, van der: Resultaten van een geneeskundig onderzoek van 3091 mannen en vrouwen. Amsterdam: PhD thesis, University of Amsterdam, 1959.
16. Master AM, Friedman R, Dack S: The electrocardiogram after standard exercise as a functional test of the heart. Am Heart J 1942;24:777-793.

17. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S: The electrocardiogram in population studies. A classification system. Circulation 1960;vol XXI:1160-1175.
18. Rautaharju PM, Warren JW, Jain U, Wolf HK, Nielsen CL: Cardiac Infarction Injury Score: an electrocardiographic coding scheme for ischemic heart disease. Circulation 1981;64:249-256.
19. Vandenbroucke JP, Matroos AW, Van der Heide-Wessel C, Van der Heide RM: Parental survival, an independent predictor of longevity in middle aged persons. Am J Epidemiol 1984;119:742-750.
20. Manual of the international statistical classification of diseases, injuries and causes of death. Volume I, Geneva: World Health Organisation, 1977.
21. Leon AS, Jacobs DR, DeBacker G, Taylor HL: Relationship of physical characteristics and life habits to treadmill exercise capacity. Am J Epidemiol 1981;113:653-660.

6. PQ INTERVAL AND CARDIOVASCULAR MORTALITY RISK IN MIDDLE-AGED: A PROSPECTIVE STUDY IN THE NETHERLANDS[1]

Evert G Schouten MD, Catja Broekhoff, Astrid M P Heijnen, Jacqueline M Dekker MSc, Frans J Kok PhD, Jan Pool MD PhD, Jan P Vandenbroucke MD PhD

6.1 Abstract

Atrioventricular conduction is under the influence of the balance of the autonomic nervous system. PQ-interval length reflects conduction velocity and may therefore be regarded as a measure of autonomic balance.

The prognostic value of PQ-interval length for all-cause, cardiovascular and coronary heart disease mortality, was investigated in a follow-up study of 3,091 middle-aged Dutch civil servants and spouses, who participated in a general health survey.

Contrary to expectation, no association was observed between PQ-interval length, whether adjusted for heart rate or not, and mortality. This absence of predictive power might be due to opposite effects of autonomic nervous system activity and of heart rate on atrioventricular conduction. This may result in a PQ interval that is constant regardless of autonomic balance. Nevertheless, if a more adequate method of heart rate adjustment would come available, PQ-interval length might prove to be a predictor of cardiovascular mortality.

6.2 Introduction

Indicators of autonomic imbalance by impaired parasympathetic activity in the heart, like decreased baroreceptor sensitivity, decreased heart-rate variability or high resting heart rate, were found to be associated with the risk of arrhythmia and sudden death in patients recovering from myocardial infarction (1-9). In this kind of autonomic imbalance the parasympathetic part of the autonomic nervous system is dominated by the sympathetic part, resulting

---

[1] Submitted.
Supported by the Netherlands Heart Foundation (grant 86.060)

in unopposed sympathetic activity. This may lead to electrical instability of the myocardium, resulting in abnormal impulse generation and conduction, and development of life threatening arrhythmias, especially under circumstances of myocardial damage (10-12). Moderate parasympathetic dominance, on the contrary, reduces heart rate and increases electrical stability, thus exerting a protective effect on mortality (10-12).

Variation in PQ-interval length is thought to be determined by the balance between sympathetic and parasympathetic activity on the atrioventricular node (13). Therefore PQ-interval length may well be an easily measured indicator of the balance between sympathetic and parasympathetic innervation of the heart. In that case a short PQ interval, indicating relative sympathetic overactivity, may be a risk factor for cardiovascular mortality. The long term implications of variation in autonomic balance in the general population are largely unknown, although certain established risk factors like hypertension and stress are probably related.

We investigated the association between PQ-interval length and all-cause, cardiovascular and coronary heart disease mortality in a population of 3,091 apparently healthy men and women, in a 28- year period of follow up.

6.3 Population and methods

Study population

In 1953 and 1954, a cohort of 1,583 men and 1,508 women, civil servants of the city of Amsterdam and their spouses, aged between 40 and 65 years, participated in a general health survey. They were an age- and sex-stratified random sample from those who volunteered (54%) out of a total of 11,700 eligible civil servants, with or without their spouses. Survival information until 1981 was available for 1,582 men and 1,506 women.

As it was not feasible to evaluate electrocardiographic information of all individuals, the case-cohort design was used to obtain the population for the present study. In the case-cohort design all cases are identified, while a random sample is drawn from the cohort, to obtain information about the population from which those cases arose. From another point of view this design resembles a case-control study, in which the usual non-cases sample is replaced by the sample from the cohort, consisting of cases as well as non-cases (14-16).
The magnitude of the sample from the cohort, 730 men and 502 women, was chosen to be

about twice the expected number of cardiovascular deaths, estimated as 40% of the total number of deceased. Because measurement and coding of the electrocardiograms had to be started when information on survival was available, but information on cause of death was not, all deceased, including those of non-cardiovascular origin, had to be included in the study population, to make sure that no cardiovascular deaths would be left out. Excluded from this study population (1,239 men, 858 women) were those subjects with missing information on cause of death (18 men, 10 women, mostly due to emigration) and PQ interval (16 men, 12 women) leaving a final case-cohort study population of 1,205 men and 836 women. In all analyses the number of subjects in the sample is the same, but the number of cases from the rest of the cohort depends on follow-up period and mortality category.

To evaluate the possibility that an association between PQ- interval length and mortality might be secondary to existing heart disease, analysis was also carried out in a subpopulation excluding subjects with signs of manifest heart disease.

Data collection

The original study in 1953 and 1954 consisted of a detailed medical history obtained by interview, a physical examination and some laboratory examinations. A 12-lead electrocardiogram was recorded with a one-channel ink-jet Mingograph electrocardiographic recorder (Elema). A second electrocardiogram was recorded within 1 minute after light exercise which consisted of a sex, age and weight standardized Master Two Step Test (17). The results of this study were published by Van der Heide, who was one of two physicians who performed the physical examinations (18).

In 1981 a mortality follow-up of 99.9% of the population was carried out, by means of the records of the pension offices. Further details of this mortality follow-up have been published previously (19). In 1989 the primary cause of death was assessed in the records of the Dutch Central Bureau of Statistics for those deceased until 1981, using death certificate numbers acquired from the Dutch Central Bureau of Genealogy. Mortality was classified using ICD revision 9 (20) as all-cause, cardiovascular (codes 390-459) and coronary heart disease mortality (codes 410-414). Death certificates, originally coded under ICD revisions 6 and 7 were recoded by officers from the Central Bureau of Statistics, using the original notification forms.

In 1988 and 1989 the electrocardiograms were coded in a blind setting, according to the Minnesota Code (21) and the Cardiac Infarction Injury Score (22) Measurements of PQ,

QT and RR interval, ST-segment level and T-top amplitude were performed as well. PQ-interval length, at rest and after exercise, and length of the preceding RR interval were measured in 10 msec units. PQ interval was defined as the time interval (msec.) between the beginning of the deflection of the P wave until the start of the first deflection of the QRS complex, representing conduction from the sino auricular node via the atrioventricular node and the His bundle to the ventricles. The longest PQ interval in any of the recorded complexes of lead I, II or III was used in the analysis. The RR interval was specified as the time span (msec) between two consecutive R tops, representing momentaneous heart rate (21).

Data analysis

Differences in risk factors and mortality in the sample from the cohort, between categories of PQ interval were tested, using Students t-test. For risk analysis PQ-interval length at rest was divided in approximate tertiles, cut off points 150 and 170 msec for men and 140 and 160 msec for women. Subjects with PQ interval > 210 msec, regarded as impaired conduction, were excluded from risk analysis. In the analysis, the third tertile was used as the reference. Heart-rate adjustment was carried out, by dividing PQ-interval length by RR-interval length or by its square root and by means of linear regression equations based on the data in the sample from the cohort.

To evaluate the confounding effect of baseline age and the cardiovascular risk factors blood pressure, serum cholesterol, body-mass index and smoking, a stratified analysis was performed. For this purpose we used three age strata with cut off points 50 and 60 years and strata based on approximate tertiles for the other confounders.

In multivariate analysis the association between PQ-interval length and mortality from cardiovascular disease, coronary heart disease and all causes was investigated, using logistic regression procedures with adjustment for cardiovascular risk factors.

Under the case-cohort design, contrary to the case-control design, relative risk (cumulative incidence ratio) can be estimated directly. To obtain a valid significance test for this relative risk, we estimated and tested the corresponding case-control odds ratio's with identical logistic models,using only the non-cases from the sample as referents, as recommended by Miettinen (15).

The associations were investigated additionally in a subpopulation of subjects without certain signs of heart disease. Excluded were subjects with reported angina, typical electrocardiographic infarction patterns, ST-segment and T-wave changes, ventricular hypertrophy,

intraventricular conduction disturbances and a Cardiac Infarction Injury Score (CIIS) (22) over 20 (in total 205 men, 114 women).

For significance testing in all analyses a two-sided significance level of 5% was chosen.

6.4 Results

The distribution of PQ-interval length in the sample from the cohort is presented in figure 6.1 for both men and women. For the majority of the population the intervals are within normal limits (120 - 200 msec.). Mean and standard deviation of PQ-interval length at rest are 163.6 $\pm$ 22.3 msec. for men and 157.8 $\pm$ 21.6 msec. for women.

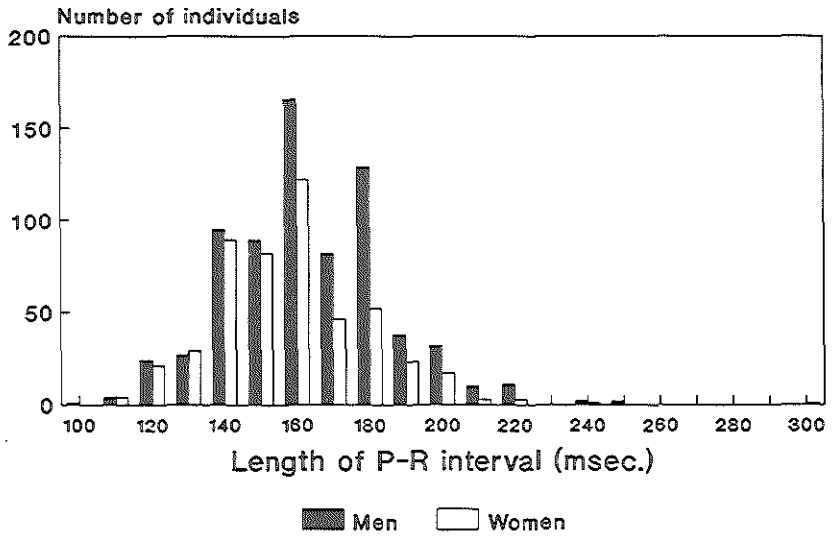


Figure 6.1 Distribution of PQ-interval length in the sample from the cohort (714 men, 493 women)

PQ interval

Table 6.1 shows the means (percentages) and standard deviations of relevant study parameters in the four categories of PQ-interval length for both men and women. Body-mass index differed significantly between category I and III in men and women, RR-interval length only in women. Among women, mean values of age and diastolic blood pressure and mortality percentages are significantly higher in the impaired conduction category compared to the reference category.

Fifteen-years age-adjusted and multivariate relative risks of PQ-interval length for all cause, cardiovascular and coronary heart disease mortality, are presented in table 6.2. None of the relative risks shown in table 6.2 are significantly different from 1.0. The same is true for the total follow-up period of 28 years, for PQ-interval length after exercise, and for the results from the subpopulation without signs of heart disease at baseline (data not shown). More extreme cut points for PQ-interval length did not produce different results. Analysis with PQ divided by RR or by the square root of RR and with PQ adjusted for RR or its square root by means of linear regression, gave no indication of an association with cardiovascular mortality either.

6.5 Discussion

If PQ-interval length, an easily obtained indicator of autonomic balance, would be an independent predictor of cardiovascular mortality, it might contribute meaningfully to cardiovascular risk profile. However no statistically significant relationship was observed between PQ-interval length and death, either from all causes, cardiovascular or coronary heart disease. Mean and standard deviation of PQ-interval length at rest for men and women in this study are comparable with results from other investigations (23-25). At present no studies relating PQ-interval length to mortality in the general population, that would enable comparison, are known to the authors.

With respect to the quality of the information, it is possible that misclassification occurred in certification and coding of cause of death (26) as well as in measurement and coding of PQ-interval length. This misclassification, being nondifferential because of the blindness of the coders of the electrocardiograms as well as the causes of death, will tend to dilute a true association between PQ-interval length and mortality. PQ intervals were measured by a single coder, eliminating inter-observer variability.

Table 6.1 Mean (percentage) and standard deviation of study parameters in categories of PQ interval in the sample representing the cohort.

MEN	I[a] n=240	I[a] n=248	III[a] n=211	IMPAIRED[c] n=15
Age (years)	52.8 ± 7.6	52.3 ± 7.5	52.9 ± 7.8	51.7 ± 8.1
Blood pressure (mm Hg)	78.7 ± 10.8	78.9 ± 10.0	79.9 ± 10.9	77.7 ± 8.6
Cholesterol[@] (mmol/l)	6.7 ± 1.4	6.7 ± 1.3	6.5 ± 1.2	6.0 ± 1.1
Body mass index (kg/m²)	24.2* ± 2.8	24.7 ± 2.6	25.0 ± 2.7	24.7 ± 2.1
Percentage smokers	71.7	72.2	68.3	60.0
Number of cigarettes among smokers (weekly)	73.4 ± 53.5	96.9 ± 52.3	81.0 ± 52.1	97.5 ± 37.6
RR interval at rest	856.8* ± 149.0	880.2 ± 150.7	986.9 ± 146.9	958.7 ± 215.7
Mortality (%)all-cause	57.5	53.2	55.0	53.3
CVD (CHD)	28.3 (13.3)	22.6 (14.5)	24.7 (10.9)	20.0 (13.3)
WOMEN	I[b] n=143	II[b] n=204	III[b] n=141	IMPAIRED[c] n=5
Age (years)	51.4 ± 7.4	51.9 ± 7.4	52.0 ± 7.2	59.4 ± 4.6
Blood pressure (mm Hg)	86.3 ± 13.2	87.7 ± 13.2	87.8 ± 13.5	110.0* ± 19.7
Cholesterol[@] (mmol/l)	7.1 ± 1.5	7.2 ± 1.7	7.3 ± 1.5	7.2 ± 1.4
Body mass index (kg/m²)	25.9* ± 3.3	26.2 ± 3.4	27.9 ± 3.8	28.3 ± 18.5
Percentage smokers	35.0	37.8	37.6	40.0
Number of cigarettes among smokers (weekly)	15.9 ± 20.5	19.3 ± 25.3	19.4 ± 27.7	4.0 ± 4.2
RR interval at rest	781.6* ± 130.5	804.1 ± 130.5	805.7 ± 141.9	748.0 ± 121.5
Mortality (%)all-cause	30.1	34.3	34.8	80.0*
CVD (CHD)	12.6 (4.9)	15.7 (6.9)	12.1 (5.7)	40.0* (20.0*)

CVD, Cardiovascular disease; CHD, Coronary heart disease.

[a] I: PQ ≤ 150 msec
II: 150 < PQ ≤ 170 msec
III: 170 < PQ ≤ 210 msec

[b] I: PQ ≤ 140 msec
II: 140 < PQ ≤ 160 msec
III: 160 < PQ ≤ 210 msec

[c] Impaired conduction: PQ > 210 msec

[@] 40 missing values for men, 9 missing values for women

* significantly different from reference-category III (t-test: $p < 0.05$)

Table 6.2 Case-cohort relative risks of PQ interval at rest for all cause, cardiovascular (CVD) and coronary heart disease (CHD) mortality, after 15 years of follow-up.

	ALL-CAUSE MORTALITY					
	men n=1028*			women n=631*		
relative risk	I[a]	II[a]	III[a]	I[b]	II[b]	III[b]
age adjusted[c]	1.0	1.0	1.0	0.7	0.7	1.0
multivariate[d]	1.0	1.0	1.0	0.7	0.7	1.0
	CVD MORTALITY					
	n=861*			n=547*		
age adjusted[c]	0.9	1.1	1.0	0.7	0.9	1.0
multivariate[d]	0.9	1.0	1.0	0.7	0.9	1.0
	CHD MORTALITY					
	n=795*			n=508*		
age adjusted[c]	1.1	1.5	1.0	0.8	1.5	1.0
multivariate[d]	1.1	1.5	1.0	0.8	1.6	1.0

[x] number represents sample and cases outside sample
[a] I: PQ $\leq$ 150 msec
II: 150 < PQ $\leq$ 170 msec
III: 170 < PQ $\leq$ 210 msec
[b] I: PQ $\leq$ 140 msec
II: 140 < PQ $\leq$ 160 msec
III: 160 < PQ $\leq$ 210 msec
[c] adjusted for age
[d] adjusted for age, blood pressure, cholesterol, body-mass index and smoking

Like other electrocardiographic intervals, PQ interval is thought to be influenced by heart rate (24-26) and adjustment for heart rate may be necessary. PQ interval was reported to decrease slightly in exercise (27), however, we are not aware of any recommended correction formulas. In our material anyway, correlations between PQ- and RR-interval length were small (Pearson correlation coefficient: 0.15 for men, 0.05 for women). Moreover, a number of different methods of heart-rate adjustment did not produce any relevant association. This may be explained by the fact that PQ interval depends not only on the autonomic nervous system balance, but also on the heart rate as such. These effects tend to modify PQ interval in opposite directions, sympathetic activity enhancing, increasing heart rate impairing conduction in the atrioventricular node. This may result in a constant PQ-interval length regardless of autonomic balance. Furthermore it is possible that a single measurement is not sufficient to

characterize an individuals PQ interval, because of short term or long term biological variation. Conduction in the atrioventricular node has been reported to be slowed down by parasympathetic activity (28), whereas conduction in the atria may be accelerated (13).

In conclusion we did not find the hypothesized association between PQ interval as a measure of cardiac autonomic imbalance, and cardiovascular and coronary heart disease mortality. Before deciding there is no such association in a healthy population, more information on PQ variability and the relation between PQ and RR interval is needed.

REFERENCES

1. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD: Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. Circulation 1988;78:969-79.
2. Schwartz PJ, Zaza A, Pala M, Locati E, Beria G, Zanchetti A: Baroreflex sensitivity and its evolution during the first year after myocardial infarction. J Am Coll Cardiol 1988;12:629-636.
3. Eckberg DL, Drabinsky M, Braunwald E: Defective parasympathetic control in patients with heart disease. New Engl J Med 1971;285:877-883.
4. La Rovere MT, Specchia G, Mortare A, Schwartz PJ: Baroreflex sensitivity, clinical correlates and cardiovascular mortality among patients with first myocardial infarction. Circulation 1988;78:816-824.
5. Vybiral T, Bryg RJ, Maddens ME, Boden WE: Effect of passive tilt on sympathetic and parasympathetic components of heart rate variability in normal subjects. Am J Cardiol 1989;63:117-120.
6. Bigger JT, Kleiger RE, Fleiss JL, Rolnitzky LM, Steinman RC, Miller JP: Components of heart rate variability measured during healing of acute myocardial infarction. Am J Cardiol 1988;61:208-215.
7. Kleiger RE, Miller JP, Bigger JT, Moss AJ: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256-262.

8. Dyer AR, Persky V, Stamler J, Paul O, Schekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA: Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. Am J Epidemiol 1980;112:736-749.
9. Kannel WB, Kannel C, Paffenbarger RS, Cupples LA: Heart rate and cardiovascular mortality: The Framingham Study. Am Heart J 1987;113:1489-1494.
10. Schwartz PJ, Stone HL: The analysis and modulation of autonomic reflexes in the prediction and prevention of sudden death. in: Zipes DP, Jalife J, eds. Cardiac electrophysiology and arrhythmias. London: Grune and Stratton Inc, 1985.
11. Malliani A, Schwartz PJ, Zanchetti A: Neural mechanisms in life-threatening arrhythmias. Am Heart J 1980;100:705-715.
12. Schwartz PJ, Stone HL: The role of the autonomic nervous system in sudden coronary death. Ann NY Acad Sc 1982:162-190.
13. Corr PB, Yamada KA, Witkowski FX: Mechanisms controlling cardiac autonomic function and their relation to arrhythmogenesis. in: Fozard HA et al., eds. The heart and cardiovascular system. New York: Raven Press, 1986.
14. Miettinen OS: Theoretical epidemiology. Principles of occurrence research in medicine. New York, Chichester, Brisbane, Toronto, Singapore: John Wiley & Sons, 1985.
15. Miettinen OS: Design options in epidemiologic research. An update. Scand J Work Environ health 1982;suppl 1:7-14.
16. Miettinen OS: The 'case-control' study: valid selection of subjects. J Chron Dis 1985;38:543-548.
17. Master AM, Friedman R, Dack S: The electrocardiogram after standard exercise as a functional test of the heart. Am Heart J 1942;24:777-93.
18. Heide RM van der: Resultaten van een geneeskundig onderzoek van 3091 gezonde mannen en vrouwen, 40-65 jaar oud. Amsterdam: PhD thesis University of Amsterdam, 1959.
19. Vandenbroucke JP, Matroos AW, Van der Heide-Wessel C, Van der Heide RM: Parental survival, an independent predictor of longevity in middle-aged persons. Am J Epidemiol 1984;119:742-750.
20. Manual of the international statistical classification of diseases, injuries and causes of death. Volume I, Geneva: World Health Organisation, 1977.

21. Prineas RJ, Crow RS, Blackburn H: The minnesota code manual of electrocardiographic findings. Standards and procedures for measurement and classification. Boston, Bristol, London: John Wright, PSG Inc, 1982.
22. Rautaharju PM, Warren JW, Jain U, Wolf HK, Nielsen CL: Cardiac Infarction Injury Score: an electrocardiographic coding scheme for coronary heart disease. Circulation 1981;64:249-256.
23. Simonson E: Differentiation between normal and abnormal in electrocardiography. St. Louis: The C.V. Mosby Company, 1961.
24. Mihalick MJ, Fisch C: Electrocardiographic findings in the aged. Am Heart J. 1974;87:117-128.
25. Simonson E, Blackburn H, Puchner TC, Eisenberg P, Ribeiro F, Meja M: Sex differences in the electrocardiogram. Circulation 1960;12:598-601.
26. Mackenbach JP, Duyne van WMJ, Kelson MC: Certification and coding of two underlying causes of death in the Netherlands and other countries of the European Community. J of Epidemiol and Comm Health 1987;41:156-160.
27. Irisawa H, Seyama I: The configuration of the P wave during mild exercise. Am Heart J 1966:467-472.
28. Prystowski EN, Jackman WM, Rinkenberger RL, Heger JJ, Zipes DP: Effect of autonomic blockade on ventricular refractoriness and atrioventricular nodal conduction in humans. Evidence supporting a direct cholinergic action on ventricular muscle refractoriness. Circ Res 1981:49:511-518.

7. QT-INTERVAL PROLONGATION PREDICTS CARDIOVASCULAR MORTALITY IN AN APPARENTLY HEALTHY POPULATION[1]

Evert G. Schouten MD, Jacqueline M. Dekker MSc, Peter Meppelink MD, Frans J. Kok PhD, Jan P. Vandenbroucke MD PhD, Jan Pool MD PhD

7.1 Abstract

In myocardial infarction patients heart-rate adjusted QT interval (QT_c), an electrocardiographic indicator of sympathetic balance, is prognostic for survival. In a 28-year follow up, the association between QT_c and all-cause, cardiovascular and ischemic heart disease mortality was studied in a population of 3,091 apparently healthy Dutch civil servants and their spouses, aged 40-65 years, who participated in a medical examination in 1953-1954.

Moderate ($420 < QT_c \leq 440$ msec) and extensive ($QT_c > 440$ msec) QT_c prolongation significantly predict all-cause mortality during the first 15 years among men (adjusted relative risk [RR] 1.5 and 1.7, respectively) and among women (RR 1.7 and 1.6). In men, cardiovascular mortality (RR 1.6 and 1.8) and ischemic heart disease mortality (RR 1.8 and 2.1) mainly account for this association. In women, the association can not be attributed specifically to cardiovascular and ischemic heart disease mortality. Relative risks for a subpopulation without any sign of heart disease at baseline are similar. The same is observed for QT_c prolongation after light exercise, although here most associations are not statistically significant, probably because of smaller numbers in the QT_c-prolongation categories.

Our results suggest that QT_c, contributes independently to cardiovascular risk. If autonomic imbalance is an important mechanism, it might be speculated, that changes in life style e.g. with regard to physical exercise and smoking may have a preventive impact.

---

[1] Circulation 1991, accepted for publication.
Supported by the Netherlands Heart Foundation (grant 86.060).

7.2 Condensed abstract

Heart-rate adjusted QT interval (QT_c), a measure of autonomic balance, is prognostic for survival in myocardial infarction patients. Mortality during 28 years was studied in relation to QT_c in 3,091 apparently healthy subjects, age 40-65.

Moderate ($420 < QT_c \leq 440$ msec) and extensive ($QT_c > 440$ msec) QT_c prolongation significantly predict mortality in the first 15 years. In men, cardiovascular (adjusted relative risk [RR] 1.6 and 1.8) and ischemic heart disease mortality (RR 1.8 and 2.1) mainly account for this effect. Associations for QT_c after light exercise, generally are similar, however, most are not significant.

Our results suggest that QT_c contributes independently to cardiovascular mortality risk.

7.3 Introduction

Heart rate adjusted QT-interval prolongation ($QT_c > 440$ msec) is regarded as an indicator of imbalanced distribution of sympathetic nervous system activity on the heart. In experimental investigations, manipulation of the sympathetic nervous system affects QT-interval duration (1,2). In these experiments QT prolongation is associated with a lowered ventricular fibrillation threshold and with the occurrence of ventricular arrhythmias after coronary occlusion (3,4). This is generally viewed as a consequence of nonuniform recovery of excitability of the myocardium (5). In patients with recent myocardial infarction (6,7) and in patients who had 24-hour electrocardiography (8), QT_c prolongation ($QT_c > 440$ msec) in the standard 12-lead electrocardiogram was reported to be a strong prognostic indicator of sudden cardiac death. Recently, in a preliminary report from the Cardiac Arrhythmia Suppression Trial (CAST) (9), certain type IC antiarrhythmic drugs were associated with an increased risk of death from arrhythmia and cardiac arrest among myocardial infarction patients. This adverse effect is possibly related to a prolonged QT interval due to these drugs (10).

The relation between QT_c and mortality until now has exclusively been studied in patients with specific autonomic or cardiovascular disease. Since electrocardiography is a simple, non-invasive and cheap functional test of the heart, it may well be used in periodic medical examination of non-diseased populations. Combined with other risk indicators, information on QT_c prolongation might have implications for prevention with respect to life

style, since physical exercise is reported to have a favorable (11,12), cigarette smoking an unfavorable (13) influence on autonomic balance.

In the present study, the predictive value of QT_c at rest and after light exercise, on all-cause, cardiovascular and ischemic heart disease mortality was studied in a 28-year follow up of 3,091 apparently healthy civil servants in the Netherlands.

7.4 Subjects and methods

Study population

In 1953-1954, a cohort of 1,583 men and 1,508 women, civil servants and spouses of civil servants of the city of Amsterdam, aged between 40 and 65 years, participated in a general health survey. Its purpose was to study the feasibility of a medical screening of apparently healthy persons, to detect early manifestations of disease. About 54% of the 11,700 eligible civil servants volunteered, with or without their spouses. The cohort consisted of an age- and sex-stratified sample with about equal numbers in five-year age and sex categories. Information on survival or cause of death was missing for 19 men and 12 women, leaving 1,564 men and 1,496 women (896 and 521 deaths in the total follow-up period, respectively).

Coding of electrocardiograms is tedious and time consuming. Therefore, instead of studying the complete cohort, the case-cohort sampling design was applied (14-16). According to this approach, all deaths were enrolled in the study as cases. They were not studied in relation to a sample of non-case referents, like in a nested case-control study, but in relation to a random sample from the cohort. The deaths in this referent sample are playing a role both as "case" and as "referent". This way, electrocardiograms of only a part of the non-cases had to be coded. We took a sample of about twice the expected number of cardiovascular deaths (expectation: 40% of all deaths). This yielded sample sizes of 730 men and 502 women (sampling fraction 46.1% and 33.2 %, respectively). Coding of electrocardiograms, however, had to start when ascertainment of cause of death was still going on. Therefore, to include all cardiovascular deaths, coding had to be performed on all deaths. In this way, electrocardiograms were evaluated for a total of 1,219 men and 848 women. Exclusion of 14 men and 9 women missing data on QT_c, left a study population of 1,205 men and 839 women, including all deaths in the cohort (883 and 512, respectively). In all analyses the sample, representing the cohort, is identical, but the number of additional, non-sample deaths depends upon the

duration of follow up and on the cause of death category of any particular analysis.

To eliminate the possibility that an observed association might be a consequence of already manifest heart disease, associations were studied in a subpopulation without signs of heart disease at baseline as well. Excluded were subjects who reported typical angina, or with electrocardiographic infarction patterns, certain ST-segment and T-wave changes, ventricular hypertrophy, intraventricular conduction disturbances or with a Cardiac Infarction Injury Score (CIIS) (17) over 20 (205 men, 114 women).

Data collection

The general health survey in 1953-1954 consisted of a detailed medical history obtained by a structured interview, a physical examination, an electrocardiogram, a chest X-ray and some laboratory examinations. All results were published in a PhD thesis by Van der Heide (18), who was one of two physicians who performed the examinations.

At baseline in 1953-1954 a 12-lead electrocardiogram was recorded on a one-channel, Elema ink jet electrocardiographic recorder, type Mingograph. A second recording was made after the Master Two-Step Test (19). Recently the electrocardiograms were classified and coded according to the Minnesota Code (20) and the Cardiac Infarction Injury Score (17). Coders were blinded for other baseline information and survival. Minute measurements of PQ, QT and RR interval, ST-segment level and T-wave amplitude were made as well.

The longest QT-interval in lead I, II or III was measured from the beginning of the first deflection of the QRS complex to the end of the T-top, where it merges with the electric baseline. Adjustment for heart rate was made according to Bazett's formula: $QT_c = QT/\sqrt{RR}$ (21).

Blood pressure readings in multiples of 5 mm Hg were taken in supine position on the right arm, using a standard mercury sphygmomanometer with a 12 cm cuff. Total serum cholesterol was measured according to Saifer and Kammerer's modification of the Liebermann-Burchard reaction (22). Body weight and length were measured to calculate body-mass index and subjects were asked about their smoking habits. For serum cholesterol information on 40 men and 9 women, for body-mass index information on 1 woman was missing.

In 1981 survival of 99.9% of the population was established through the records of the

Civil Servants Pension Fund (A.B.P.) (23). This was possible since all participants by then were receiving their old-age pension. The pension fund monitors survival of all civil servants and their spouses very closely, for financial reasons. Survivors were documented as still receiving a pension in 1981. In 1989, the cause of death until 1981 was established for 98.0% of the deceased men and 98.1% of the women using the registers of the Dutch Central Bureau of Statistics (C.B.S.). Loss to follow up of cause of death was almost entirely due to emigration. The necessary death-certificate number was obtained from the Dutch Central Bureau of Genealogy.

The classification of causes of death was based on the International Classification of Diseases, 9th revision (24). For the analysis total mortality, cardiovascular (ICD-9 390-460) and ischemic heart disease mortality (ICD-9 410-414) were selected. Causes of death before 1969, originally coded according to the 6th and 7th revision, were recoded to the 9th revision by the Central Bureau of Statistics, using the original death certificates. The 8th revision did not differ substantially from the 9th, with respect to the chosen mortality categories.

Data analysis

Participants were classified in 3 categories of QT_c at rest and after exercise: $QT_c \leq 420$ msec, $420 < QT_c \leq 440$ msec and $QT_c > 440$ msec. In the sample overall differences of means of relevant characteristics between these groups were tested by analysis of variance and, if significant, by the Tukey-Kramer method (25) to adjust for multiple comparisons. Percentages were tested by t-tests for the difference between two proportions.

To evaluate the effect of cardiovascular risk factors as potential confounders, a stratified analysis was performed. For this purpose age strata were used with cut-off points 50 and 60 years and strata based on approximate tertiles for the other confounders. For men cut-off points of approximate confounder tertiles were 70 and 80 mm Hg for blood pressure, 5.9 and 7.0 mmol/l for serum cholesterol, 23.4 and 25.6 kg/m^2 for body-mass index and 3 and 70 cigarettes/week for smoking. For women these cut-off points were 80 and 90 mm Hg, 6.2 and 7.5 mmol/l and 24.7 and 27.6 kg/m^2, respectively. Smoking for women was divided in two categories, either smoking or non-smoking.

Relative risk of death was estimated using logistic regression analysis to adjust for two sets of potential confounders: 1) age alone, and 2) all potential confounders. For both sets of confounders a separate analysis was performed for all-cause, cardiovascular and ischemic heart disease mortality. Since application of logistic regression to case-cohort data as such

does not produce a valid relative risk, we used a modification, so that the deaths that had been drawn in the sample, were used only once as cases. This procedure yields an unbiased estimate of the true multivariate relative risk (i.e. not the odds ratio) (26). Testing the significance of this relative risk estimate must be performed by an approximate method: the odds ratio, calculated in case-control design was tested instead of the relative risk (15).

If competing mortality by other causes is differential in the QT_c-prolongation groups, the cause-specific relative risks will not be adequately estimated by the cumulative incidence ratio. The incidence density ratio would then be the preferred measure of association, since it accounts for differences in person-time at risk (26). However, only crude and pooled incidence density ratios can be estimated under case-cohort design, while standard methods for testing significance are not available. To evaluate the validity of the relative risk estimates, age-adjusted case-cohort incidence density ratios for cardiovascular and ischemic heart disease mortality were estimated for comparison.

7.5 Results

Table 7.1 shows significant differences between QT_c categories normal ($\leq$420 msec), moderately prolonged (420 - $\leq$440 msec) and/or extensively prolonged (>440 msec) in mean age and diastolic blood pressure in both men and women. Differences in mortality percentages between persons with and without QT_c prolongation were most pronounced and statistically significant in men for 15-year mortality. For 28-year mortality significant differences were observed for all-cause mortality in both sexes and for cardiovascular mortality only in women. Means of baseline characteristics and mortality percentages in the random sample were almost identical to those in the total cohort and none of the differences observed were statistically significant.

Table 7.1 Baseline characteristics and mortality in categories of QT_c at rest in the random sample from the cohort.

MEN	$QT_c \leq 420$ n=605*	$420 < QT_c \leq 440$ n=75*	$QT_c > 440$ n=36*
Mean ± standard deviation:			
Age [years]	52.3 ± 7.6	53.5 ± 7.8	56.2 ± 6.4*
Total serumcholesterol [mmol/l]	6.7 ± 1.3	6.7 ± 1.2	6.4 ± 1.1
Diastolic blood pressure [mm Hg]	79 ± 10	81 ± 10	84 ± 12*
Body-mass index [kg/m²]	24.6 ± 2.6	25.0 ± 3.1	24.6 ± 2.6
% current smokers	71.5	65.3	66.6
cigarettes/week among smokers	74 ± 51	76 ± 59	80 ± 62
Percentage:			
15-year mortality all causes	18.5	37.3†	44.4†
CVD (IHD)	8.9 (5.6)	18.7† (12.0†)	22.2† (11.1)
28-year mortality all causes	52.2	66.6†	77.8†
CVD (IHD)	23.5 (12.4)	30.7 (16.0)	36.1 (16.7)
WOMEN	$QT_c \leq 420$ n=316*	$420 < QT_c \leq 440$ n=100*	$QT_c > 440$ n=79*
Mean ± standard deviation:			
Age [years]	51.2 ± 7.3	52.6 ± 7.0	53.9 ± 7.9*
Total serumcholesterol [mmol/l]	7.2 ± 1.5	7.2 ± 1.8	7.0 ± 1.3
Diastolic blood pressure [mm Hg]	86 ± 12	90 ± 15*	92 ± 16*
Body-mass index [kg/m²]	26.3 ± 3.6	26.8 ± 3.4	26.5 ± 3.4
% current smokers	37.3	33.0	39.2
cigarettes/week among smokers	21 ± 28	11 ± 17	15 ± 15
Percentage:			
15-year mortality all causes	8.5	12.0†	16.5†
CVD (IHD)	3.8 (2.5)	3.0 (2.0)	8.9 (2.5)
28-year mortality all causes	30.7	33.0	48.1†
CVD (IHD)	12.3 (6.0)	13.0 (7.0)	24.1† (6.3)

CVD, cardiovascular disease; IHD, ischemic heart disease

* Individual parameters have missing data

* Significant F-test ($p < 0.05$) over the three prolongation groups; indicated value significantly different from $QT_c \leq 420$ (Tukey-Kramer test, $p < 0.05$)

† Significantly different from $QT_c \leq 420$ (t-test for the difference between two proportions, $p < 0.05$)

Only age appeared to be a confounding variable of some importance, therefore the results are not presented for each confounder separately. In tables 7.2 and 7.3 the case-cohort relative risks (RR) in the QT_c categories for 15- and 28-year all-cause, cardiovascular and ischemic heart disease mortality are presented, adjusted for age and other potential confounders. They were estimated for the study population as a whole as well as for a subpopulation, excluding participants with signs of heart disease at baseline. For comparison age-adjusted incidence density ratios are included in the tables as well.

Adjusted for age and other potential confounders, the relative risks of 15-year all-cause mortality differed significantly from 1.0 for moderate (RR men 1.5, women 1.7) and extensive QT_c prolongation (RR men 1.7, women 1.6), compared to normal QT_c. After 28 years these associations were weaker. In the subpopulation relative risks were of similar magnitude, however not all statistically significant.

For cardiovascular mortality a statistically significant multivariate relative risk was observed after 15 years of follow up in men with moderate (RR 1.6) and extensive QT_c prolongation (RR 1.8). In the male subpopulation only the 15-years cardiovascular mortality relative risk of moderate QT_c prolongation was significant (RR 1.9).

Fifteen-year ischemic heart disease mortality in men was significantly associated with moderate (RR=1.8) and extensive QT_c prolongation (RR=2.1). In the subpopulation without known heart disease, this was observed, again only in men, for moderate QT_c prolongation after 15 years (RR=2.4) and after 28 years (RR=1.5). However, here the number of cases of extensive prolongation was small.

Most of the age-adjusted incidence density ratios in tables 7.2 and 7.3 were somewhat larger than the corresponding relative risks (no significance test possible).

The same analysis was performed for QT_c after exercise, adjusted according to Bazett, as well as by means of a linear regression model derived from the sample. The number of subjects with QT_c prolongation after exercise was considerably smaller than at rest. Associations in general were of similar magnitude, but only multivariate relative risk for 15-year all-cause mortality was significant.

Table 7.2 Relative risks for all-cause, CVD and IHD mortality in categories of QT_c prolongation at rest, compared to $QT_c \leq 420$ among men.

MEN	15-year follow up			
	TOTAL POPULATION n=898		SUBPOPULATION[θ] n=736	
QT_c (msec)	420-440	>440	420-440	>440
ALL CAUSES				
Age-adjusted RR	1.5*	1.8*	1.7*	1.6
Multivariate+RR	1.5*	1.7*	1.7*	1.5
CVD	n=806		n=663	
Age-adjusted RR	1.6*	2.0*	2.0*	1.4
IDR[@]	1.8	2.3	2.2	1.5
Multivariate+RR	1.6*	1.8*	1.9*	1.2
IHD	n=768		n=641	
Age-adjusted RR	1.8*	2.2*	2.4*	1.1
IDR[@]	2.0	2.5	2.7	1.2
Multivariate+RR	1.8*	2.1*	2.4*	1.0
	28-years follow up			
	TOTAL POPULATION n=1,205		SUBPOPULATION[θ] n=1,000	
ALL CAUSES				
Age-adjusted RR	1.1	1.3*	1.2*	1.4
Multivariate+RR	1.1	1.3*	1.2*	1.4*
CVD	n=953		n=786	
Age-adjusted RR	1.3	1.5	1.3	1.4
IDR[@]	1.5	1.9	1.7	1.8
Multivariate+RR	1.2	1.4	1.3	1.4
IHD	n=854		n=711	
Age-adjusted RR	1.4	1.5	1.6*	1.1
IDR[@]	1.7	1.9	2.0	1.3
Multivariate+RR	1.4	1.5	1.5*	1.2

CVD, cardiovascular disease; IHD, ischemic heart disease
RR, Relative risk; IDR, Incidence density ratio
θ Subjects with signs of heart disease at baseline excluded
+ Adjusted for age, total serum cholesterol, diastolic blood pressure, current smoking and body-mass index
* $p < 0.05$, two-sided significance test based on corresponding case-control odds ratio
@ Case-cohort incidence density ratio, calculated to evaluate the effect of competing mortality, not tested for significance (see methods section)

Table 7.3 Relative risks for 15 and 28 years of follow up for all causes, CVD and IHD mortality in categories of QT_c at rest among women.

WOMEN	15-year follow up			
	TOTAL POPULATION n=591		SUBPOPULATION[θ] n=508	
QT_c (msec)	420-440	>440	420-440	>440
ALL CAUSES				
Age-adjusted RR	1.8*	1.8*	1.7*	1.9
Multivariate[+]RR	1.7*	1.6*	1.6	1.6
CVD	n=534		n=466	
Age-adjusted RR	1.7	1.8	1.4	1.9
IDR[@]	1.6	1.7	1.4	1.9
Multivariate[+]RR	1.5	1.4	1.3	1.7
IHD	n=503		n=442	
Age-adjusted RR	1.2	1.1	0.3	0.8
IDR[@]	1.2	1.1	0.3	0.9
Multivariate[+]RR	1.0	1.0	0.3	0.9
	28-years follw up			
	TOTAL POPULATION n=839		SUBPOPULATION[θ] n=725	
ALL CAUSES				
Age-adjusted RR	1.3	1.2*	1.3	1.2
Multivariate[+]RR	1.3	1.1	1.3	1.1
CVD	n=650		n=565	
Age-adjusted RR	1.3	1.4	1.4	1.3
IDR[@]	1.2	1.4	1.3	1.4
Multivariate[+]RR	1.3	1.2	1.3	1.2
IHD	n=558		n=489	
Age-adjusted RR	1.4	1.2	1.4	1.3
IDR[@]	1.3	1.3	1.4	1.5
Multivariate[+]RR	1.4	1.1	1.4	1.3

CVD, cardiovascular disease; IHD, ischemic heart disease
RR, Relative risk; IDR, Incidence density ratio
[θ] Subjects with signs of heart disease at baseline excluded
[+] Adjusted for age, total serum cholesterol, diastolic blood pressure, current smoking and body-mass index
* $p < 0.05$, two-sided significance test based on corresponding case-control odds ratio
[@] Case-cohort incidence density ratio, calculated to evaluate the effect of competing mortality, not tested for significance (see methods section)

7.6 Discussion

The results of our study show that in a middle-aged population, heart-rate adjusted QT-interval (QT_c) at rest is an independent predictor of total mortality in both sexes. In men, this predictive value is mainly determined by cardiovascular and ischemic heart disease mortality. The association appeared not to be a consequence of manifest heart disease at baseline.

Goldberg et al. (27) in the only similar, recently published study, did not observe a significant association between QT_c and all-cause mortality, deaths due to sudden cardiac events or coronary artery disease in 30 years of follow up of the original Framingham cohort. There may be several reasons for this disparity. Differences in population, and methods may play a role: the age range of the study populations was not the same, the Framingham population being somewhat younger. For QT measurements, we took the longest single interval in standard lead I, II or III, while Goldberg c.s. took the average of 2 to 3 measurements from any electrocardiographic lead with the longest QT interval. Risk analysis was performed using different QT_c categories, including the reference category, which in their study was <360 msec. versus ≤ 420 msec. in ours. Moreover mortality experienced by the reference category in the Framingham cohort was surprisingly high, particularly in the last part of the follow up, casting doubt on their adequacy as a reference group. Finally, the fifteen-year period in which we observed the strongest associations, was not considered separately by Goldberg.
Clinical studies in myocardial infarction patients (6,7), and patients who had 24-hour electrocardiography (8) a predictive value of QT_c in relation to sudden death has been demonstrated before.

Manipulation of the autonomic nervous system in animal experiments demonstrated the influence of imbalanced sympathetic activity on heterogeneity of repolarization in the myocardium, resulting in QT-interval prolongation and increased incidence of ventricular arrhythmias, in the presence and absence of infarction (2-5). This mechanism is also held responsible for the increased risk of sudden cardiac death due to ventricular fibrillation, associated with prolonged QT interval ($QT_c > 440$ msec) in patients with recent myocardial infarction (6,7).

The observed association might be secondary to existing heart disease, causing both QT_c prolongation and death. In that case, however, exclusion of subjects with signs of heart disease at baseline would have weakened the associations.

Next some potential methodological problems will be discussed. Our study population may not be a true representation of the total middle-aged population in the Netherlands, being

confined to relatively healthy working civil servants. For an etiologic study this is not regarded as a serious problem.

In the present study the case-cohort design (14-16) was used, in order to limit the number of electrocardiograms that had to be coded. If the cohort sample size is a small multiple of the size of the case series, loss of precision is expected to be limited. A comparison of baseline characteristics and mortality between the total cohort and the sample did not reveal substantial differences. Therefore the sample was considered as representative.

Bias resulting from competing mortality by other causes of death in the cause-specific analyses, as judged from the incidence density ratios, was small and mainly in the direction of the null value.

Error in the measurement and coding of QT interval, as well as in the diagnosis and coding of causes of death, may have resulted in some misclassification. Although QT_c does not vary much within individuals (6), a single measurement may be insufficient to characterize a persons long-term QT-interval length, and heart rate adjustment according to Bazett (21) may be inadequate for both low and high heart rates (28).

All mentioned potential sources of error will have led to non-differential misclassification, resulting in dilution of the really existing association between QT_c prolongation and mortality.

A bias because of pharmacological effects interfering with QT length at baseline is not likely, because at the time of the original investigation such medication was hardly available and seldom used, particularly in a healthy population.

Although a stronger association was expected, the pattern for QT_c after exercise was similar, but most of the estimates were not significant, evidently because of smaller numbers. This may be due to inadequacy of Bazett's adjustment method in exercise, and/or to the low level of the exercise in the Master test. Adjustment through linear regression analysis based on the data at hand, however, did not make much difference. QT_c during exercise in stead of shortly after, might have given different results.

The association between QT_c prolongation and cardiovascular mortality may be explained in several ways. Patients with congenital Long QT Syndrome (29) show an extremely high incidence of ventricular fibrillation and sudden cardiac death, often triggered by physical or emotional stress. This syndrome, however, is very rare and patients would have

died before the age of 40. In healthy humans extreme physical and psychological stress sometimes induce ventricular arrhythmias as well (30-33), and sympathetic imbalance as manifest in QT_c prolongation may increase this risk in a similar way. Second, QT_c prolongation may increase risk of sudden death in subjects who, although having been healthy at baseline, subsequently developed coronary heart disease. This probably is the most likely explanation of the observed associations. Third, QT_c prolongation may be a risk factor for cardiovascular morbidity as well, thus resulting in an association with cardiovascular mortality. The association with total mortality, finally, might demonstrate that autonomic imbalance is an indicator of poor health in general.

The difference between men and women in the cause-specific associations is not clear. It may have a biologic background, or indicate greater misclassification in cardiovascular and ischemic heart disease mortality in women compared to men, in past decades.

Our conclusion is that in this middle-aged population, QT_c prolongation is predictive of mortality. QT_c prolongation probably indicates imbalanced distribution of sympathetic nervous activity to the heart, although other explanations (congenital, electrolyte disturbances, LVH) are possible. The association appears to be independent of cardiovascular risk factors and is in men, but not in women, largely explained by cardiovascular and ischemic heart disease mortality, but is not a consequence of existing heart disease. It would be interesting to investigate the possibility that QT_c prolongation is a risk factor not only of cardiovascular mortality, but of morbidity as well.

QT-interval length is derived from a simple non-invasive diagnostic method. If the observations are confirmed in other studies, combined with other risk factors, information on QT-interval length may represent an improvement of cardiovascular risk profile. Since physical exercise seems to result in a favorable, smoking and stress in a less favorable autonomic balance (11-13), it might be speculated that preventive life-style changes may improve autonomic balance in general, and with it mortality risk in persons with prolonged QT interval.

REFERENCES

1. Yanowitz F, Preston JB, Abildskov JA: Functional distribution of right and left stellate innervation to the ventricles. Circulation Res 1966;18:416-428.

2. Kahima T, Tamaka H, Minagoe S, Toda H: Electrocardiographic changes induced by the stellate ganglion block in normal subjects. J Electrocardiol 1981;14:169-174.
3. Schwartz PJ, Snebold NG, Brown AM: Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. Am J Cardiol 1976;37:1035-1040.
4. Schwartz PJ, Stone HL, Brown AM: Effects of unilateral stellate ganglion blockade on the arrhythmias associated with coronary occlusion. Am Heart J 1975;92:589-599.
5. Vassallo JA, Cassidy DM, Kindwall E, Marchlinski FE, Josephson ME: Nonuniform recovery of excitability in the left ventricle. Circulation 1988;78:1365-1372.
6. Ahnve S: QT-interval prolongation in acute myocardial infarction. Eur Heart J 1985;6 suppl:85-95.
7. Schwartz PJ, Wolf S: QT-interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074-1077.
8. Algra A: Electrocardiographic risk factors for sudden death. A study with 245 cases of sudden death during a two-year follow-up after 24-hour electrocardiography in 6693 patients. Rotterdam: PhD thesis, Erasmus University Rotterdam, 1990, pp 39-45.
9. The Cardiac Arrhythmia Suppression Trial Investigators: Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. New Engl J Med 1989;321:406-412.
10. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: CAST and beyond. Implications of the Cardiac arrhythmia suppression trial. Circulation 1990;81:1123-1127.
11. Billman GE, Schwartz PJ, Stone HL: The effects of daily exercise on susceptibility to sudden cardiac death. Circulation 1984;69:1182-1189.
12. Blumenthal JA, Fredikson M, Kuhn CM, Ulmer RL, Walsh-Riddle M, Appelbaum M: Aerobic exercise reduces levels of cardiovascular and sympathoadrenal responses to mental stress in subjects without prior evidence of myocardial ischemia. Am J Cardiol 1990;65:93-98.
13. Hayano J, Yamada M, Sakakibara Y, Fujinami T, Yokoyama K, Watanabe Y, Takata K: Short- and long-term effects of cigarette smoking on heart rate variability. Am J Cardiol 1990;65:84-88.
14. Miettinen OS: Theoretical epidemiology. Principles of occurrence research in medicine. New York, Chichester, Brisbane, Toronto, Singapore: John Wiley & Sons, 1985.

15. Mietinen OS: Design options in epidemiologic research. An update. Scand J Work Environ Health 1982;suppl 1:7-14.
16. Miettinen OS: The "case-control" study: valid selection of subjects. J Chron Dis 1985;38:543-548.
17. Rautaharju PM, Warren JW, Jain U, Wolf HK, Nielsen CL: Cardiac Infarction Injury Score: an electrocardiographic coding scheme for ischemic heart disease. Circulation 1981;64:249-256.
18. Heide RF van der: Resultaten van een geneeskundig onderzoek van 3091 gezonde mannen en vrouwen, 40-65 jaar oud. Amsterdam: PhD thesis, University of Amsterdam, 1959.
19. Master AM, Friedman T, Dack S: The electrocardiogram after standard exercise as a functional test of the heart. Am Heart J 1942;777-793.
20. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S: The electrocardiogram in population studies. A classification system. Circulation 1960;vol XXI:1160-1175.
21. Bazett HC: An analysis of the time relations of electrocardiograms. Heart 1920;7:353-370.
22. Saifer A, Kammerer DF: Photometric determination of total cholesterol in plasma or serum by a modified Liebermann-Burchard reaction. J Prot Chem;1946:164-167.
23. Vandenbroucke JP, Matroos AW, Van der Heide-Wessel C, Van der Heide RM: Parental survival, an independent predictor of longevity in middle aged persons. Am J Epidemiol 1984;119:742-750.
24. Manual of the international statistical classification of diseases, injuries, and causes of death, 9th ed, vol 1. Geneva: World Health Organisation, 1977.
25. Kramer CY: Extension of multiple range tests to group means with unequal numbers of replication. Biometrics 1956;12:307-310.
26. Rothman KJ: Modern Epidemiology. Boston/Toronto, Little, Brown and Company, 1986, pp 61-69.
27. Goldberg RJ, Bengtson J, Zuoyao C, Anderson KM, Locati E, Levy D: Duration of the QT interval and total and cardiovascular mortality in healthy persons (The Framingham heart study experience). Am J Cardiol 1991;67:55-58.
28. Puddu PE, Jouve R, Mariotti S, Giampaoli S, Lanti M, Reale R, Menotti A: Evaluation of 10 QT-prediction formulas in 881 middle-aged men from the seven countries study: emphasis on the cubic Fridericia's equation. J Electrocardiol 1988;21,(3):219-229.

29. Schwartz PJ, Periti M, Malliani A: The long Q-T syndrome. Am Heart J 1975;89:378-390.
30. Malliani A, Schwartz PJ, Zanchetti A: Neural mechanisms in lifethreatening arrhythmias. Am Heart J 1980;100:705-715.
31. Verrier RL, Corbalan R: Psychologic stress and threshold for repetitive ventricular response. Science 1973;182:834-836.
32. Lown B, DeSilva RA, Lenson R: Roles of psychologic stress and autonomic nervous system changes in provocation of ventricular premature complexes. Am J Cardiol 1978;41:979-985.
33. Reich P, DeSilva RA, Lown B, Murawski J: Acute psychological disturbances preceding life-threatening arrhythmias. JAMA 1981;246,3:233-235.

8. ST SEGMENT AND T WAVE PREDICT CARDIOVASCULAR MORTALITY IN MIDDLE-AGED MEN AND WOMEN[1]

Evert G. Schouten MD, Jacqueline M. Dekker MSc,
Jan Pool MD PhD, Frans J. Kok PhD, Rix ten Veen,
Caroline Vreugdenhil, Jan P. Vandenbroucke MD PhD

8.1 Abstract

ST-segment and T-wave abnormalities as defined according to the Minnesota classification system, are predictive of coronary heart disease morbidity and mortality. In 28 years of follow up of 3,091 middle aged, apparently healthy men and women, the association between these and more subtle ST and T abnormalities in standard lead I, and all-cause, cardiovascular (CVD) and coronary heart disease (CHD) mortality was investigated.
ST-segment depression ≥ 1/2 mm in men was significantly associated with 15-year CHD mortality compared with iso-electric ST segment (multivariate relative risk (RR) 2.2). For T-wave inversion, risk among men (RR 3.7) and women (RR 6.5) was significantly increased compared with T wave greater than 1 mm. Among the more subtle abnormalities, slight elevation of the ST segment in men was inversely associated with CVD (RR 0.5) and CHD mortality (RR 0.4), while in women T-wave amplitude equal to 1 mm was associated with CVD (RR 2.2) and CHD mortality (RR 2.8). Associations after 28 years of follow up and for ST and T abnormalities after moderate exercise were less strong.

The increased risk of ST depression and T inversion is presumably due to coronary disease. The protective effect of ST elevation may indicate absence of such disease or may indicate a favorable autonomic balance. Anyhow, it is the first empirical evidence, that nicely curved upsloping type of ST-segment, that clinicians always liked best, indicates a favorable prognosis. ST-segment and T-wave abnormalities in a healthy population have independent predictive value for CVD and CHD mortality, even when their magnitude would normally leave them unnoticed.

---

[1] Submitted.
Supported by the Netherlands Heart Foundation (grant 86.060).

8.2 Introduction

Electrocardiographic abnormalities of repolarization like ST-segment depression or elevation and T-wave flattening or inversion, especially when exercise-induced, indicate myocardial ischemia in coronary patients (1-5). The diagnostic value of these electrocardiographic findings for the presence of coronary heart disease, however, is relatively low (6-9), due to a considerable prevalence of these findings in persons without coronary heart disease. In ambulatory electrocardiographic monitoring, transient episodes of these abnormalities, not accompanied by angina pectoris, are encountered not only in patients with coronary heart disease, but in healthy persons as well (10-14). Even in carefully selected normal populations, ST-T abnormalities in the resting electrocardiogram have been observed to be associated with coronary events like myocardial infarction, coronary heart disease mortality and sudden death (15-22). In all these studies ST and T abnormalities are defined according to the Minnesota classification, which is a diagnosis oriented classification for cardiac disease (23). Because variation in ST segment and T wave, not large enough to be coded under the Minnesota Code, nevertheless may indicate variation in autonomic nervous system function, in the present study a more detailed measurement and coding of these ECG parameters was carried out, and the association with all-cause, cardiovascular and coronary heart disease mortality was investigated.

8.3 Population and methods

Study population

In 1953-1954, a cohort of 1,583 men and 1,508 women, civil servants and spouses of civil servants of the city of Amsterdam, age between 40 and 65 years, participated in a general health survey. Its purpose was to study the feasibility of a medical screening of apparently healthy persons, to detect early cases of disease. About 54% of the 11,700 eligible civil servants volunteered, with or without their spouses. The cohort consisted of an age- and sex-stratified sample with about equal numbers in five-year age and sex categories. Information on survival or cause of death was missing for 19 men and 12 women, mostly because of emigration, leaving 1,564 men and 1,496 women (896 and 521 deceased in the total follow-up period, respectively).

Coding of electrocardiograms is tedious and time consuming. Therefore, instead of studying the complete cohort, we used the case-cohort sampling design of Miettinen (24-26). In this approach all cases are identified and studied in addition to a random sample from the cohort. By means of the sample, the distribution of study parameters in the total cohort is estimated. We decided to draw a random sample of about twice the expected number of cases of cardiovascular death (expectation: 40% of the deceased). This yielded a sample size of 717 men and 494 women (sampling fractions 45.8% and 33.0% respectively). Coding of electrocardiograms was started when cause-of-death ascertainment was still going on. Therefore, to make sure all cardiovascular deaths would be included in the study, electrocardiograms of all deceased had to be coded. This way, electrocardiograms of a total of 1,219 men and 848 women were evaluated, comprising all persons in the sample extended with the deaths in the rest of the cohort. Exclusion of 10 men and 14 women with missing information on ST-T, left a study population of 1,209 men (887 deceased) and 834 women (508 deceased).

To evaluate the possibility that associations between usually neglected minor abnormalities and mortality might still be a consequence of already manifest coronary heart disease, some of them were studied in a subpopulation without signs of heart disease at baseline as well. Therefore, subjects who reported typical angina, or with electrocardiographic infarction patterns, ventricular hypertrophy or intraventricular conduction disturbances, were excluded.

Data collection

The general health survey in 1953-1954 consisted of a detailed medical history obtained by interview, a physical examination, an electrocardiogram, a chest X-ray and some laboratory examinations. All results were published in a PhD thesis by Van der Heide (27), who was one of two physicians who performed the examinations.

At baseline in 1953-1954 a 12-lead electrocardiogram was recorded on an Elema one-channel, ink-jet electrocardiographic recorder, type Mingograph. A second five-lead recording was made within one minute after the Master Two Step Test (28). Recently the electrocardiograms were classified and coded according to the Minnesota Code (23) by coders blinded for baseline characteristics and outcome. Detailed measurements of PQ, QT and RR interval, ST-segment and T-wave amplitude were performed as well.

ST segment and T wave

The level of the ST segment was measured in lead I at 80 msec past the J-point in quarters of millimeters (0.025 mV) at rest and after exercise, T-wave amplitude was measured in millimeters (0.1 mV) in the same lead.

In 1981 information on survival of 99.9% of the total population was added to the original data of this health survey, from the records of the Civil Servants Pension Fund (A.B.P.). Details of this follow-up procedure were published elsewhere (29). The cause of death until 1981 was established in 1989 for 98.0% of the deceased men and 98.1% of the women using the registers of the Dutch Central Bureau of Statistics (C.B.S.). The necessary death certificate number was obtained from the Dutch Central Bureau of Genealogy.

The classification of causes of death was based on the International Classification of Diseases, 9th revision (30). For the analysis all-cause mortality, cardiovascular (ICD-9 codes 390-460), and coronary heart disease mortality (ICD-9 codes 410-414) were selected. Causes of death before 1969, originally coded according to the 6th and 7th revision, were recoded to the 9th revision by the Central Bureau of Statistics, using the original death certificates. The 8th revision hardly differs from the 9th, with respect to the two mortality categories.

Data analysis

Participants were classified in 4 categories of ST at rest and after exercise in standard lead I: ST elevated, ST iso-electric, ST depression 1/4 mm and ST-depression $\geq$ 1/2 mm. With respect to T-wave amplitude they were classified in the categories T $>$ 1 mm, T = 1 mm, iso-electric T-wave and T-wave inversion. Iso-electric ST-segment and T-wave amplitude $>$1 mm were chosen as the reference categories. Differences in means and percentages of relevant characteristics between these ST and T categories in the sample of the cohort were tested by two-sample t-tests.

Minnesota Code items 4 and 5 were divided in major (codes 4.1 and 4.2 and 5.1 and 5.2) and minor abnormalities (codes 4.3 and 5.3).

To evaluate the effect of cardiovascular risk factors as potential confounders, a stratified analysis was performed. For this purpose we used age strata with cut points 50 and 60 years and strata based on approximate tertiles for the other confounders. For men cut points of confounder tertiles were 70 and 80 mm Hg for blood pressure, 5.9 and 7.0 mmol/l for serum cholesterol, 23.4 and 25.6 kg/m^2 for body mass index and 3 and 70 cigarettes/week for smoking. For women these cut points were 80 and 90 mm Hg for blood pressure, 6.2 and 7.5 mmol/l for serum cholesterol and 24.7 and 27.6 kg/m^2 for body mass index. Smoking for

women was divided in two categories, either smoking or non-smoking.

Case-cohort relative risks (cumulative incidence ratios) adjusted for potential confounding variables were estimated using logistic regression analysis. Categories of potential confounders were entered into the model as indicator variables. In this analysis, the referent group is not a sample from the non-cases in the cohort, like in a case-control study, but a random sample from the cohort as a whole, including the cases. The resulting logistic "odds ratio" in the case-cohort approach estimates relative risk (cumulative incidence ratio) without need of the "rare disease assumption".

In all analyses the sample, representing the cohort, is identical, but the number of cases and therefore the size of the case-cohort study population differs by chosen period of follow up and cause-of-death category, because of the different number of deaths involved in the rest of the cohort.

8.4 Results

In table 8.1 baseline characteristics and mortality are presented in categories of ST-segment level in the sample of the cohort. For age, total serum-cholesterol and mortality percentage significant differences are observed mainly between the ST-depression categories and iso-electric ST segment. Similar differences are observed with respect to T-wave amplitude for the categories T inversion and T = 1 mm (table 8.2).

For comparison with results reported in the literature, in table 8.3 the case-cohort relative risks for major (code 4.1, 4.2, 5.1 and 5.2) and minor (other 4 and 5 codes) ST-segment and T-wave abnormalities, coded in the full 12-lead electrocardiogram according to the Minnesota-Code items 4 and 5 are presented. In men the major ST and T codes from the Minnesota Code show a strong and statistically significant association with mortality. Associations among men for the minor codes and among women for both major and minor codes, are much weaker and not significant.

Table 8.4 presents the associations for depression and elevation of the ST-segment, measured in standard lead I. Among men, age-adjusted and multivariate relative risks (RR) of **ST-segment depression** $\geq$ 1/2 mm were greatest for 15-year coronary heart disease mortality (RR 2.4 and 2.2, respectively) and differed significantly from 1.0. Among women, the corresponding risk ratios were 2.1 and 1.9, but not statistically significant. For smaller ST-

segment depressions no important relative risk was observed.

Relative risks of **ST-segment elevation** among men for cardiovascular (RR 0.5 and 0.5) and coronary heart disease mortality (RR 0.4 and 0.4) were significantly less than 1.0. For women associations were weaker and based on very small numbers of mortality cases.

Table 8.5 shows the results for the T-wave measured in lead I relative to the reference category T > 1 mm. Age-adjusted and multivariate relative risks of the men for **T-wave inversion**, compared with T-wave amplitude > 1 mm, were 3.0 and 2.9 for cardiovascular and 3.8 and 3.7 for ischemic heart disease mortality, all statistically significant. The relative risks of the women were 6.8 and 6.3, and 7.3 and 6.5, respectively, all except the last significant.

The associations for **iso-electric T wave** (T = 0, only calculated for men) were smaller, though increasing from all-cause to coronary heart disease mortality, and most were not significant.

Among women only, **T-wave amplitude = 1 mm** (T = 1) was significantly associated with cardiovascular and coronary heart disease mortality (age-adjusted and multivariate RR: 2.3 and 2.2, and 3.0 and 2.8, respectively).

The associations for 28-year mortality and for T-wave amplitude measured in the electrocardiogram after exercise were similar, but most were somewhat weaker.

The strong inverse association for ST elevation persisted when persons with evidence of manifest heart disease at baseline were excluded, while the associations for ST depression ≥ ½ mm were somewhat weaker, among men only. When ST segment and T wave were considered together in a multivariate model, ST elevation and T-wave inversion remained as strongly predictive as before, while ST depression lost some (in women all) of its predictive value (data not shown).

Table 8.1 Baseline characteristics and mortality (mean ± standard deviation or percentage) in categories of ST-segment level, for men and women as observed in a sample from the cohort.

MEN	ST elevation (n=149)	ST = 0 (n=518)	ST= ¼mm depression (n=26)	ST ≥ ½mm depression (n=24)
Age (years)	51.5 ± 7.6	52.5 ± 7.5	56.5 ± 7.2†	58.3 ± 6.5†
Cholesterol‡ (mmol/l)	6.8 ± 1.5	6.8 ± 1.3	6.7 ± 1.0	7.1 ± 1.4
Diastolic BP* (mm Hg)	78.4 ± 9.0	78.6 ± 10.3	86.9 ± 14.1†	84.2 ± 13.5†
Body-mass index (kg/m²)	24.7 ± 2.7	24.5 ± 5.0	25.4 ± 2.6	25.5 ± 2.4
Heart rate (bpm)				
at rest	70.0 ± 12.5	70.5 ± 11.9	72.7 ± 11.9	74.6 ± 16.3
after exercise	72.0 ± 13.0	73.3 ± 12.5	73.7 ± 13.1	75.2 ± 15.4
Smokers (%)	54.4†	65.4	69.2	54.2
Number of cigarettes among smokers	78.7 ± 51.8	74.6 ± 54.0	61.1 ± 49.3	56.9 ± 74.6
15-year mortality (%)	19.5	21.2	26.9	45.8†
CVD*	7.4	10.2	11.5	41.7*
CHD*	4.0	6.2	7.7	29.2†
WOMEN	(n=64)	(n=341)	(n=45)	(n=44)
Age (years)	49.3 ± 7.3†	51.4 ± 7.1	55.1 ± 7.7†	55.5 ± 6.0†
Cholesterol‡ (mmol/l)	7.5 ± 2.0	7.3 ± 1.5	7.4 ± 1.3	7.6 ± 1.5
Diastolic BP* (mm Hg)	86.6 ± 11.7	86.4 ± 12.6	89.2 ± 14.7	96.0 ± 18.0†
Body-mass index (kg/m²)	26.5 ± 3.6	26.3 ± 3.5	26.2 ± 3.8	27.0 ± 3.1
Heart rate (bpm)				
at rest	76.9 ± 12.7	76.9 ± 12.7	81.6 ± 14.1	82.4 ± 15.7
after exercise	81.3 ± 13.3	80.9 ± 13.8	89.9 ± 14.9	87.4 ± 18.8
Smokers (%)	43.8	37.5	33.3	25.0
Number of cigarettes among smokers	18.6 ± 21.6	17.8 ± 25.8	20.6 ± 19.8	19.0 ± 27.7
15-year mortality (%)	1.6†	8.8	15.6	29.5†
CVD*	1.6	3.8	2.2	13.6†
CHD*	1.6	2.3		6.8

* BP: Blood pressure; CVD: Cardiovascular disease; CHD: Coronary heart disease
† $p < 0.05$, two sided student t-test for difference with category ST = 0
‡ Serum cholesterol men: 40, women: 9 missing observations

Table 8.2 Baseline characteristics and mortality (mean ± standard deviation or percentage) in categories of T-wave amplitude, for men and women as observed in a sample from the cohort.

MEN	T inversion (n=13)	T = 0 (n=7)	T = 1mm (n=175)	T ≥ 2mm (n=522)
Age (years)	61.9 ± 4.1†	53.9 ± 9.0	55.5 ± 6.6†	51.6 ± 7.6
Cholesterol‡ (mmol/l)	6.8 ± 1.7	6.7 ± 1.5	6.8 ± 1.5†	6.8 ± 1.3
Diastolic BP* (mm Hg)	93.5 ± 19.5†	86.4 ± 12.8†	79.6 ± 10.5	78.3 ± 9.9
Body-mass index (kg/m²)	25.8 ± 2.7	26.6 ± 2.4	24.1 ± 2.8†	24.8 ± 2.6
Heart rate (pbm)				
at rest	76.4 ± 14.8	74.9 ± 12.3	73.9 ± 12.5†	69.3 ± 11.7
after exercise	76.4 ± 13.0	76.0 ± 9.2	75.7 ± 14.0	72.1 ± 12.2
Smokers (%)	38.5	85.7	68.0	61.5
Number of cigarettes among smokers	38.5 ± 32.7	115.5 ± 89.0	80.9 ± 57.3	71.8 ± 51.9
15-year mortality (%)	69.2†	42.9	31.4†	17.2
CVD*	61.5†	28.6	12.6	8.6
CHD*	46.2†	14.3	6.3	5.6
WOMEN	(n=6)	(n=0)	(n=117)	(n=368)
Age (years)	61.8 ± 2.6†		53.1 ± 7.9†	51.2 ± 7.0
Cholesterol‡ (mmol/l)	7.7 ± 1.7		7.4 ± 1.6	7.3 ± 1.6
Diastolic BP* (mm Hg)	104.2 ± 28.0†		88.2 ± 15.3	86.9 ± 12.3
Body-mass index (kg/m²)	28.2 ± 3.0†		26.2 ± 3.5	26.4 ± 3.5
Heart rate (pbm)				
at rest	79.1 ± 16.1		79.5 ± 13.7	77.3 ± 13.0
after exercise	83.9 ± 17.5		82.2 ± 14.9	81.5 ± 14.4
Smokers (%)	0		39.3	37.0
Number of cigarettes among smokers	-		21.2 ± 28.2	17.2 ± 23.4
15-year mortality (%)	66.7†		17.9†	
CVD*	50.0†		11.1†	1.4
CHD*	16.7†		6.0†	1.1

* BP: Blood pressure; CVD: Cardiovascular disease; CHD: Coronary heart disease
† $p < 0.05$, two sided student t-test for difference with category T≥2
‡ Serum cholesterol men: 40, women: 9 missing observations

Table 8.3 Case-cohort* relative risk of major and minor Minnesota ST (4) and T (5) items for all-cause, cardiovascular and coronary heart disease mortality. Reference: no Minnesota 4, 5 code, respectively.

	Minnesota 4		Minnesota 5	
MEN	major	minor	major	minor
	all-cause (N=901)†			
age-adjusted	2.7 (1.4 - 5.2)‡	1.6 (0.8 - 3.4)	2.4 (1.3 - 4.6)	1.2 (0.6 - 2.3)
multivariate§	2.5 (1.6 - 4.2)	1.4 (0.8 - 2.5)	2.4 (1.5 - 3.8)	1.1 (0.6 - 1.9)
	cardiovascular (N=728)†			
age-adjusted	4.4 (2.5 - 8.9)	2.2 (0.9 - 5.1)	3.5 (1.7 - 7.0)	1.5 (0.7 - 3.3)
multivariate	3.6 (2.1 - 6.5)	1.9 (0.9 - 4.0)	3.0 (1.7 - 5.2)	1.3 (0.6 - 2.9)
	coronary heart disease (N=659)†			
age-adjusted	4.9 (2.2 - 10.9)	1.7 (0.5 - 5.3)	3.9 (1.7 - 8.7)	0.9 (0.3 - 2.9)
multivariate	4.1 (2.1 - 7.9)	1.4 (0.5 - 4.2)	3.5 (1.6 - 7.7)	0.7 (0.2 - 2.6)
WOMEN				
	all-cause (N=587)†			
age-adjusted	1.7 (0.9 - 3.3)	0.9 (0.4 - 2.3)	2.1 (0.9 - 5.0)	1.3 (0.6 - 2.8)
multivariate	1.5 (0.9 - 2.5)	0.9 (0.5 - 1.9)	1.8 (1.0 - 3.5)	1.1 (0.6 - 2.1)
	cardiovascular (N=500)†			
age-adjusted	2.1 (0.9 - 4.8)	1.6 (0.6 - 4.7)	2.4 (0.8 - 6.7)	1.6 (0.6 - 4.1)
multivariate	1.5 (0.7 - 3.1)	1.5 (0.6 - 3.8)	1.7 (0.6 - 4.5)	1.2 (0.5 - 2.9)
	coronary heart disease (N=460)†			
age-adjusted	1.9 (0.5 - 7.0)	0.9 (0.1 - 7.4)	--	--
multivariate	1.3 (0.4 - 4.5)	0.7 (0.1 - 4.4)	--	--

* cases relative to a random sample from the cohort

† N: number of all cases + number of non-cases in the sample

‡ 95% confidence interval

§ adjusted for age, total serum cholesterol, diastolic blood pressure, smoking and body-mass index

Table 8.4 Case-cohort* relative risk of 15-year all-cause, cardiovascular and coronary heart disease mortality for categories of ST-segment level in resting electrocardiogram. Reference: iso-electric ST-segment.

MEN	ST elevation	ST = ¼ mm depression	ST ≥ ½ mm depression
		all cause (N=901)†	
age-adjusted	0.7 (0.4-1.1)‡	0.9 (0.4-2.0)	1.2 (0.9-1.6)
multivariate§	0.8 (0.6-1.1)	0.8 (0.5-1.4)	1.2 (0.8-1.8)
		cardiovascular (N=728)†	
age-adjusted	0.5 (0.3-0.9)	0.9 (0.4-2.1)	2.0 (1.3-3.1)
multivariate	0.5 (0.3-0.9)	0.8 (0.4-1.6)	1.9 (1.1-3.0)
		coronary heart disease (N=659)†	
age-adjusted	0.4 (0.2-0.8)	0.9 (0.3-3.0)	2.4 (1.4-4.4)
multivariate	0.4 (0.2-0.8)	0.8 (0.3-2.1)	2.2 (1.2-3.9)
WOMEN	ST elevation	ST = ¼ mm depression	ST = ½ mm depression
		all cause (N=587)†	
age-adjusted	0.5 (0.2-1.0)	1.2 (0.8-1.8)	1.7 (1.2-2.5)
multivariate	0.5 (0.2-1.0)	1.2 (0.7-2.0)	1.5 (0.9-2.4)
		cardiovascular (N=500)†	
age-adjusted	0.7 (0.2-1.8)	0.8 (0.3-1.9)	2.2 (1.2-2.9)
multivariate	0.7 (0.2-2.2)	0.8 (0.3-2.0)	1.8 (0.9-3.6)
		coronary heart disease (N=460)†	
age-adjusted	0.5 (0.1-3.3)	0.3 (0.1-2.3)	2.1 (0.9-5.1)
multivariate	0.4 (0.0-4.0)	0.3 (0.1-2.2)	1.9 (0.6-6.3)

* cases compared to a random sample from the cohort
† N: number of all cases + number of non-cases in the sample
‡ 95-per cent confidence interval
§ adjusted for age, total serum cholesterol, diastolic blood pressure, smoking and body-mass index

Table 8.5 Case-cohort* relative risks of 15-year all-cause, cardiovascular and coronary heart disease mortality for categories of T-wave amplitude in resting electrocardiogram. Reference: T-wave > 1 mm

MEN	T inversion	T = 0	T = 1 mm
		all cause (N=901)†	
age-adjusted	1.9 (1.3-2.8)	1.6 (0.9-2.9)	1.3 (1.0-1.6)
multivariate§	2.1 (1.2-3.5)	1.4 (0.6-3.5)	1.2 (1.0-1.6)
		cardiovascular (N=728)†	
age-adjusted	3.0 (1.8-5.0)	2.6 (1.1-6.4)	1.1 (0.8-1.4)
multivariate	2.9 (1.7-5.1)	2.7 (0.9-8.1)	1.1 (0.7-1.6)
		coronary heart disease (N=659)†	
age-adjusted	3.8 (2.0-7.2)	2.8 (0.8-9.6)	0.9 (0.6-1.5)
multivariate	3.8 (2.0-7.3)	2.9 (0.7-11.6)	1.1 (0.7-1.8)
WOMEN	T inversion	T = 0	T = 1 mm
		all cause (N=587)†	
age-adjusted	4.2 (2.1-8.4)		1.8 (1.3-2.5)
multivariate	4.3 (1.9-9.6)		1.7 (1.2-2.5)
		cardiovascular (N=500)†	
age-adjusted	6.8 (2.9-25.7)		2.3 (1.4-3.8)
multivariate	6.0 (2.0-17.9)		2.2 (1.3-3.9)
		coronary heart disease (N=460)†	
age-adjusted	7.3 (2.0-27.1)		3.0 (1.3-7.1)
multivariate	6.3 (0.8-48.4)		2.8 (1.1-7.1)

* cases compared to a random sample from the cohort
† N: number of all cases + number of non-cases in the sample
‡ 95-per cent confidence interval
§ adjusted for age, total serum cholesterol, diastolic blood pressure, smoking and body-mass index

8.5 Discussion

In this 28-year prospective study in an apparently healthy middle-aged group of civil servants, particularly among men an increased risk of all-cause, cardiovascular and coronary heart disease mortality for ST-segment depression and T-wave inversion in standard lead I of the resting electrocardiogram was observed. Of the more subtle abnormalities, surprisingly, ST-segment elevation of 1/4 mm or more showed a strong inverse association with mortality risk.

In the literature several other investigators reported an increased coronary heart disease mortality risk (15-17,19) or an increased risk of sudden death (20,21) in the presence of ST-segment depression and T-wave inversion in apparently healthy, mostly male populations. However, in all studies ST and T abnormalities were classified according to the Minnesota system (23), and are therefore not comparable to the detailed measurements in one lead, performed in this study. For comparison we therefore in addition investigated the associations for major and minor Minnesota ST and T items. This confirmed results of others reported in the literature.

Although the predictive value of findings after exercise is thought to be higher (6,31,32), in the presented study associations in general were weaker for ST and T measurements in the electrocardiogram after exercise. Analysis of ST-segment level and T-wave amplitude changes after exercise relative to the resting state, did not produce any consistent associations, except for a borderline significantly increased risk of a rise in ST-segment level among those who had an iso-electric ST segment at rest. The weaker associations after exercise may be a consequence of the lag time before the recording was made and of the mild nature of the exercise applied in the Master test. Heart rates at rest and after exercise indeed were similar.

We are not aware of any study reporting an inverse association between ST-segment elevation and cardiovascular mortality or morbidity in a healthy population. In patients with heart disease, ST-segment elevation usually of more than one mm, especially when exercise induced, is assumed to indicate severe myocardial ischemia, or severely impaired ventricular function and extremely bad prognosis (33,34).

A number of potential methodological problems may have affected the validity of the presently reported study. The study population may not be a true representation of the total middle-aged population in the Netherlands, consisting of relatively healthy working civil ser-

vants. Biological representativeness, however was regarded as more important than statistical representativeness.

Possibly measurement and coding errors of ST segment and T wave as well as diagnostic and coding errors of causes of death have resulted in misclassification. Moreover, a single measurement may be insufficient to characterize a persons long-term ST-segment level or T-wave amplitude. This explains the weaker associations in the full 28-year period of follow up. All mentioned potential sources of error would lead to non-differential misclassification, resulting in dilution of the really existing associations.

A bias because of pharmacological effects interfering with ST-segment level and T-wave amplitude at baseline is not likely, because at the time of the original investigation such medication was hardly used, in this healthy population.

We used the case-cohort sampling design in order to limit the number of electrocardiograms to be coded. If under this design the cohort sample size is a small multiple of the size of the case series, loss of precision is expected to be limited. Because the referent group is a random sample from the source population and not from the non-cases like in a classical case-control study, odds ratios obtained from logistic regression procedures in case-cohort design, can be regarded as unbiased estimates of relative risk (cumulative incidence ratio)(24-26). A comparison of baseline characteristics between the total cohort and the sample did not reveal substantial differences. Therefore we consider the sample to be representative.

To account for competing mortality by other causes of death in the cause specific analyses, we verified crude and age-adjusted associations in person time analysis, calculating incidence density ratios. These appeared to be similar or slightly higher than the reported cumulative incidence ratios.

With the most important risk factors of cardiovascular disease as potential confounders in the analysis, we believe to have taken care of confounding sufficiently. Only age adjustment had a substantial impact on the associations.

Although transient ST and T abnormalities are observed during ambulatory monitoring of healthy individuals (12-14), an increased cardiovascular and coronary heart disease mortality risk among persons with ST-segment depression $\geq$ 1/2 mm and T-wave inversion in this apparently healthy population possibly are the consequence of an increased prevalence of subclinical coronary disease in these groups. In some cases these abnormalities may be secondary to other conditions like ventricular hypertrophy and electrolyte disturbances (2).

Another explanation might be that these changes are due to autonomic dysbalance. Reports in the literature that ST-segment depressions are more prevalent in women, however, have less predictive power in them than in men (35,18), are confirmed by the present study. For T-wave abnormalities, the reverse seems to be the case.

The protective effect of ST-segment elevation 80 msec after the J-point, similarly, may be secondary to a decreased prevalence of ischemic heart disease. Almost all elevations were smaller than 1 mm and the J-point was not or considerably less elevated. Therefore, they in fact represent the nicely curved upsloping ST segment, indicating uncompromised coronary circulation. Another explanation might be, that these changes are due to autonomic imbalance. Anyhow, this observation represents the first empirical evidence supporting the intuitive opinion in clinical practice, that the nicely curved upsloping ST segment is to be preferred over the stretched iso-electric ST segment.

In conclusion, ST-segment depression and T-wave inversion in the electrocardiogram predict cardiovascular and coronary heart disease mortality in an apparently healthy population, particularly among men. ST-segment elevation on the contrary, indicates low mortality risk. These effects may be secondary to existing coronary heart disease, but may also be related to an (ab)normal autonomic balance.

This study demonstrates that the electrocardiogram of apparently healthy individuals carries independent predictive information.

REFERENCES

1. Cohn K, Kamm B, Peteih M, Brand R, Goldschlager N: Use of treadmill score to quantify ischemic response and predict extent of coronary disease. Circulation 1979;59:286-296.
2. Ellestad MH: Stress testing. principles and practice. Philadelphia: F.Davis. 1980:95-102.
3. Mattingly TW: The postexercise electrocardiogram. Its value in the diagnosis and prognosis of coronary arterial disease. Am J Cardiol 1962:395-409.
4. Robb GP, Marks HH: Postexercise electrocardiogram in arteriosclerotic heart disease. Its value in diagnosis and prognosis. JAMA 1967;200:110-118.

5. Beard EF, Garcia E, Burke GE, Dear WE: Postexercise electrocardiogram in screening for latent ischemic heart disease. A study with clinical follow-up observation. Dis Chest 1969;56:405-408.
6. Bruce RA, DeRouen TA, Hossack KF: Value of maximal exercise test in risk assessment of primary coronary heart disease events in healthy men. Five years experience of the Seattle Heart Watch Study. Am J Cardiol 1980;46:371-378.
7. Epstein SE: Value and limitations of the electrocardiographic response to exercise in the assessment of patients with coronary artery disease. Am J Cardiol 1978;42:667-674.
8. Bruce RA: Values and limitations of exercise electrocardiography. Circulation 1974;50:1-3.
9. Detrano R, Salcedo E, Passalacqua M, Friis R: Exercise electrocardiographic variables: A critical appraisal. J Am Coll Cardiol 1986;8:836-847.
10. Armstrong WF, Jordan JW, Morris SN, McHenry PL: Prevalence and magnitude of ST-segment and T-wave abnormalities in normal men during continuous ambulatory electrocardiography. Am J Cardiol 1982;49:1638-1642.
11. Schang SJ, Pepine CJ: Transient asymptomatic ST-segment depression during daily activity. Am J Cardiol 1977;39:396-401.
12. Quyyumi AA, Wright C, Fox K: Ambulatory electrocardiographic ST-segment changes in healthy volunteers. Br Heart J 1983;50:460-464.
13. Deanfield JE, Ribiero P, Oakley K, Krikler S, Selwyn P: Analysis of ST-segment changes in normal subjects: Implications for ambulatory monitoring in angina pectoris. Am J Cardiol 1984;54:1321-1325.
14. Kohli RS, Cashman PMM, Lahiri A, Raftery EB: the ST-segment of the ambulatory electrocardiogram in a normal population. Br Heart J 1988;60:4-16.
15. Blackburn H, Raylor HL, Keys A: The electrocardiogram in prediction of five-year coronary heart disease incidence among men aged forty through fifty-nine. Circulation 1970;42 suppl:154-161.
16. Rose G, Baxter PJ, Reid DD, McCartney P: Prevalence and prognosis of electrocardiographic findings in middle-aged men. Br Heart J 1978;40:636-643.
17. Reunanen A, Pyörälä K, Punsar S, Aromaa A: Predictive value of ECG findings with respect to coronary heart disease mortality. Adv Cardiol 1978;21:310-312.

18. Liao Y, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Colette P, Stamler J: Major and minor electrocardiographic abnormalities and risk of death from coronary heart disease, cardiovascular diseases and all causes in men and women. J Am Coll Cardiol 1988;12:1494-1500.
19. Ostrander LD: The relation of "silent" T-wave inversion to cardiovascular disease in an epidemiologic study. Am J Cardiol 1970;25:325-328.
20. Kreger BE, Cupples LA, Kannel WB: The electrocardiogram in prediction of sudden death: Framingham study experience. Am Heart J 1987;113:377-382.
21. Rabkin SW, Mathewson FAL, Tate RB: The electrocardiogram in apparently healthy men and the risk of sudden death. Br Heart J 1982;47:546-552.
22. Kagan A, Yano K, Reed DM, MacLean CJ: Predictors of sudden cardiac death among Hawaiian-Japanese men. Am J Epidemiol 1989;130:268-277.
23. Prineas RJ, Crow RS, Blackburn H: The Minnesota Code manual of electrocardiographic findings. Boston: John Wright PSG Inc., 1982.
24. Miettinen OS: Theoretical epidemiology. Principles of occurrence research in medicine. New York, Chichester, Brisbane, Toronto, Singapore, John Wiley & Sons, 1985.
25. Miettinen OS: Design options in epidemiologic research. An update. Scand J Work Environ Health 1982;suppl 1:7-14.
26. Miettinen OS: The "case-control" study: valid selection of subjects. J Chron Dis 1985;38:543-548.
27. Heide van der RF: Resultaten van een geneeskundig onderzoek van 3091 gezonde mannen en vrouwen, 40-65 jaar oud. Amsterdam: PhD thesis, University of Amsterdam, 1959.
28. Master AM, Friedman T, Dack S: The electrocardiogram after standard exercise as a functional test of the heart. Am Heart J 1942;777-793.
29. Vandenbroucke JP, Matroos AW, Van der Heide-Wessel C, Van der Heide RM: Parental survival, an independent predictor of longevity in middle aged persons. Am J Epidemiol 1984;119:742-750.
30. Manual of the international statistical classification of diseases, injuries, and causes of death, 9th ed, vol 1. Geneva: World Health Organisation, 1977.
31. Bruce RA, Fisher LD: Exercise-enhanced assessment of risk factors for coronary heart disease in healthy men. J Electrocardiology 1987;suppl:162-166.

32. Kattus AA, Jorgensen CR, Worden RE, Alvaro AB: ST-segment depression with near-maximal exercise in detection of preclinical coronary heart disease. Circulation 1971;44:585-595.

33. Fortuin NJ, Friesinger GC: Exercise-induced ST-segment elevation. Clinical, electrocardiographic and arteriographic studies in twelve patients. Am J Med 1970;49:459-464.

34. Bruce RA, Fisher LD, Pettinger M, Weiner DA, Chaitman BR: ST-segment elevation with exercise: a marker for poor ventricular function and poor prognosis. Coronary Artery Surgery Study (CASS) confirmation of Seattle Heart Watch results. Circulation 1988;77:897-905.

35. Bruce RA, Irving JB: Exercise electrocardiography. in: The Heart, arteries and veins. Willis Hurst ed., fourth edition. New York, McGraw-Hill Book Company 1978.

9. THE ELECTROCARDIOGRAPHIC INDICATORS COMBINED

9.1 Introduction

In the previous chapters, associations between individual electrocardiographic indicators of autonomic balance and all-cause, cardiovascular and coronary heart disease mortality have been reported, adjusted for age and cardiovascular risk factors. QT-interval length, ST-segment level and T-wave amplitude appeared to be prognostic of cardiovascular and of coronary heart disease mortality, particularly in men.

Having assessed these separate effects, the question arises, whether the individual contributions to prognosis are largely independent of each other, or whether some of them estimate the same effect and in fact are redundant. If these variables are independent of each other in their prognosis of mortality, in combination they might improve the prediction already provided by the established cardiovascular risk factors alone.

In this chapter the combined predictive value of QT interval, ST segment and T wave measurements will be addressed, together with age, diastolic blood pressure, serum cholesterol, smoking and body-mass index. In paragraph 9.2 the methods used in this chapter are briefly described. The results from the logistic models in terms of relative risks and confidence intervals are presented and interpreted in paragraph 9.3. Paragraph 9.4 gives an impression of the fit of the logistic models and visualizes the excess prognostic impact of the electrocardiographic variables in Receiver Operating Characteristic (ROC) curves.

9.2 Methods

For the present purpose, the electrocardiographic characteristics and cardiovascular risk factors were categorized in exactly the same way as in the individual analysis reported in the previous chapters. They were introduced into logistic regression models as indicator variables, comparing categories of determinants with a reference category. Individuals who had missing values for any of the independent variables, were excluded from all analyses.

Two logistic regression models with different sets of independent variables were considered in the explanation of 15 and 28-year coronary heart disease mortality in men and of 28-year coronary heart disease mortality in women. First a model including age and cardiovascular risk factors was considered, second a model using age and risk factors in combination with

QT-interval length, ST-segment level and T-wave amplitude. The analysis was confined to coronary heart disease mortality, because most of the individual associations were strongest for that category. The number of 15-year coronary heart disease deaths in women was too small to allow evaluation in an extensive multivariate model. As was performed for the individual electrocardiographic parameters, the results were verified in the subpopulation from which individuals with signs of prevalent heart disease at baseline were excluded. Estimation was carried out with the special case-cohort pseudo-likelihood methods described in chapter 3.

Model fit was evaluated using the risk grouping strategy (1). In this strategy observed and predicted numbers of coronary heart disease deaths are compared in quintiles of the risk predicted by the logistic models from the individual covariate sets. The predicted numbers of coronary heart disease deaths are calculated from the average risk in the quintiles. In order to obtain a valid estimate of risk from a model based on case-cohort sampling, the logistic intercept has to be adjusted by multiplication with a factor depending on the fraction of cases and referents of the complete cohort, that are included in the analysis (2): In the present analysis this comes down to multiplication of the intercept with the natural logarithm of the sampling fraction, used to obtain the cohort sample.

In order to compare the prognostic performance of the models with and without the electrocardiographic variables Receiver Operating Characteristic (ROC) curves were used, graphing the true positive rate as a function of the false positive rate for different cut-off points of predicted risk (3).

9.3 Mutually adjusted associations

Risk factors

In tables 1 to 3, relative risks of 15- and 28-year coronary heart disease mortality and 95%-confidence intervals (95%-CI) are presented, as estimated by logistic models with and without electrocardiographic characteristics, in the total case-cohort population and in the subpopulation without signs of manifest heart disease. The relative risks for age and diastolic blood pressure are significantly different from 1 in men and women, serum cholesterol and cigarette smoking in men only. Introduction of the electrocardiographic variables into the models hardly influenced the relative risks for these risk factors. Using some recalculations,

the relative risks for the cardiovascular risk factor categories were compared with the logistic coefficients reported from the United States Cohort of the Seven Countries Study (4) for 15-years coronary heart disease mortality. They appeared to agree quite well.

Electrocardiographic parameters

In men significant relative risks of 15-year coronary heart disease mortality were observed for moderate QT prolongation (QT 420-440 msec) compared with normal QT (1.8, 95%-CI: 1.1-3.2), slightly elevated ST compared with iso-electric ST (0.4, 95%-CI: 0.2-0.8) and T inversion (2.7, 95% CI: 1.0-7.3). Twenty-eight-year mortality relative risks are somewhat weaker and significant for moderate QT prolongation (1.5, 95%-CI: 1.0-2.2) and ST elevation (0.5, 95%-CI: 0.3-0.8). As far as these associations, could be calculated in the subpopulation that initially had no signs of heart disease, they were similar.

Among women for 28-year coronary heart disease mortality, only a T wave of 1 mm compared with T wave $\geq$ 2mm showed a statistically significant relative risk (1.7, 95%-CI: 1.0-2.8). This association was also similar, however not significant, in the subpopulation.

Extensive QT prolongation in men, lost some of its predictive power when considered in combination with the other electrocardiographic parameters. This may be an indication that, as hypothesized in chapter 1, QT-interval length and ST-segment level at least partly measure the same kind of autonomic imbalance, i.e. left/right sympathetic imbalance. However, it may as well be due to the fact that the number of 15-year coronary deaths in this category was rather small. The remarkable inverse (not significant) associations among women for ST depression in the combined model were not present, when ST items were considered on their own, but emanated when the T-wave items were introduced into the model. This is presumably due to the very strong association that appeared to exist between the ST and T-items in women. Such a strong association may preclude adequate separation of the individual effects. The impact of the other electrocardiographic characteristics was not clearly different from that reported for the characteristics separately.

As was the case for the analyses of the individual electrocardiographic variables in the previous chapters, the risk ratios in general were very similar in the subpopulation without any sign of heart disease, giving no ground for the suspicion that prevalent heart disease might be responsible for the observations.

9.4 Model fit and prediction

Observed/predicted

Tables 9.4 to 9.6 present the observed and model-predicted numbers of coronary heart disease deaths in the complete cohort, grouped according to deciles of predicted risk in the sample. This analysis was carried out in order to get an impression of the overall fit of the logistic regression models to the observations. The comparison between observed and predicted numbers of deaths in deciles of predicted risk in tables 4 to 6, indicates satisfactory model fit and does not give rise to serious question of the validity of the estimated associations because of gross violation of the model assumptions.

ROC curves

The figures 9.1 to 9.3 depict the prognostic power of the models with and without the electrocardiographic characteristics for 15- and 28-year coronary death, by means of ROC curves.

Usually ROC curves are applied to characterize the power of diagnostic tests in discriminating diseased from non-diseased individuals. They may be used as well, to indicate the power of a prognostic test. The logistic models in the present study may be regarded as a prognostic test. The curves display the 'true positive rate' as a function of the 'false positive rate', when different cut-off points are chosen of levels of predicted risk. Here, the true positive rate, or sensitivity denotes the proportion of coronary deaths correctly predicted; the false positive rate, or one minus the specificity, is the proportion of survivors and non-coronary deaths incorrectly predicted as coronary deaths. The closer a ROC curve approximates the upper left hand corner of the figure, the better the performance of the combination of variables with respect to prognosis. Only the curves for 15-year coronary heart disease mortality in men are visually clearly separated from each other, indicating a substantial contribution of the information on QT-interval length, ST-segment level and T-wave amplitude to the prognosis of 15-year coronary heart disease mortality. At 28-year follow up, a contribution is not clearly apparent anymore, probably because in such a long follow-up period, competing causes play an increasingly important role and predictive power of baseline characteristics diminishes. Unfortunately we were not able to investigate the 15-year period in women for coronary heart disease mortality, but when 15-year cardiovascular mortality was considered, there was some contibution of the electrocardiographic parameters

Weinstein (3) characterizes performance of diagnostic tests rather arbitrarily as 'poor', 'fair' or 'good', according to the shape of the ROC curves. The performance of all six models considered in this chapter, could in these terms be indicated as 'fair'. A prognostic test, however, tries to discriminate persons who will acquire the disease from those who will not, long before actual disease occurrence, while a diagnostic test seeks discrimination of persons already having the disease. Therefore, qualifications of test performance may have a different meaning for prognostic tests. A test of long-term prognosis may be expected to have worse performance than a diagnostic test. It must also be realized, that evaluating the performance of tests in the population in which they were originally developed, may present an overly favorable picture.

In conclusion, the selected electrocardiographic characteristics contribute to the prediction of 15-year coronary heart disease mortality in middle-aged men. Although this may also be the case for women, this could not be assessed with certainty because of an insufficient number of coronary deaths. The prognostic power over the 28-year period is considerably less.

Table 9.1 Case-cohort† relative risks (95% confidence intervals)‡ of cardiovascular risk factors and selected electrocardiographic characteristics for 15-year coronary heart disease mortality.

MEN		Model 1: CVD* risk factors		Model 2: Model 1 + ECG	
		total n=97/672§	subgroup n=67/550	total n=97/672	subgroup n=67/550
Age	50-60 yrs	3.4 (1.8-6.3)	2.7 (1.4-5.2)	3.2 (1.7-6.0)	2.8 (1.4-5.5)
	>60 yrs	4.3 (2.3-8.2)	3.8 (1.9-7.5)	3.7 (1.9-7.3)	3.8 (1.8-8.0)
Diastolic BP*	70-80 mmHg	1.2 (0.6-2.2)	0.9 (0.5-1.8)	1.1 (0.6-2.1)	1.0 (0.5-2.0)
	>80 mmHg	2.1 (1.1-3.9)	1.7 (0.8-3.5)	1.8 (1.0-3.3)	1.8 (0.9-3.6)
Serum cholesterol	>5.9 mmol/l	1.5 (0.9-2.5)	1.2 (0.7-2.2)	1.5 (0.9-2.6)	1.1 (0.6-2.0)
	>7.0 mmol/l	1.8 (1.1-3.0)	1.7 (1.0-3.0)	1.7 (1.0-2.9)	1.4 (0.8-2.5)
Cigarette smoking	3-70 /week	1.6 (1.0-2.5)	1.5 (0.8-2.7)	1.7 (1.0-2.7)	1.3 (0.7-2.4)
	>70 /week	1.7 (1.0-2.0)	2.1 (1.1-4.0)	1.8 (1.0-3.3)	2.1 (1.1-4.0)
BMI*	23.4-25.6 kg/m²	0.9 (0.5-1.6)	0.6 (0.3-1.3)	0.9 (0.5-1.6)	0.5 (0.3-1.1)
	>25.6 kg/m²	1.4 (0.9-2.4)	1.2 (0.7-2.2)	1.4 (0.9-2.4)	1.1 (0.6-2.0)
QT interval	420-440 msec			1.8 (1.1-3.2)	2.4 (1.3-4.3)
	>440 msec			1.6 (0.8-3.4)	1.1 (0.3-3.9)
ST segment	slightly elevated			0.4 (0.2-0.8)	0.3 (0.1-0.6)
	depressed 1/4 mm			0.8 (0.3-2.3)	0.3 (0.0-2.1)
	depressed ≥1/2 mm			1.3 (0.5-3.4)	
T-wave amplitude	1 mm			0.9 (0.5-1.5)	0.8 (0.4-1.4)
	0 mm			2.4 (0.5-10.4)	
	<0 mm			2.7 (1.0-7.3)	

* CVD: cardiovascular disease; ECG: electrocardiographic characteristics; BP: blood pressure; BMI: body-mass index.
† Cases relative to a sample from the cohort.
‡ Calculated according to special case-cohort method of Le Cessie et al.
§ Number of cases/number of individuals in the sample.

Table 9.2 Case-cohort relative risks (95% confidence intervals)† of cardiovascular risk factors and selected electrocardiographic characteristics for 28-year coronary heart disease mortality.

MEN		Mode 1: CVD* risk factors		Model 2: Model 1 + ECG*	
		total n=220/672§	subgroup n=168/550	total n=220/672	subgroup n=168/550
Age	50-60 yrs	2.2 (1.5-3.2)	1.9 (1.3-2.8)	2.1 (1.5-3.1)	1.9 (1.3-2.8)
	>60 yrs	2.8 (1.8-4.1)	2.5 (1.6-4.0)	2.5 (1.7-3.9)	2.5 (1.6-3.9)
Diastolic BP*	70-80 mmHg	1.3 (0.9-2.0)	1.2 (0.8-1.8)	1.3 (0.9-1.9)	1.2 (0.8-1.9)
	>80 mmHg	1.5 (1.0-2.2)	1.3 (0.8-2.0)	1.3 (0.9-2.0)	1.2 (0.8-1.9)
Serum cholesterol	>5.9 mmol/l	1.3 (0.9-1.8)	1.2 (0.8-1.8)	1.3 (0.9-1.9)	1.2 (0.8-1.7)
	>7.0 mmol/l	1.6 (1.1-1.2)	1.5 (1.0-2.2)	1.5 (1.1-2.1)	1.4 (0.9-2.1)
Cigarette smoking	3-70/week	1.3 (1.0-1.8)	1.4 (0.9-2.0)	1.3 (1.0-1.8)	1.3 (0.7-2.4)
	>70 /week	1.5 (1.0-2.2)	1.7 (1.1-2.7)	1.7 (1.1-2.5)	1.5 (1.0-2.2)
BMI*	23.4-25.6 kg/m²	1.1 (0.8-1.7)	1.0 (0.7-1.5)	1.1 (0.8-1.6)	1.0 (0.6-1.5)
	>25.6 kg/m²	1.5 (1.1-2.2)	1.5 (1.0-2.3)	1.5 (1.1-2.2)	1.5 (1.0-2.3)
QT interval	420-440 msec			1.5 (1.0-2.2)	1.6 (1.1-2.6)
	>440 msec			1.3 (0.8-2.4)	1.5 (0.7-3.3)
ST segment slightly elevated				0.5 (0.3-0.8)	0.4 (0.3-0.7)
	depressed 1/4 mm			1.1 (0.6-2.0)	1.0 (0.5-2.2)
	depressed ≥1/2 mm			1.3 (0.5-3.4)	
T-wave amplitude	1 mm			0.9 (0.6-1.3)	0.9 (0.6-1.3)
	0 mm			1.0 (0.3-3.7)	
	<0 mm			1.5 (0.7-3.3)	

* CVD: cardiovascular disease; ECG: electrocardiographic characteristics; BP: blood pressure; BMI: body-mass index.
† Cases relative to a sample from the cohort.
‡ Calculated according to special case-cohort method of Le Cessie et al.
§ Number of cases/number of individuals in the sample.

Table 9.3 Case-cohort relative risks (95% confidence intervals)† of cardiovascular risk factors and selected electrocardiographic characteristics for 28-year coronary heart disease mortality among women.

WOMEN		Model 1: CVD* risk factors		Model 2: Model 1 + ECG*	
		total n=88/476§	subgroup n=69/401	total n=88/476	subgroup n=69/401
Age	50-60 yrs	3.4 (1.6-6.9)	4.5 (2.0-10.3)	3.4 (1.6-7.1)	4.6 (2.0-10.4)
	>60 yrs	5.9 (2.7-12.7)	6.9 (2.8-17.3)	5.6 (2.5-12.8)	6.8 (2.7-17.3)
Diastolic BP*	80-90 mmHg	1.4 (0.8-2.4)	1.6 (0.9-2.8)	1.5 (0.8-2.6)	1.7 (0.9-3.0)
	>90 mmHg	1.9 (1.1-3.3)	1.8 (1.0-3.4)	1.9 (1.1-3.3)	1.8 (0.9-3.4)
Serum cholesterol	>6.2 mmol/l	1.0 (0.6-1.8)	0.9 (0.5-1.8)	1.0 (0.6-2.0)	0.9 (0.5-1.9)
	>7.5 mmol/l	1.5 (0.9-1.7)	1.5 (0.8-2.8)	1.5 (0.9-2.7)	1.4 (0.8-2.7)
Cigarette smoking	any	1.0 (0.6-1.6)	1.1 (0.7-1.9)	1.0 (0.6-1.6)	1.1 (0.7-2.0)
BMI*	24.7-27.6 kg/m²	0.8 (0.4-1.5)	0.8 (0.4-1.7)	0.8 (0.4-1.4)	0.9 (0.4-1.8)
	>27.6 kg/m²	1.1 (0.6-2.0)	1.4 (0.7-2.7)	1.2 (0.6-2.0)	1.7 (0.9-3.0)
QT interval	420-440 msec			1.3 (0.8-2.3)	1.2 (0.6-2.3)
	>440 msec			1.0 (0,5-1.9)	1.0 (0.5-2.0)
ST segment	slightly elevated			1.0 (0.5-2.0)	0.9 (0.5-1.9)
	depressed 1/4 mm			0.8 (0.3-1.8)	0.8 (0.3-2.0)
	depressed ≥1/2 mm			0.5 (0.2-1.2)	
T-wave amplitude	1 mm			1.7 (1.0-2.8)	1.7 (0.9-2.3)
	0 mm				
	<0 mm			3.4 (0.5-21.2)	

* CVD: cardiovascular disease; ECG: electrocardiographic characteristics; BP: blood pressure; BMI: body-mass index.
† Case relative to a sample from the cohort.
‡ Calculated according to special case-cohort method of Le Cessie et al.
§ Number of cases/number of individuals in the sample.

Table 9.4 Observed and predicted numbers of 15-year coronary heart disease deaths in quintiles of predicted risk (%). Model 1: risk factors; model 2: risk factors and QT, ST and T items. N Cases/sample: 97/672.

MEN	Model 1			Model 2		
quintile*	av.pred.risk*	pred.number*	obs.number*	av.pred.risk	pred.number	obs.number
1	1.4	4.4	2	1.2	3.8	3
2	2.9	8.3	12	2.6	8.1	7
3	5.1	16.9	15	4.3	13.3	11
4	7.6	22.7	31	7.0	21.8	31
5	17.9	42.1	38	9.4	45.3	45

* Abbreviations: av.pred.risk: average of predicted risk (%) in the quintiles;
pred. number: number of deaths predicted by the model
obs. number: number of deaths observed in the cohort

Table 9.5 Observed and predicted numbers of 28-year coronary heart disease deaths in quintiles of predicted risk (%). Model 1: risk factors; model 2: risk factors and QT, ST and T items. N Cases/sample: 220/672.

MEN	Model 1			Model 2		
quintile	av.pred.risk*	pred.number*	obs.number*	av.pred.risk	pred.number	obs.number
1	5.9	18.4	13	5.2	16.0	3
2	9.5	29.4	29	8.9	27.4	23
3	13.1	40.5	46	12.3	39.0	47
4	17.1	54.3	50	16.8	52.6	55
5	22.9	72.0	82	24.4	76.7	82

* Abbreviations: av.pred.risk: average of predicted risk (%) in the quintiles;
pred. number: number of deaths predicted by the model
obs. number: number of deaths observed in the cohort

Table 9.6 Observed and predicted numbers of 28-year coronary heart disease deaths in quintiles of predicted risk (%). Model 1: risk factors; model 2: risk factors and QT, ST and T items. N Cases/sample: 88/476.

WOMEN	Model 1			Model 2		
quintile	av.pred.risk*	pred.number*	obs.number*	av.pred.risk	pred.number	obs.number
1	1.4	3.9	3	1.3	3.8	3
2	2.2	6.8	8	2.2	6.3	6
3	4.8	14.1	10	4.4	13.1	8
4	7.6	22.8	29	7.4	21.9	32
5	12.5	38.0	38	13.2	39.3	39

* Abbreviations: av.pred.risk: average of predicted risk (%) in the quintiles;
pred. number: number of deaths predicted by the model
obs. number: number of deaths observed in the cohort

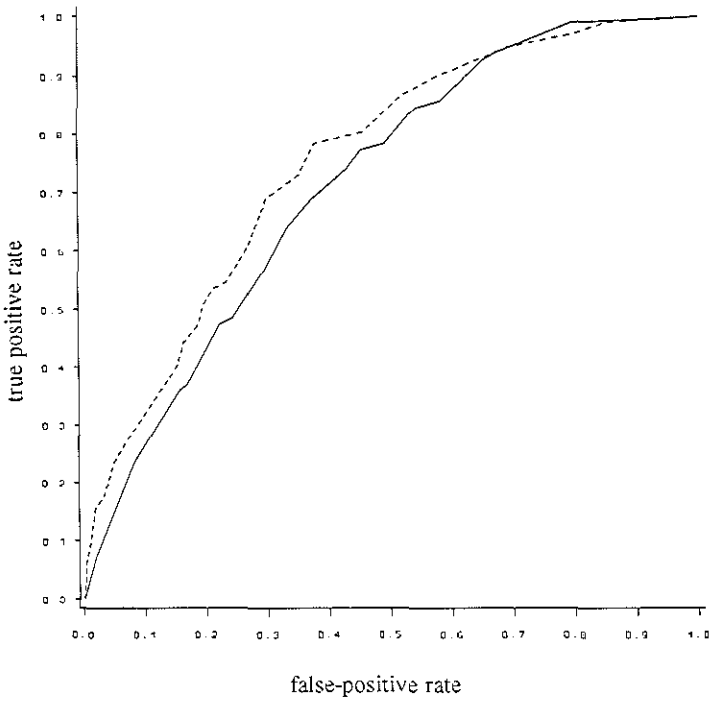


Figure 9.1 ROC curves of logistic models with (---) and without (———) electrocardiographic variables, in prediction of 15-year coronary heart disease mortality among men.

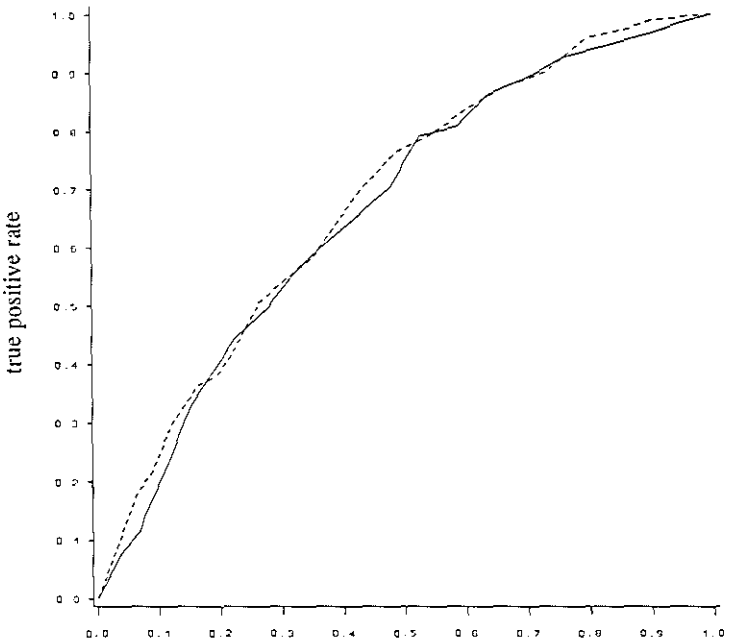


Figure 9.2 ROC curves of logistic models with (---) and without (———) electrocardiographic variables, in prediction of 28-year coronary heart disease mortality among men.

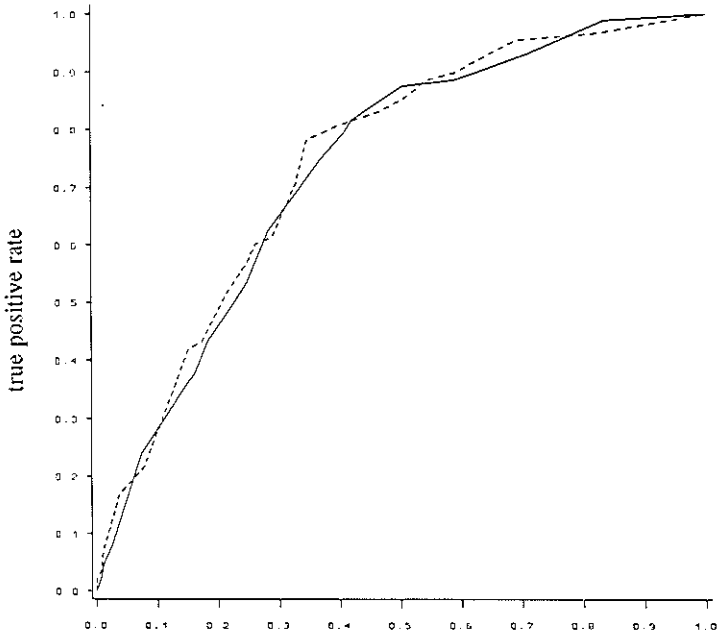


Figure 9.3 ROC curves of logistic models with (---) and without (———) electrocardiographic variables, in prediction of 28-year coronary heart disease mortality among women.

REFERENCES

1. Hosmer DW, Lemeshow S: Applied logistic regression. New York, John Wiley, 1989.
2. Maisels MJ, Gifford K, Antle CE, Leib GR: Jaundice in the healthy newborn infant: a new approach to an old problem. Pediatrics 1988;81:505-511.
3. Weinstein MC, Fineberg HV: Clinical decision analysis. Philadelphia, WB Saunders Company, 1980.
4. Keys A, Menotti A, Aravanis C, et al.: The Seven Countries Study: 2,289 deaths in 15 years. Prev Med 1984;13:141-154.

10. GENERAL DISCUSSION

10.1 Introduction

The aim of the present study was to assess the predictive value of presumed electrocardiographic indicators of autonomic imbalance for cardiovascular mortality in an essentially non-diseased population. In addition, the performance of a number of cost-efficient epidemiologic research designs for estimation of exposure-disease associations were compared with the full-cohort design. The reason for this methodological digression was to investigate the validity of the case-cohort sampling design. This design was applied in the present study, in order to limit the measurement and coding of electrocardiograms.

As stated in the aim of the study (chapter 1), heart rate, PQ-interval length, QT-interval length, ST-segment level and T-wave amplitude as potential electrocardiographic indicators of autonomic imbalance, were investigated in relation to all-cause, cardiovascular and coronary heart disease mortality.

QT interval, ST segment and T wave in the resting electrocardiogram appeared to be associated with cardiovascular and coronary heart disease mortality in the study population. An increased risk of QT prolongation and a protective effect of slight ST elevation have never been observed before in populations of apparently healthy individuals. Recently QT-interval length was reported not to be associated with cardiovascular mortality in the Framingham cohort. Heart rate was predictive only for all-cause mortality in our study. Most associations, except those for T-wave amplitude, were stronger in men than in women and the results after the exercise test were weaker than at rest. The associations in a subpopulation without signs of heart disease at baseline, were very similar to those reported for the total population.

In this chapter, first the validity of the methods used in the study is addressed, with respect to the study population, the case-cohort sampling, the electrocardiographic information, the causes of death and the control of confounding. Second, the main findings are interpreted and possible biological mechanisms are discussed. Finally, the implications for health care and health research of the study results are discussed.

10.2 Validity

The validity of any observational epidemiologic study is threatened by several potential biases. These biases are the result of errors in the make up of the study population, due to recruitment, non-participation or to loss to follow up (selection bias), of errors in the gathering of the data on both exposure and outcome (information bias) or of spurious effects by extraneous factors (confounding). The errors may be either differential (systematic) or non-differential (random) (1). 'Non-differential' denotes random distribution of the error over exposure and/or outcome. For population make-up, this is just another way of putting sampling variability. For data gathering it means misclassification of electrocardiographic variables and mortality randomly distributed over categories. 'Differential' denotes error that is related with exposure or outcome, i.e. recruitment, non-participation or loss to follow up differ according to electrocardiographic characteristics and/or to mortality. With respect to the electrocardiographic and cause of death data, this term addresses misclassification that is different in categories of these variables.

Non-differential error in the make up of the study population (sampling variability) will result in reduced precision of the estimates. Non-differential error in the information, representing measurement inaccuracies, is expected to result in dilution of the estimated exposure-disease associations (bias towards the null). Differential error, on the contrary, may strengthen, weaken or even reverse the measure of association, depending on the distribution of the error over exposure and outcome. Differential error therefore has much more serious consequences and carries a greater threat to validity than non-differential error. In case of differential recruitment, non-participation or loss to follow-up, the validity of the estimated association is affected only, if the error is associated to both exposure and outcome, independently of each other (2).

Confounding is a potential source of bias in virtually every observational study. This type of bias may be adjusted in the data analysis, provided that adequate information on the confounding variables has been collected on all study subjects. Error in the information on confounders may compromize validity as well. Contrary to what was stated for exposure and outcome, both differential and non-differential error in the confounding variables may cause bias towards the null as well as away from the null.

In the following, the validity of the estimation of the exposure-disease associations as estimated in the study is discussed (internal validity). Bias resulting from the selection of the study population is addressed in connection with the recruitment of the original population as well as the case-cohort sampling. Bias as a consequence of error in the collected information is considered for the electrocardiographic and for the cause of death data. Next, possible consequences of the choice of the measure of association are discussed, and finally the issue of control of confounding is addressed in the context of the present study.

Selection of the study population

The population investigated in the present study, consisted of middle-aged civil servants of the city of Amsterdam in active duty and their spouses. Therefore, the population should be regarded as an active and healthy selection of the general middle-aged population of Amsterdam. Several mechanisms may be responsible for this selection. First of all the general health examination that provided the baseline data for the study, was explicitly announced as being intended for healthy individuals. Secondly, there may be a relation to employment, the health status of working populations usually being better than that of the general population (the so-called "healthy worker effect"). This selection process probably was less effective some decades ago than it would have been nowadays, since there was no major unemployment and considerably less health-related inability to work. Finally, participants apparently all were healthy enough to survive the second world war.

An indication of the relative health of the cohort was obtained in a comparison of its 28-year all-cause, cardiovascular and coronary heart disease mortality with the mortality expected from the rates of the total middle-aged population of the Netherlands throughout the follow-up period (Appendix 2). Among both men and women, mortality in the study population was lower than expected in all three mortality categories. The standardized mortality ratios for men and women were 0.79 and 0.64, respectively for all-cause, 0.80 and 0.55 for cardiovascular and 0.82 and 0.59 for coronary heart disease mortality, demonstrating a considerable health-related selection.

In spite of the invitation, the population consisted of an unknown number of men and women with previously diagnosed chronic disease, like carcinoma, diabetes and colitis. Not previously detected abnormalities that called for immediate therapy were present in 41 men and 74 women. Unfortunately, there was no information on the invited participants who did not respond to the invitation. The loss to follow-up of about 1% was too small to represent a

serious validity problem.

In conclusion, on average, the original cohort was a healthy selection of the general population, but did not consist solely of non-diseased individuals. Lack of statistical representativeness is no major threat for the validity of an etiologic epidemiological study, like the one reported in this thesis. Etiologic inference, however, demands biological rather than statistical representativeness. For biological representativeness, we would have preferred a population of healthy individuals. This might have been achieved by excluding all persons with known diseases, particularly if these might cause disturbed autonomic function, like diabetes. Information on such diagnosis, however, was not available on an individual basis. We did confirm, however, the observed associations in a subpopulation of persons without signs of heart disease as defined by interview and electrocardiogram.

The case-cohort sampling design

The case-cohort sampling scheme was applied in the present study, because hand coding and measurement of all electrocardiograms was not feasible. The case-cohort design implies studying all deaths, and a random sample of the cohort (3). The price paid for the cost efficiency of this approach, is some loss of precision because of additional sampling variability. If the sample is truly random, however, the case-cohort sampling does not result in additional selection bias. This was confirmed by the empirical comparisons of the case-cohort design with the full-cohort design in chapter 3. The new methods used for the multivariate analysis in the present study, appeared to be valid according to statistical theory (4) as well as in practical application.

Summarizing, the application of the case-cohort design will have resulted in a small loss of precision of the estimated associations. As far as can be judged, the validity of the estimates has not been compromized by the case-cohort sampling.

Exposure: the electrocardiogram

The inevitable errors in the measurement and coding of the electrocardiograms will have resulted in misclassification of the exposure variables of interest. However, since electrocardiograms were distributed randomly between coders, who were blinded for other baseline characteristics and survival, this misclassification may be assumed to be non-differential with respect to the endpoint. The experience of the present study illustrates that coding of electrocardiograms had better be performed by technicians, as Rose (5) suggested already in 1965.

Medical doctors may have preconceived opinions about the relevance of certain minor abnormalities, which interfere with coding.

There are other potential sources of non-differential misclassification of exposure in the present study: First there is the possibility that the studied electrocardiographic characteristics may not be perfect indicators of autonomic balance. Second, these characteristics as observed in the baseline electrocardiogram, may not have been representative for the full follow-up period. This may partly reflect the fact that the autonomic balance, even in the resting state, is not constant, but may have changed in the course of time. In the absence of conditions like myocardial infarction, electrolyte disturbances, use of certain drugs or diabetes, such changes presumably are related to changes in life style, e.g. physical activity (6,7), smoking (8) and stress (9,10). In the present study, however, changes in life style are expected to have had only minor effects on the classification of individuals relative to each other, since participants were civil servants of middle age and spouses, having rather settled life habits.

The only conceivable way differential misclassification might have occurred and be responsible for the obervations, would be errors in the measurement and coding, related to major electrocardiographic abnormalities like pathological Q waves, which are themselves associated with mortality. In that case, however, the associations would have disappeared when investigated in the subpopulation without signs of heart disease.

In conclusion, any misclassification of exposure in the present study, probably has been non-differential in character. As argued previously, non-differential misclassification is not a likely explanation for the observed associations, since on the contrary, it would have concealed a really existing association. Whatever the limitations, electrocardiographic data recorded as early as 1953 of a sizeable population of apparently healthy men as well as women, offered a unique opportunity to evaluate the long- term predictive value of the characteristics of interest.

Endpoint: the cause of death

Since autonomic imbalance is known to affect survival of cardiac patients, cause-specific mortality in 28 years of follow-up, registered by the Central Bureau of Statistics (C.B.S.), was chosen as the endpoint of the present investigation. As stated in chapter 2, there may be inaccuracies in the causes of death, resulting from errors on several levels. To improve the accuracy of the endpoints and their constancy over the total follow-up period, we decided not to investigate detailed causes of death, like acute myocardial infarction, but wider

categories: death due to cardiovascular disease and due to coronary heart disease. By doing this and by having the C.B.S. recode the causes of death in the early period of follow up, using the original certification forms, we expect to have achieved sufficiently uniform and accurate endpoints in the present study.

Misclassification of these endpoints because of inaccuracies is presumed to be non-differential with respect to exposure, since diagnosis, certification and coding of the causes of death took place in the past, when the study had not yet been planned. The only conceivable opportunity for differential misclassification is the use of electrocardiograms by the certifying physicians in the assessment of the cause of death. Minor electrocardiographic abnormalities, as investigated in this study, however, probably will not have contributed to their diagnosis. Therefore bias because of non-differential misclassification of the study endpoints will have diluted the observed associations.

The measure of association

The measure of association that would have been best suited for the present study, is the rate ratio (incidence density ratio), since it accounts for differences in person-time at risk (1). This is particularly important, since the follow up covered a long period of 28 years. The main concern in this respect is a difference in competing mortality from other causes, between exposure categories. Such exposure-related competitive mortality might bias the risk ratios for cardiovascular and coronary heart disease mortality.

However, since the new pseudo likelihood methods for estimation of the rate ratio were not available until much of the data analysis was completed, the analysis concentrated on the risk ratio (cumulative incidence ratio). Where possible, the estimated risk ratios were verified by calculating crude and age-adjusted rate ratios. Most of the rate ratios were somewhat higher than the corresponding risk ratios, indicating no important effect of exposure-related competing mortality. Besides, even in the absence of exposure-related competing mortality, the rate ratio is expected to exceed the risk ratio, provided it is greater than one. This is because a risk ratio greater than one implies that exposed have cumulated less person-time than unexposed, since a greater number of them died before the end of the follow up. This results in greater relative disparity between the rates of exposed and non-exposed than between their risks.

Confounding

To be a confounder of the association between an electrocardiographic characteristic and mortality, a variable itself must be an independent risk factor for mortality, and must be associated with this characteristic (1). Bearing this in mind, age and the established cardiovascular risk factors diastolic blood pressure, smoking, total serum cholesterol and body-mass index were considered as potential confounders. Diastolic blood pressure was preferred over systolic blood pressure, because it was assumed that correction for systolic blood pressure might lead to overadjustment, since systolic blood pressure may be more strongly influenced by autonomic balance. In the analysis, age and diastolic blood pressure appeared to be the main confounders, while the other risk factors contributed very little.

The adjustment of confounding may not have been fully adequate, since tertile division may be too crude. Finer classification was not feasible, however, because of small numbers of exposed. The advantage of categorisation, however, is that the categories of confounders can be brought in the multivariate model as indicator variables, making no presumptions about the shape of the associations over different levels, and thus minimizing the risk of obtaining biased results because of violation of the model assumptions. Furthermore, like pointed out for the exposure variables, a single measurement of a confounder at baseline may be insufficient to characterize its level during the full follow-up period. The effect this may have had on the validity of the estimated associations is unknown.

Regardless of the small impact of most cardiovascular risk factors in the present study, the rationale of adjustment for the cardiovascular risk factors may be questioned, since some of them may be part of a causal pathway relating autonomic balance to mortality. The adjusted associations, however do give an idea of the association of autonomic balance and mortality independent of the established risk factors.

10.3 Inference

Autonomic balance variation in the study population presumably partly reflects endogenous differences in autonomic nervous system function, partly acquired differences, which in healthy individuals are possibly related to life style. The well-known Idiopathic Long QT-Syndrome (13), however, is not a likely explanation of these differences, since it is extremely rare and patients suffering from this disease would seldomly reach middle age.

Although in many studies looking into cardiovascular disease etiology, disease incidence would be the preferred endpoint, we only had information on mortality. In the present study, however, mortality may be a more relevant outcome, since the most important consequence of autonomic imbalance reported thus far, is an effect on the survival of cardiac patients (14,15). Postulated biological mechanisms explaining this, primarily implicate sudden death because of ventricular arrhythmia. In our study, using the officially registered causes of death, we did not have the opportunity to discriminate between sudden and non-sudden causes of death. Nevertheless, in a major proportion of the coronary heart disease deaths ventricular arrhythmia is expected to have played an important role. First, therefore, possible biological mechanisms relating autonomic imbalance to ventricular arrhythmia in patients with myocardial damage, will be mentioned. Next an attempt will be made to explain the findings of the present study in non-diseased individuals, keeping these biological mechanisms in mind. Finally, the results of the methodological digression concerning the case-cohort design will be addressed.

Biological mechanism

As was described in chapter 1, two types of autonomic imbalance of the heart are often distinguished: sympathetic/parasympathetic imbalance and left/right sympathetic imbalance. In cardiac patients an association between autonomic imbalance and survival has been quite well established (14,15). A general model explaining the role of the autonomic nervous system among other factors, in the occurrence of sudden death in these patients, is the following: In an environment of myocardial damage (the "substrate"), autonomic activity acts as a "modulator". Imbalance of this activity may induce a high risk state, that facilitates the occurrence of ventricular fibrillation and sudden death in the presence of an ectopic beat (the "trigger") (16). Although a role of autonomic imbalance in the occurrence of sudden death seems to be undisputed, the postulated electrophysiological mechanisms, responsible for this modulating role are still rather speculative. Next these mechanisms will be addressed.

The electrophysiological mechanism relating sympathetic/parasympathetic imbalance to sudden death may be through influence on phase IV of the action potential. Sympathetic activity accelerates the slow depolarization occurring in this phase and consequently induces a greater tendency for ectopic activity (17). Possible indicators of this imbalance are decreased baroreflex sensitivity, decreased heart rate variability and high resting heart rate.

Prolonged QT-interval is regarded by some investigators as an indicator of left/right

sympathetic imbalance. The phenomenon believed to underly QT prolongation is dispersed and prolonged repolarization of the ventricle, caused by imbalanced distribution of sympathetic activity. This may result in ventricular arrhythmia in three ways: 1. It may facilitate reentry, which means that an impulse reenters an area already depolarized before by that same impulse (18,19). 2. It may stimulate triggered activity, initiated by oscillations of electrical baseline shortly after repolarization, called afterdepolarizations (20). 3. Prolonged repolarization of the ventricle extends the vulnerable period of the ventricle for ectopic activity and may this way increase the risk of occurrence of ventricular fibrillation.

Consequently, through different electrophysiological mechanisms, both types of imbalance may lower ventricular fibrillation threshold particularly in the presence of damaged myocardial tissue. Furthermore, in cases of acute myocardial infarction sympathetic hyperactivity is obviously present. If this goes unopposed by adequate parasympathetic counteractivity (the first type of imbalance), it may increase oxygen requirements of the myocardial tissue, and that way worsen prognosis.

The results observed

In this apparently healthy population, associations were studied between minor electrocardiographic abnormalities and cardiovascular and coronary heart disease mortality. Heart rate and PQ-interval length in the present study were regarded as indicators of sympathetic/parasympathetic balance, while QT-interval length was assumed to represent left/right sympathetic balance. ST-segment level and T-wave amplitude may be influenced by either type of balance. The associations observed in the study population between QT-interval length, ST-segment level and T-wave amplitude, and all-cause, cardiovascular and coronary heart disease mortality, probably are produced by an increased risk of death due to ventricular arrhythmia, through the biological mechanisms delineated above for cardiac patients. Myocardial damage ("substrate"), as a consequence of coronary heart disease, though not yet present at baseline, evidently developed in the course of the follow-up in numerous participants. Moreover, simultaneous occurrence of autonomic imbalance and coronary heart disease is enhanced by the fact that, as mentioned previously, autonomic imbalance probably is associated with a stressfull sedentary lifestyle and in connection with this, with an unfavorable cardiovascular risk profile as well (6-10). The reported associations with mortality were independent of age and established cardiovascular risk factors. Therefore they are apparently not the result of an unfavorable cardiovascular risk profile.

There may be other explanations for the observed results. Prevalent heart disease at baseline might induce autonomic imbalance and might thus result in a spurious association with cardiovascular and coronary heart disease death. This is, however, not a likely explanation for the observed results, since these were similar for the subpopulation without signs of heart disease at baseline. A minor role of subclinical heart disease at baseline, however, can not be completely ruled out.

Furthermore, autonomic imbalance might be an indicator of poor health in general. Since poor overall health may be expected to influence survival, this would result in an association between autonomic imbalance and all-cause mortality. May this be an explanation for the association with all-cause mortality observed for heart rate, it is not, however, for associations between the other parameters and cardiovascular and coronary heart disease mortality.

Since no association was observed between PQ interval and mortality, PQ probably is no valid measure of autonomic balance. This may be due to the fact that, at present, there is no adequate method of heart rate correction for this interval. Furthermore, the autonomic modulation of impulse conduction in the atrioventricular node may not be manifest in the PQ interval, which consists of atrial and His bundle components as well.

Most of the results for women were weaker than for men, except the association between T-wave inversion and flat T-wave and mortality. The explanation for these sex differences is not clear. They may have an unknown biologic background, they may indicate greater misclassification of cardiovascular mortality in women, or they may simply be a consequence of the relatively small number of cardiovascular and coronary heart disease deaths among women in the cohort.

The weaker associations for the electrocardiographic parameters after exercise are thought to be due to the light nature and short duration of the exercise of the Master Test and to the time delay before the recording was made. As expected the predictive value of the baseline characteristics decreaes with increasing duration of follow up.

10.4 Implications

In this final paragraph, the implications of the reported findings and applied methods will be addressed. Where possible, partly speculative conclusions will be drawn and recommendations given with regard to both health care and health research.

Health care

The primary aim of the study was to shed some more light on the etiology of cardiovascular and coronary heart disease mortality and on the prognostic value of a simple non-invasive procedure for diagnosis and screening. The results of course will have to be verified in other populations, but nevertheless may have implications for coronary heart disease prevention and therapy.

Usually neglected characteristics of the resting electrocardiogram, like QT prolongation, and minor ST and T abnormalities appear to be prognostic of coronary heart disease mortality in this population of mainly healthy individuals. These characteristics, nowadays routinely obtainable with computerized recording techniques, indicate imbalance of the autonomic influences on the heart. This imbalance probably explains the observed associations with mortality. A limitation of the study may seem the fact that the results are based on only a single electrocardiographic recording. This is, however, in agreement with the way electrocardiography is used in practice for preventive purposes in populations of apparently healthy individuals. The observed prognostic value may advocate further use of electrocardiography not only for secondary prevention (screening of undetected coronary heart disease), but for primary prevention (screening for coronary heart disease risk) as well. In the latter application it may provide a useful addition to screening for the established cardiovascular risk factors.

There is some evidence of a role of physical activity as a determinant of autonomic balance (6-10). This is in support of existing evidence for the benefit of regular physical exercise for the entire healthy population. Regular exercise may shift the distribution of autonomic balance in a favorable direction. A syndrome recognized some decades ago, called 'vasoregulatory asthenia', probably is an extreme manifestation of what we called sympathetic/parasympathetic imbalance (11). This syndrome was reported to react favorably on physical training (12). The presence of autonomic imbalance in combination with an unfavorable cardiovascular risk profile, probably indicates even more adverse prognosis, and may justify more intensive preventive efforts.

Although a range of potent drugs now are available for influencing autonomic balance, by selectively blocking or stimulating parts of the autonomic nervous system, specific drug therapy of individuals with signs of autonomic imbalance is not recommended on the basis of the observed results. This may be different in the presence of other signs or symptoms e.g.

hypertension. If autonomic imbalance occurs in combination with myocardial damage, i.e. after myocardial infarction, the results of the present study might represent additional ground for prescription of drug therapy, in order to improve survival.

Research procedures

The availability of the database of the original health examination and the existence of a national register of causes of death provided the opportunity to carry out the present historical cohort study. This implied acceptance of certain limitations attached to population and data, which will briefly be discussed with respect to their implications for future health research. For convenience of fellow epidemiologists, the experience in the follow-up of the causes of death will be more extensively addressed.

As mentioned previously, the population of the present study was not exactly defined with respect to its health status. Future studies, whether carried out in concurrent or in historical design, should preferably confine to initially healthy individuals. Since a 30-year follow up is hardly feasible anymore, prospective studies will need to be rather large-scale in order to yield enough cases of the required endpoint over a shorter time period.

A major limitation of the use of electrocardiograms in the present study was the need for hand processing. Digital recording and processing as currently applied, will facilitate prospective as well as historical studies in the future. In the meantime methods for analogue-digital conversion of electrocardiograms, for instance by techniques used in cartography, might open new prospects. Addition of an uninterrupted recording of longer duration will increase the value of such electrocardiographic data. Sequential recordings throughout a long follow up may allow more accurate classification of individuals according to their autonomic balance.

The case-cohort approach, used to limit the number of electrocardiograms to be processed, appeared to be very useful in the present study. If the validity of the developed multivariate methods withstands criticism, it may be the first choice cost-efficient alternative for full-cohort design. Since the pseudo likelihood risk ratio method obviously can be used in full-cohort design as well, the present study extended epidemiologic methods with an easily available multivariate relative risk model.

The national register held by the Central Bureau of Statistics (C.B.S.), was the only source available for the causes of death. The consent of the Chief Inspector of Public Health (Geneeskundig Hoofdinspecteur van de Voksgezondheid) of the Netherlands, required to use the causes of death of the study population for research, was obtained promptly in 1985. In the past this was sufficient to authorize the C.B.S. to provide the requested causes of death. At present, however, new regulations with respect to confidentiality and patients' rights are being prepared: the Registration of Persons Act (Wet Persoonsregistraties) and the Medical Treatment Act (Wet op de Geneeskundige Behandelingsovereenkomst). In the absence of a written consent of the individual and his physician, in the Netherlands it is now becoming virtually impossible to obtain individual cause of death information for epidemiologic research, even on an anonymous basis. This is in contrast with the situation in some other countries, e.g the United Kingdom. In these countries, regulations with respect to extraction of information from medical records are less prohibitive (21). Recently in the Netherlands, this situation has aroused considerable debate between epidemiologists, holders of data banks and lawyers (22-25).

The causes of death eventually came available, however, unfortunately not without considerable delay because of the mentioned confidentiality problems. Since special provisions permitting research under certain conditions, are lacking until now in the Netherlands, the C.B.S. required an official agreement with the present investigator, his university and the investigator of the original study. The realization of this agreement and completion of the data linkage for the present study ultimately took four years!

According to this agreement, the part of the data analysis for this thesis, requiring knowledge of the individual causes of death, was performed by the investigator in the offices of the C.B.S..

From the experience of the present investigation it must be concluded, that in principle epidemiologic research using the causes of death from the Dutch register held by the C.B.S., is very well possible where coverage and data quality are concerned, and that such research can produce results that have public health importance. In practice, however, the current difficulties in obtaining the information and subsequently in data analysis, are such, that epidemiologists should take them into account, when designing their studies. However justified regulations with respect to confidentiality may be, the current practice in the Netherlands severely frustrates health research. Unless legal exceptions will be created for research, epidemiologic studies like the present one will hardly be feasible in the future.

In the meantime, in case of a concurrent study, it is advisable to do the utmost to obtain individual written permission of participants and their physicians for using the future cause of death for epidemiologic research. In a retrospective study or a historical cohort study, collection of data on the cause of death from medical records of treating physicians, if possible, may be preferable.

Future research

The observations of the present study, in particular those for QT-interval and ST-segment will of course have to be confirmed in other healthy populations. On the basis of the experience and results of the present study, some suggestions regarding future observational as well as experimental studies come to mind.

As current concepts of the relation between autonomic balance and electrocardiographic characteristics are rather speculative, knowledge might be augmented by animal experiments and electrophysiological studies of patients. This may improve the basis for interpretation of some of the reported observations, e.g. PQ interval, and may provide new parameters of autonomic function, that can be used in observational studies. If any value is to be attached to the reduced strength of the associations after light exercise, this might indicate the possibility that exercise diminishes autonomic imbalance. This might also be an area for further investigation.

An additional parameter, certainly valuable for observational research, is heart rate variability, an alleged indicator of sympathetic/parasympathetic balance. Furthermore, simple provocation tests, like the Valsalva manoeuvre or a change from recumbent to standing position may prove to be more sensitive measures of autonomic reactivity. Particularly the role of physical activity and physical fitness and their interplay with cardiovascular risk factors deserves further attention, since physical activity and fitness may be key determinants of autonomic balance. It might be worthwile to extend future research to cardiovascular morbidity, in order to investigate the question, whether autonomic imbalance in addition to being prognostic of survival, might be an independent risk factor for coronary heart disease occurrence as well.

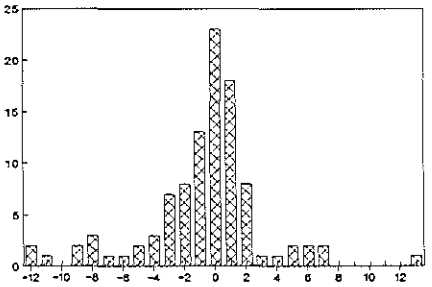
Finally the effect of changes in physical activity and risk factors on autonomic balance may be investigated in intervention studies. This may be particularly important with respect to preventive public health strategies.

REFERENCES

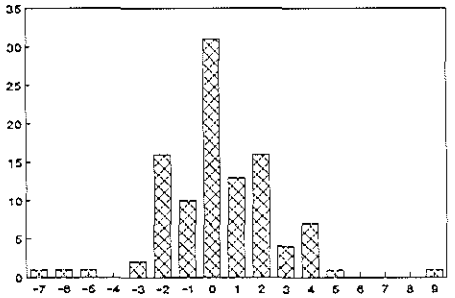
1. Rothman KJ: Modern Epidemiology. Boston/Totonto: Little, Brown and Company, 1986.
2. Hennekens CH, Buring JE: Epidemiology in medicine. Boston/Toronto: Little, Brown and Company, 1987.
3. Miettinen OS: Theoretical epidemiology. Principles of occurrence research in medicine. New York: John Wiley and Sons, 1985.
4. Le Cessie S, Van Houwelingen JC, Dekker JM, Schouten EG: Maximum likelihood and pseudo likelihood estimates in the case-base design. Submitted.
5. Rose G: The coding of survey electrocardiograms by technicians. Br Heart J 1965;27:595-599.
6. Slattery ML, Jacobs DL: Physical fitness and cardiovascular disease mortality: the US Railroad Study. Am J Epidemiol 1988;27:571-580.
7. Billman GE, Schwartz PJ, Stone HL: The effects of daily exercise on susceptibility to sudden cardiac death. Circulation 1984;69:1182-1189.
8. Hayano J, Yamada M, Sakakibara Y, Fujinami T, Yokoyama K, Watanabe Y, Takata K: Short and long term effects of cigarette smoking on heart rate variability. Am J Cardiol 1990;65:84-88.
9. Blumenthal JA, Fredrikson M, Kuhn CM, Ulmer M, Walsh Riddle M, Appelbaum M: Aerobic exercise reduces levels of cardiovascular and sympatho-adrenal responses to mental stress in subjects without prior evidence of myocardial ischaemia. Am J Cardiol 1990;65:93-98.
10. Leon AS, Jacobs DR, DeBacker G, Taylor HL: Relationship of physical characteristics and life habits to treadmill exercise capacity. Am J Epidemiol 1981;113:653-660.
11. Holmgren A, Jonsson B, Levander M, Linderholm H, Sjöstrand T, Ström G: Low physical working capacity in suspected heart cases due to inadequate adjustment of blood flow (vasoregulatory asthenia). Acta Med Scand 1957;158:413-436.
12. Holmgren A, Jonnson B, Levander-Lindgren M, Lunderholm H, Mossfeldt F, Sjöstrand T, Ström G: Physical training of patients with vasoregulatory asthenia. Nord Med 1957;58:1710-1714.
13. Schwartz PJ: The idiopathic long QT-syndrome. Ann Int Med 1983;99:561-562.

14. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256-62.
15. Schwartz PJ, Wolf S: QT-interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57: 1074-1077.
16. Myerburg RJ, Kessler KM, Bassett AL, Castellanos A: A biological approach to sudden cardiac death: structure, function and cause. Am J Cardiol 1989;63:1512-1516.
17. Verrier RL: Neural factors and ventricular electrical instability. in: Wellens HJJ, Kulbertus HE eds. Sudden death. The Hague, M Nijhof 1980.
18. Kuo CS, Reddy CP, Munakata K, Surawicz B: Arrhythmias dependent predominantly on dispersion of repolarization. in: Zipes DP, Jalife J, eds. Cardiac electrophysiology and arrhythmias. London, Grune and Stratton inc. 1985.
19. Janse MJ: Reentry rhythms. In: Fozzard HA, Haber E, jennings RB, Katz AM, Morgan HE eds. The heart and cardiovascular system, vol 2. New York , Raven Press, 1986.
20. Wit AL, Rosen MR: Afterdepolarizations and triggered activity. In: Fozzard HA, Haber E, jennings RB, Katz AM, Morgan HE eds. The heart and cardiovascular system, vol 2. New York , Raven Press, 1986.
21. Medical Research Council: Responsibility in the use of personal medical information for research: principles and guide to practice. Br Med J 1985;290:1120-1124.
22. Vandenbroucke JP: Het Centraal Bureau voor de Statistiek: begraafplaats van onze doodsoorzaken. Ned Tijdschr Geneesk 1989;133:2112-2114.
23. Bonte JTP: Het Centraal Bureau voor de Statistiek, broedplaats voor doodsoorzakenstatistiek. Ned Tijdschr Geneesk 1990;134:134-135.
24. Vandenbroucke JP: Medische ethiek en gezondheidsrecht; hinderpalen voor de verdere toename van kennis in de geneeskunde? Ned Tijdschr Geneesk 1990;134:5-6.
25. Leenen HJJ: Medische ethiek en gezondheidsrecht; hinderpalen voor de verdere toename van kennis in de geneeskunde? Ned Tijdschr Geneesk 1990;134:926.

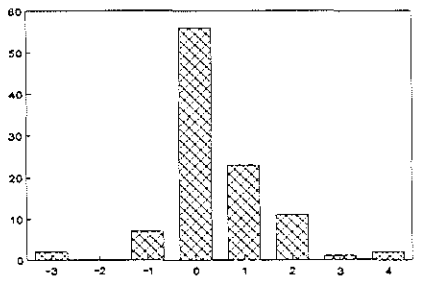
APPENDIX 1



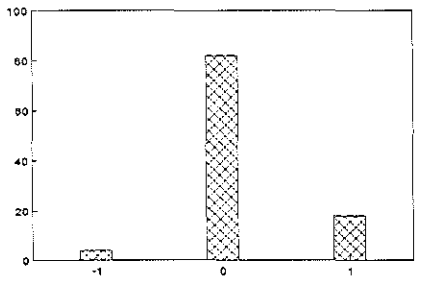
RR (ms)



QT (ms)



ST (0.025 mV)



T (0.1 mV)

Distribution of differences between duplicate measurements of RR- and QT-interval length, ST-segment level and T-wave amplitude.

APPENDIX 2

Calculation of observed and expected mortality

The cohort of 3,091 apparently healthy Amsterdam civil servants that provided the baseline data for the present study, was assumed to be a healthy selection of the general population. Consequently in this cohort a lower mortality might be expected than in the general population of the Netherlands. In order to verify this, the number of deaths observed in the population was compared with the number expected on the basis of the death rates for the Netherlands.

Observed

The person-time experience of the cohort was divided in five-year age and calender periods for the period 1953 to 1977 and in five-year age one-year calender periods for the last four years (1978 to 1981). This was carried out for men and women separately, by means of a Fortran computer program (1). Deaths from all causes, cardiovascular and coronary heart disease observed in these age-period categories were counted.

Expected

The mortality expected in the cohort was calculated using the person-years in the mentioned age- and calender-time categories and applying them to the corresponding incidence densities of the median year of each of the five-year periods, as published by the Dutch Central Bureau of Statistics (C.B.S.) in different publications (2,3). For the last four years the incidence reported for the inddividual years were used (4-7).

REFERENCES

1. Coleman M, Douglas A, Hermon C, Peto J: Cohort study analysis with a Fortran computer program. Int J Epidemiol 1986;15:134-137.
2. Sterfte naar belangrijke doodsoorzaken 1950-1977. 's-Gravenhage: Staatsuitgeverij, 1980.
3. Compendium Gezondheidsstatistiek Nederland 1986. 's-Gravenhage: Staatsuitgeverij, 1986.

4. Overledenen naar doodsoorzaak, leeftijd en geslacht - Serie A1 - jaar 1978. 's-Gravenhage: Staatsuitgeverij, 1979.
5. Overledenen naar doodsoorzaak, leeftijd en geslacht - Serie A1 - jaar 1979. 's-Gravenhage: Staatsuitgeverij, 1980.
6. Overledenen naar doodsoorzaak, leeftijd en geslacht - Serie A1 - jaar 1980. 's-Gravenhage: Staatsuitgeverij, 1981.
7. Overledenen naar doodsoorzaak, leeftijd en geslacht - Serie A1 - jaar 1981. 's-Gravenhage: Staatsuitgeverij, 1982.

Appendix 2

Table 1. Observed and expected all-cause, cardiovascular (CVD) and coronary heart disease (CHD) deaths among 1,583 men from 1953 to 1981.

period	Person-years	All-cause		CVD deaths		CHD deaths	
		Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
1953-1957	6867.8	57	61.1	25	22.8	14	14.1
1958-1962	7305.4	111	130.0	56	53.9	35	30.6
1963-1967	6636.7	147	192.6	70	90.2	42	51.3
1968-1972	5759.6	207	259.3	100	127.4	66	71.4
1973-1977	4629.5	238	291.4	109	142.8	51	74.3
1978	778.7	45	58.6	24	28.0	16	14.5
1979	740.0	33	57.4	14	28.1	5	13.3
1980	707.0	39	58.7	17	27.9	6	13.0
1981	223.1	19	19.7	10	9.4	2	4.3
Totaal	33647.8	896	1128.8	425	530.5	237	286.8
SMR			0,79		0.80		0.82

Table 2. Observed and expected all-cause, cardiovascular (CVD) and coronary heart disease (CHD) deaths among 1,508 women from 1953 to 1981.

period	Person-years	All-cause		CVD deaths		CHD deaths	
		Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
1953-1957	7464.6	9	53.3	3	17.9	0	7.1
1958-1962	7360.2	34	77.8	9	31.2	3	11.0
1963-1967	7068.1	82	119.9	41	56.4	13	21.8
1968-1972	6587.9	109	180.8	41	92.9	18	38.3
1973-1977	5861.6	171	228.2	83	121.4	41	49.5
1978	1069.9	41	50.4	17	27.3	7	11.1
1979	1030.9	33	50.2	17	29.2	7	10.4
1980	1005.3	31	52.1	13	27.8	4	10.5
1981	973.7	11	54.5	5	29.1	2	10.9
Totaal	36918.6	521	815.8	229	419.9	95	161.3
SMR			0.64		0.55		0.59

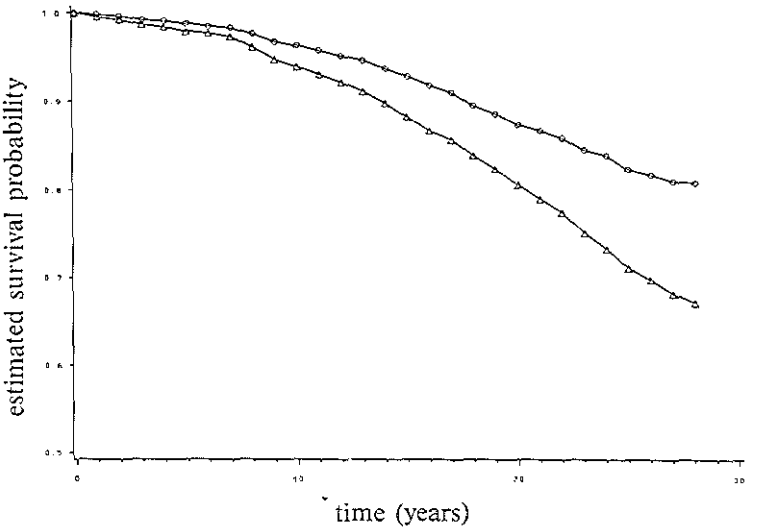


Figure 1. Kaplan-Meyer curve, men.
△—△ : cardiovascular mortality (CVD)
○—○ : coronary heart disease mortality (CHD)

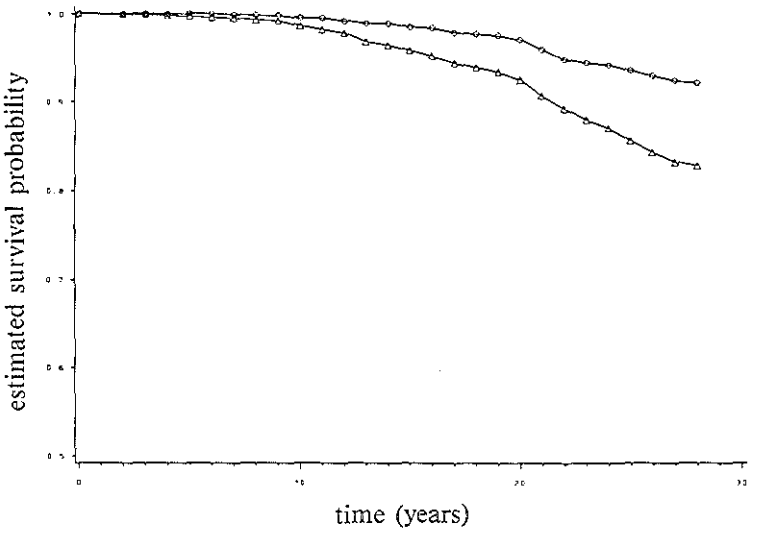


Figure 2. Kaplan-Meyer curve, women.
△—△ : cardiovascular mortality (CVD)
○—○ : coronary heart disease mortality (CHD)

SUMMARY

Although electrocardiography is primarily employed in patients, for diagnostic purposes, associations have been reported between electrocardiographic abnormalities classified according to the Minnesota Code, and cardiovascular morbidity and mortality risk, in populations of apparently healthy individuals. The electrocardiogram, however, may hold more information with respect to cardiovascular risk, than is extracted by the Minnesota Code. The study reported in this thesis[1], deals with such electrocardiographic characteristics, which in majority do not meet Minnesota criteria. These characteristics comprise heart rate, PQ-interval length, QT_c-interval length, ST-segment level and T-wave amplitude. They probably indicate the balance between the influences of different parts of the autonomic nervous system on the heart. Heart rate and PQ interval are taken as indicators of sympathetic/parasympathetic balance, QT_c-interval length as indicator of left/right sympathetic balance, and finally ST-segment level and T-wave amplitude may exhibit the influence of either type of balance. The aim of the present study was to determine the predictive value of these electrocardiographic parameters for all-cause, cardiovascular and coronary heart disease mortality, taking the established cardiovascular risk factors into account. An additional aim was to elaborate the case-cohort sampling design and its methodology, applied in the study, and to compare it with other cost-efficient designs (Chapter 1).

In 1953-1954 a general health examination, including electrocardiography at rest and after a light exercise test, was conducted among a cohort of 3,091 civil servants of the city of Amsterdam and spouses. Survival of this population was assessed in 1981 with the help of the Civil Servant Pension Fund (A.B.P.) and the causes of death of those who died until then, were established in 1989 through the registers of the Central Bureau of Statistics (C.B.S.). For the present study the categories all-cause, cardiovascular and coronary heart disease mortality were distinguished and studied for follow-up durations of 15 and 28 years.

Following the case-cohort sampling design, all deaths were taken into the study as cases, while the cohort was represented by a random sample. After exclusion of a small number of subjects for whom the information on survival or cause of death was missing, the final case-cohort study population consisted of 1,219 male and 848 female participants, 723 and 498 of them being members of the sample, respectively. Most of the investigated associations were also verified in a subpopulation from which individuals with signs of heart disease at baseline

[1] This study was supported by the Netherlands Heart Foundation (grant 86.060).

were excluded. The purpose of this was, to make sure that the associations were not a consequence of already existing heart disease. The electrocardiograms were measured and coded on a large number of items: the Minnesota Code, the Cardiac Infarction Injury Score (CIIS) and the mentioned potential electrocardiographic indicators of autonomic balance (**Chapter 2**).

The case-cohort approach, applied in order to limit processing of electrocardiograms, was one of several cost-efficient design options. Other options were the case-control design and the nested case-control design. The case-cohort design was preferred in the present study for several reasons: a) The design allows estimation of risk ratio (cumulative incidence ratio), rate ratio (incidence density ratio) and even of the underlying absolute incidence measures. b) The random sample of the cohort used as the reference in this design, provides a source of information about the cohort, that is not available in case-control studies. c) It does not require a rare disease assumption to estimate the risk ratio. (**Chapter 3**).

In order to obtain an impression of the performance of the case-cohort approach at different sampling fractions, it was compared with the nested case-control and full-cohort approach in estimation of the association between hypertension and cardiovascular mortality. Hypertension was taken as exposure, since it was available for the total cohort. To overcome the drawback of lacking multivariate case-cohort methods, we applied specially developed new pseudo-likelihood methods for calculation of risk ratio and rate ratio, using logistic regression and Poisson regression, respectively. As an example, the age-adjusted risk ratio (95% confidence interval) of hypertension in th efull cohort was 2.02 (1.50-2.70) and in case-cohort approach using a sample of 50% of the cohort 2.05 (1.47-2.86). The validity of the pseudo likelihood risk ratio estimate was evaluated further by repeated estimation, at fixed sampling fractions of 25 and 50 per cent of the cohort. The results indicate that the new multivariate case-cohort methods, are valid and may imply that in the future this sampling design will be the first-choice approach in situations where high costs preclude full-cohort analysis. An attractive implication of the risk ratio method is, that a multivariate model for estimation of the true risk ratio, is now at every investigators disposal. Except for analysis of case-cohort data, this model can be generalized for use in the full cohort, representing an advance in risk-ratio methods (**Chapter 4**).

In the following, the main results of the electrocardiographic characteristics in relation to mortality are presented, separately and in combination. Results observed for the electrocardiograms after a light exercise test as well as those observed in the subpopulation without signs of heart disease at baseline, were similar to the presented results. Since the new case-cohort rate ratio methods were not available, until part of the study was completed, the analysis concentrated on the risk ratio. The calculated risk ratios were, however, verified by crude and age-adjusted rate ratios.

Among men, multivariate relative risks of the three 15-year mortality categories for heart rate, ranged from 1.2 to 1.4 per 20 beats per minute increment, all but one significant. Among women they ranged from 1.3 to 1.5, only significant for all-cause mortality. The lack of specificity with regard to cause of death, suggests that the associations may be a consequence of an unfavorable overall health, rather than an effect of autonomic imbalance (**Chapter 5**).

Contrary to expectation, PQ-interval length appeared not to be prognostic of mortality, which probably indicates that PQ is not a valuable marker of autonomic balance. This might be due to mutually opposing effects of autonomic activity and heart rate on conduction in the AV node, or to the fact that PQ interval consists of atrial and His-bundle components as well. (**Chapter 6**).

Moderate and extensive QT_c prolongation significantly predict all-cause mortality during the first 15 years among men and women. In men, cardiovascular mortality (adjusted relative risk, RR: 1.6 and 1.8) and coronary heart disease mortality (RR: 1.8 and 2.1) mainly account for this association. The observed unfavorable prognosis of QT_c is interpreted as a consequence of autonomic imbalance (**Chapter 7**).

ST-segment and T-wave abnormalities, defined according to the Minnesota Code, showed the expected associations with mortality. Among the more subtle abnormalities in standard lead I, slight elevation of the ST segment in men was inversely associated with 15-year mortality (coronary heart disease mortality RR: 0.4, 95%-CI: 0.2-0.8), while in women an association existed for flat T-wave RR: 2.8, 95%-CI: 1.1-7.1). These associations might be due to differences in prevalence of non-detected coronary heart disease, but more likely to autonomic balance, since they persisted in the subpopulation. The remarkable protective effect

of slight ST elevation, representing a nicely curved upsloping ST segment is unprecedented. It provides the first empirical evidence for the intuitive feeling among doctors, that this kind of ST interval is 'well shaped' (**Chapter 8**).

Finally, QT_c interval, ST segment and T wave, the most important predictors so far, were considered jointly in relation to coronary heart disease mortality. In men moderate QT_c prolongation, slightly elevated ST, and T inversion kept the previously reported predictive value. Because of the small number of 15-year coronary deaths, among women only 28-year coronary mortality relative risk was investigated, yielding flat T wave as the only significant parameter.

ROC curves, evaluating the prognostic performance of the conbination indicate that they contribute independently to the prediction of 15-year coronary heart disease mortality in men. The small number of 15-year coronary deaths prohibited evaluation in women. The ROC curves for cardiovascular death in women, however, prognostic value over the 15-year period in women as well (**Chapter 9**).

In the General discussion the validity of the applied methods is discussed. Non-differential misclassification of exposure and outcome seems to be the chief validity problem. Although this may dilute the associations, it nevertheless does not provide reason to doubt their existence. Furthermore, in this chapter the possible biological mechanisms are addressed. The observations may fit into hypotheses relating autonomic imbalance to mortality in cardiac patients. Physical activity and physical fitness may play a role in these mechanisms as determinants of favorable autonomic balance. The applied exercise test (the Master two-step Test) probably was too light and the interval before the post exercise recording was made, too long to modify results at rest.

The observations may have implications pertaining to health care and health research. In health research, the possible role of physical activity needs to be further elucidated, because of potentially important preventive public health consequences. It might also be worthwile to study the question whether autonomic imbalance might be an independent risk factor for coronary heart disease incidence as well. If the findings are confirmed in other populations, the investigated, usually neglected electrocardiographic characteristics may improve cardiovascular risk factor screening (**Chapter 10**).

SAMENVATTING

Electrocardiografie wordt vooral toegepast bij de diagnostiek van hartlijden. Er worden in de literatuur echter tevens verbanden beschreven tussen electrocardiografische afwijkingen, gedefinieerd volgens de Minnesota Code, en het risico op cardiovasculaire morbiditeit en mortaliteit in populaties van, gezonde individuen. Het electrocardiogram bevat evenwel mogelijk meer informatie met betrekking tot het cardiovasculaire risico dan via de Minnesota Code wordt gebruikt. Het onderzoek waarvan in dit proefschrift verslag wordt gedaan[1], behandelt electrocardiografische kenmerken, die merendeels niet voldoen aan de criteria van de Minnesota Code niet halen. Tot deze kenmerken behoren de hartfrequentie, de lengte van het PQ interval, de lengte van het QT_c interval, het niveau van het ST segment en de amplitude van de T top. Dit zijn naar alle waarschijnlijkheid indicatoren van de balans tussen de effecten van verschillende delen van het autonome zenuwstelsel op het hart. Hartfrequentie en PQ interval worden beschouwd als indicatoren van de sympaticus/parasympaticus balans, QT_c interval geeft een indicatie over de balans tussen het linker en het rechter deel van het sympatische zenuwstelsel, terwijl ST-segment niveau en T-top amplitude mogelijk door beide vormen van autonome balans worden beïnvloed. Het doel van het onderzoek was het vaststellen van de voorspellende waarde van deze electrocardiografische parameters voor de totale sterfte, de cardiovasculaire sterfte en de sterfte aan coronaire hartziekten, daarbij rekening houdend met het effect van de bekende cardiovasculaire risicofactoren. Een tweede doel was stil te staan bij het in dit onderzoek toegepaste case-cohort onderzoekdesign en zijn methoden, en het te vergelijken met andere kosten-efficiënte onderzoekdesigns (**Hoofdstuk 1**).

In 1953-1954 werd een algemeen gezondheidsonderzoek uitgevoerd in een cohort van 3091 Amsterdamse gemeente-ambtenaren en echtgenoten. Dit onderzoek omvatte onder meer het vervaardigen van een electrocardiogram in rust en na een geringe lichamelijke inspanning. In 1981 werd de overlevingsstatus van deze populatie vastgesteld via het Algemeen Burgerlijk Pensioenfonds (A.B.P.) en in 1989 werd van de overledenen achterhaald wat de doodsoorzaak was geweest, via de doodsoorzakenregistratie van het Centraal Bureau voor de Statistiek (C.B.S.). Voor het onderzoek werden de doodsoorzaak-categorieën totale sterfte, cardiovasculaire sterfte en sterfte aan coronaire hartziekten bestudeerd over follow-up perioden van 15 en 28 jaar.

---

[1] Dit onderzoek werd financieel ondersteund door de Nederlandse Hartstichting (subsidienummer 86.060).

In overeenstemming met het gekozen case-cohort onderzoekdesign werden alle overledenen in het onderzoek betrokken, terwijl het cohort werd vertegenwoordigd door een willekeurig getrokken steekproef. Na uitsluiten van een klein aantal personen in verband met het ontbreken van informatie over de overlevingsstatus of de doodsoorzaak, bestond de onderzoekspopulatie uit 1219 mannelijke en 848 vrouwelijke deelnemers aan het oorspronkelijke gezondheidsonderzoek, van wie respectievelijk 723 en 498 tot de steekproef behoorden. In de electrocardiogrammen is codering verricht naar een groot aantal kenmerken afkomstig uit de Minnesota Code, de Cardiac Infarction Injury Score (CIIS), en zijn metingen verricht van de genoemde indicatoren van de autonome balans. Het merendeel van de onderzochte associaties werd tevens geverifieerd in een subgroep waaruit personen die initieel tekenen van hartaandoeningen hadden, waren verwijderd. Het doel hiervan was te onderzoeken of de waargenomen associaties mogelijk het gevolg waren van reeds aanwezige hartaandoeningen. (**Hoofdstuk 2**).

De case-cohort benadering is gekozen uit een aantal verschillende kosten-efficiënte mogelijkheden, waaronder het patiënt-controle en het 'geneste' patiënt-controle onderzoekdesign. Aan het case-cohort design is de voorkeur gegeven om een aantal redenen:

a) Dit design maakt schatten van het relatieve risico (cumulatieve incidentieratio), de rate ratio (incidentiedichtheid ratio) en zelfs van de hieraan ten grondslag liggende absolute incidentiematen mogelijk.
b) De steekproef uit het cohort die hierbij de referentiegroep vormt, levert een bron van informatie over het cohort zelf, die niet voorhanden is bij (genest) patiënt-controle onderzoek.
c) Er hoeft niet te worden voldaan aan de 'rare disease assumption' om het relatieve risico te schatten (**Hoofdstuk 3**).

Om een indruk te krijgen van de bruikbaarheid van de case-cohort benadering, is de associatie tussen hypertensie en cardiovasculaire sterfte nagegaan via deze benadering bij verschillende steekproeffracties en vergeleken met die, geschat via de geneste patiënt-controle en via de gebruikelijke cohort-benadering. Hypertensie werd gekozen als expositiefactor in plaats van een factor uit het electrocardiogram, aangezien hierover informatie beschikbaar was voor het volledige cohort. In verband met het tot nu toe ontbreken van multivariate schattingsmethoden voor de case-cohort benadering, zijn hiervoor speciaal ontwikkelde pseudolikelihood methoden voor het schatten van het relatieve risico en de rate ratio toegepast. Dit kan worden uitgevoerd met logistische regressie en Poisson regressie procedures. Een illustratie hiervan is

het voor leeftijd gecorrigeerde relatieve risico (95% BI) van hypertensie voor cardiovasculaire sterfte in het cohort van 2,02 (1,50-2,70), dat is geschat op 2,05 (1,47-2,86) via de case-cohort benadering met een steekproef uit het cohort van 50% en op 2,36 (1,56-3,56) via de geneste patiënt-controle benadering, bij een steekproef van 50% van de controles. De validiteit van de pseudolikelihood schatting van het relatieve risico is verder nagegaan via herhaalde steekproeftrekkingen bij vaste steekproeffracties van 50 en 25 %. De resultaten van de vergelijking lijken te bevestigen, dat deze nieuwe multivariate methoden valide zijn. Het case-cohort onderzoeksdesign verdient daarom wellicht in de toekomst de voorkeur in situaties waarin door hoge kosten analyseren van het volledige cohort onmogelijk is.
Een verrassende consequentie van de nieuwe methode voor het schatten van het relatieve risico is, dat hiermee een multivariaat model voor het schatten van het werkelijke relatieve risico beschikbaar is. Dit model kan behalve voor case-cohort analyse tevens worden gebruikt in het volledige cohort en betekent een uitbreiding van de epidemiologische methoden voor het schatten van het relatieve risico (**Hoofdstuk 4**).

Hierna worden de belangrijkste resultaten met betrekking tot de electrocardiografische kenmerken gepresenteerd, elk afzonderlijk en in combinatie. Aangezien de nieuwe case-cohort methoden voor het schatten van de rate ratio pas later beschikbaar kwamen, waren de analyses vooral gericht op het relatieve risico. De relatieve risico's zijn echter geverifieerd via wel te berekenen ruwe en voor leeftijd gecorrigeerde rate ratio's. De resultaten voor de electrocardiogrammen na lichte inspanning en die waargenomen in de subpopulatie zonder tekenen van hartaandoeningen waren vergelijkbaar met de gepresenteerde resultaten.

Bij de mannen varieerden de multivariate relatieve risico's voor totale, cardiovasculaire en coronaire sterfte tussen 1,2 en 1,4 per 20 slagen per minuut, op één na alle statistisch significant, bij de vrouwen tussen 1,3 en 1,5 en alleen significant voor totale mortaliteit. Het feit dat de associaties aspecifiek bleken te zijn met betrekking tot de doodsoorzaak betekent mogelijk, dat ze eerder een gevolg zijn van een minder optimale gezondheid in het algemeen, dan een effect van de autonome balans op het hart (**Hoofdstuk 5**).

Tegen de verwachting in bleek de lengte van het PQ interval niet prognostisch te zijn voor de sterfte. Dit betekent waarschijnlijk dat PQ geen geschikte indicator van de autonome balans is. Dit is misschien het gevolg van elkaar wederzijds tegenwerkende effecten van de

autonome activiteit en van de hartfrequentie op de geleidingssnelheid in de AV-knoop, of van het feit, dat het PQ interval niet alleen bestaat uit een nodale, maar bovendien uit een atriale en een His-bundel component (**Hoofdstuk 6**).

Matige en ernstige QT_c verlenging waren significant geassocieerd met totale sterfte in de eerste 15 jaar bij mannen en vrouwen. Bij mannen berust dit voornamelijk op de cardiovasculaire sterfte (relatief risico onafhankelijk van andere risicofactoren, RR: 1,6 en 1,8) en op de sterfte aan coronaire hartziekte (RR: 1,8 en 2,1). Deze ongunstige prognose wordt geïnterpreteerd als een gevolg van autonome dysbalans (**Hoofdstuk 7**).

ST-segment en T-golf afwijkingen, gedefinieerd volgens de Minnesota Code, lieten de verwachte associatie met de sterfte zien. Van de meer subtiele afwijkingen in standaard afleiding I was geringe elevatie van het ST-segment bij de mannen invers geassocieerd met de sterfte in de eerste 15 jaar (coronaire hartziekten RR: 0,4, 95% BI: 0,2-0,8), terwijl bij vrouwen een verhoogd risico is gevonden voor een vlakke T-golf (RR: 2,8, 95% BI: 1,1-7,1). Deze associaties zouden het gevolg kunnen zijn van verschillen in prevalentie van subklinische coronaire hartziekten, maar zijn waarschijnlijker afkomstig van verschillen in autonome balans, aangezien ze tevens werden aangetroffen in de subpopulatie. Het opmerkelijke beschermende effect van lichte ST-elevatie, wat in feite een sierlijk glooiend oplopend ST-segment voorstelt, is nog niet eerder beschreven. Het vormt de eerste empirische aanwijzing voor de intuïtieve overtuiging van veel artsen dat dit ST-segment behalve esthetisch fraai tevens prognostisch gunstig is (**Hoofdstuk 8**).

Tenslotte zijn de belangrijkste prognostische factoren gezamenlijk geëvalueerd in relatie tot de sterfte aan coronaire hartziekten. Bij de mannen bleef de predictieve waarde van matige QT-verlenging, geringe ST-elevatie en T-inversie behouden. Bij de vrouwen is in verband met de geringe sterfte aan coronaire hartziekten alleen de volledige 28-jaars periode onderzocht, waarbij uitsluitend een vlakke T-golf als significante parameter naar voren kwam.
De prognostische waarde van de combinatie van de genoemde factoren is geëvalueerd via ROC-curves. Deze ROC-curves lijken aan te geven dat de electrocardiografische factoren onafhankelijk bijdragen aan de voorspelling van de sterfte aan coronaire hartziekte in de eerste 15 jaar. Het geringe aantal overledenen maakte de beoordeling hiervan bij de vrouwen onmo-

gelijk. Bij hen wezen de curves voor cardiovasculaire sterfte echter wel in dezelfde richting (**Hoofdstuk 9**).

In de Algemene Discussie wordt ingegaan op de validiteit van de toegepaste methoden. Niet-differentiële misclassificatie in expositie en eindpunt wordt beschouwd als het belangrijkste potentiële validiteitsprobleem. Aangezien hiervan naar verwachting verzwakking van de werkelijk bestaande associaties het gevolg is, geeft dit geen aanleiding het bestaan van de aangetoonde associaties te betwisten. In dit hoofdstuk worden tevens de mogelijk aan deze associaties ten grondslag liggende biologische mechanismen behandeld. De waargenomen associaties zouden op dezelfde mechanismen kunnen berusten, waarmee de relatie tussen autonome dysbalans en sterfte bij hartpatiënten wordt verklaard. Fysieke activiteit en fysieke conditie spelen hierbij mogelijk een rol als determinanten van een gunstige autonome balans.
De gebruikte inspanningstest (de Master two-step Test) was waarschijnlijk te gering van intensiteit en de periode voordat de inspanningsregistratie is gemaakt te lang om de resultaten bij rust te kunnen modificeren.
De resultaten hebben niet alleen potentiële implicaties voor het gezondheidsonderzoek, maar ook voor de gezondheidszorg. De rol van fysieke activiteit dient verder te worden onderzocht, aangezien dit mogelijk belangrijke consequenties kan hebben voor preventie. Het zou interessant zijn eens te onderzoeken in hoeverre autonome dysbalans eveneens een onafhankelijke risicofactor is voor de incidentie van hart-en vaatziekten. Als de gerapporteerde bevindingen worden bevestigd in andere populaties, betekenen de onderzochte electrocardiografische kenmerken, waaraan doorgaans geen aandacht wordt besteed een nuttige aanvulling bij de screening op cardiovasculaire risicofactoren (**Hoofdstuk 10**).

CURRICULUM VITAE

Evert G. Schouten, geboren op 4 januari 1948 te Apeldoorn, doorliep vanaf 1960 de Christelijke Lycea in Zwolle en Apeldoorn en behaalde in 1966 het diploma gymnasium ß. De studie geneeskunde, begonnen in 1966 werd in 1973 afgesloten met het artsdiploma. Gedurende het jaar 1973 was hij werkzaam in het Gemeenteziekenhuis te Schiedam als algemeen artsassistent. In 1974 was hij als arts-assistent werkzaam in de praktijk van L.J. Coenders, huisarts te Tubbergen. De periode van 1975 tot 1977 oefende hij als zelfstandig gevestigd huisarts praktijk uit in Voorburg. Van 1977 tot 1983 werden de werkzaamheden als huisarts voortgezet in een associatie, opnieuw in Tubbergen. Het zelf toepassen van electrocardiografie in deze periode verklaart mede de keuze van het onderwerp van dit proefschrift. Van 1984 tot heden was hij verbonden aan de Vakgroep Gezondheidsleer (hoofd: Prof.Dr. K. Biersteker, thans: Vakgroep Humane Epidemiologie en Gezondheidsleer) van de Landbouwuniversiteit Wageningen, als universitair docent Epidemiologie.

De kennis van de Epidemiologie werd aangevuld met summer programs van de London School of Hygiene and Tropical Medicine in het Verenigd Koninkrijk en van het New England Epidemiology Institute in de Verenigde Staten. In 1988 werd hij geregistreerd als Sociaal Geneekundige, tak Algemene Gezondheidszorg, na de opleiding daartoe te hebben gevolgd bij de Stichting Sociale Gezondheidszorg te Utrecht.

Hij is gehuwd met Sibbella van der Vorm, docent verpleegkunde. Samen hebben zij vier kinderen: Jasper, Rutger, Minke en Taco.