Socioeconomic status and vascular diseases in the INVADE study

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Dedication

For the non-scientific part of my thesis, I particularly want to thank my, for the first time in writing, husband Michael for all the evenings listening to the progress of my work, his motivational skills, and his endless and affectionate support.

A special thanks goes to my parents. Since primary school, they provided me with the best and most suitable education available. I am truly honoured to be the first woman in our family to get a doctoral degree. They taught me to live my dreams and complete envisaged projects purposefully. As my father recently told me: “You got the thirst of knowledge from your mother and the necessary determination from myself.”

I guess, both of you provided me with a great combination of the two of them.

Acknowledgement

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Furthermore, I want to thank the INVADE e.V. board of management, Dr. med. Karl-Heinz Ander, Dr. med. Hans Gnahn, Dr. med. Othmar Gotzler, and Dr. med. Klaus Pürner for the chance to participate in this study. A warm thanks goes to Dr. med. Horst Bickel for his positive contribution to my work and to the study coordinators, Mrs. Astrid Biermeier and Mrs. Sigrid Stetter for the trial administration and support in the head quarter in Baldham, Germany.

Zusammenfassung

Theoretischer Hintergrund

Unter den zehn häufigsten Todesursachen in Deutschland nimmt Schlaganfall Platz sieben ein, Myokardinfarkt (MI) Rang zwei. Schlaganfall und MI verfügen über eine große Anzahl gemeinsamer Risikofaktoren, so geht fortgeschrittenes Alter beispielsweise mit einer signifikant erhöhten Inzidenzrate für Schlaganfall und MI einher. All das trägt zu einer grundlegenden sozialen und ökonomischen Belastung durch diese Krankheiten in einer überalterten Gesellschaft wie der deutschen bei. Überdies hat auch die individuelle sozioökonomische Position großen Einfluss auf die Inzidenz von Schlaganfall und MI.

Ziel der Studie

Die Zielsetzung dieser Studie war es, die Assoziation von ausgewählten sozioökonomischen Variablen, wie Bildungsniveau, Beschäftigung, Familienstand und Wohnform mit der Inzidenz von ischämischem Schlaganfall einschließlich transitorische ischämischer Attacke (TIA) sowie MI in der INVADE Kohorte (Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg), nach dem Adjustieren von etablierten Risikofaktoren, zu untersuchen.
Diese Ergebnisse ermöglichen einen gezielten, auf die gesundheitlichen Bedürfnisse der Menschen ausgerichteten Ansatz in der betreffenden Region.

Methodik

Die multivariate Cox Regression wurde angewandt, um Hazard ratios zu berechnen und die Assoziation von bekannten Risikofaktoren und selektierten sozioökonomischen Variablen auf die Inzidenz von Schlaganfall inklusive TIA und MI zu analysieren.
Alle multivariaten Analysen wurden nach Stand aktueller Literatur auf traditionelle Kovariablen kontrolliert. Diese umfassten Alter zu Studieneintritt, Geschlecht, Hypertonie, Diabetes

mellitus, Body-Mass-Index, körperliche Aktivität, Alkoholkonsum und Rauchen, um eine unabhängige Schätzung der Beziehung zwischen dem Status zu Baseline und inzidenten Ereignissen zu erreichen. Je ein Modell wurde für ischämischen Schlaganfall inklusive TIA, ischämischen Schlaganfall separat und MI berechnet.

Ergebnisse

3 908 Teilnehmer, darunter 1 600 (40,9%) Männer und 2 308 (59,1%) Frauen im Alter von 53,74 bis 101,85 Jahren (Standardabweichung (SD)= 7,8) wurden eingeschlossen. Während der Studienphase erlitten 230 (5,9%) Patienten einen ischämischen Schlaganfall inklusive TIA, 161 (4,1%) einen ischämischen Schlaganfall und 92 (2,4%) Teilnehmer einen MI.
Fortgeschrittenes Alter (B= 0,08, Standardfehler (SF)= 0,01, p= $4{,}76 \times 10^{-19}$) und Rauchen (B= 0,35, SF= 0,16, p= 0,03) waren mit einem erhöhten Risiko für ischämischen Schlaganfall inklusive TIA assoziiert. Körperliche Aktivität (B= -0,39, SF= 0,16, p= 0,02) hatte einen signifikanten positiven Effekt. Ein höherer Bildungsstatus wirkte signifikant protektiv (B= -0,85, SF= 0,42, p= 0,05). Ehe, Wohnsituation und Beschäftigung hatten keine schützende Auswirkung.
Höheres Alter (B= 0,09, SF= 0,01, p= $1{,}18 \times 10^{-17}$), gesteigertes LDL-Level (B= 0,005, SF= 0,002, p= 0,041) sowie Rauchen (B= 0,559, SF= 0,193, p= 0,004) erhöhten das Risiko für ischämischen Schlaganfall signifikant, wohingegen körperliche Betätigung (B= -0,39, SF= 0,19, p= 0,04) einen schützenden Effekt zeigte. Erneut war ein niedrigeres Bildungslevel mit einem höheren Risiko für ischämischen Schlaganfall assoziiert (B= -1,63, SF= 0,72, p= 0,03). Ehestatus, Zusammenleben und berufliche Tätigkeit zeigten keine Assoziation mit der Inzidenz von ischämischem Schlaganfall.
Fortgeschrittenes Alter (B= 0,09, SF= 0,01, p= $0{,}76 \times 10^{-9}$), Hypertonie (B= 0,45, SF= 0,26, p= 0,08) und Rauchen (B= 0,55, SF= 0,25, p= 0,03) waren signifikante Risikofaktoren für MI. Das weibliche Geschlecht (B= -0,946, SF= 0,297, p= 0,001) und hohe HDL-Konzentrationen waren signifikant protektiv (B= -0,025, SF= 0,009, p= 0,004). Bildungserfolg, Ehe, Zusammenleben und gegenwärtige sowie frühere Beschäftigung zeigten keine signifikante Assoziation mit dem Erleiden eines MI.

Interpretation

Die Entwicklung präventiver Strategien auf kommunaler Ebene hat sich als höchst effizient erwiesen. Ein Ausbau der gesundheitlichen Bildung, der sich auf die beschriebenen sozioökonomischen Diskrepanzen in der INVADE Kohorte fokussiert, könnte Inzidenzraten senken sowie die finanzielle und gesundheitliche Belastung durch vaskuläre Erkrankungen im Landkreis Ebersberg mildern.
Da Forschung eine fundamentale Rolle bezüglich der Reduzierung der Last durch Schlaganfall und MI einnimmt, können vereinte Bemühungen der Wissenschaft und Politik auf wohlgezielte Präventionsprogramme in niedrigeren sozioökonomischen Schichten zu einem Rückgang der Gesamtkosten im deutschen Gesundheitssystem beitragen.

Schlüsselwörter

INVADE Studie, ischämischer Schlaganfall, transitorische ischämische Attacke, Myokardinfarkt, sozioökonomischer Einfluss, gesundheitliche Bildung

Abstract

Theoretical background

Among the major ten causes of death in Germany, stroke ranks on place seven, while myocardial infarction (MI) is attributed to place two. Stroke and MI share a large number of risk factors. For instance, advanced age is highly associated with increased incidence rates of stroke and MI. This adds to the fundamental social and economic burden of disease in an aging society like Germany. Furthermore, the socioeconomic position of an individual has a great impact on the incidence of stroke and MI.

Aims of the study

Objective of this study was to investigate the association of selected socioeconomic variables, namely educational attainment, occupation, marital status, and cohousing, with the incidence of ischaemic stroke, ischaemic stroke including transient ischaemic attack (TIA), and MI in the INVADE cohort (Intervention project on cerebrovascular diseases and dementia in the district of Ebersberg), after having adjusted for well-established risk factors.
These findings enable a specific and medical need-orientated approach for the area in question.

Method

Multivariate Cox regression was used to calculate hazard ratios and analyse the association between well-documented risk factors, selected socioeconomic variables, and the incidence of ischaemic stroke including TIA and MI.
All multivariate analysis were adjusted for traditional covariates based on current literature. These were age at baseline, sex, hypertension, high-density lipoprotein as well as low-density lipoprotein, atrial fibrillation, diabetes mellitus, body mass index, physical activity,

alcohol consumption, and cigarette smoking in order to give an unbiased estimate for the relation between baseline status and incident events. For ischaemic stroke including TIA, ischaemic stroke, and MI, one model was calculated, respectively.

Results

3,908 participants, 1,600 (40.9%) men and 2,308 (59.1%) women, aged 53.74 to 101.85 years (SD= 7.8) were included. During the trial period, 230 (5.9%) patients suffered from ischaemic stroke including TIA, 161 (4.1%) from ischaemic stroke, and 92 (2.4%) participants from myocardial infarction.
Advanced age (B= 0.08, SE= 0.01, p= $4.76x10^{-19}$) and smoking (B= 0.35, SE= 0.16, p= 0.03) were associated with an increased hazard of ischaemic stroke including TIA. Physical activity (B= -0.39, SE= 0.16, p= 0.02) had a significant protective effect. A higher education status was significantly protective (B= -0.85, SE= 0.42, p= 0.05). However, there was no protective effect of being married, living arrangements, and occupation.
Higher age (B= 0.09, SE= 0.01, p= $1.18x10^{-17}$), high LDL concentration (B= 0.005, SE= 0.002, p= 0.041), and smoking (B= 0.559, SE= 0.193, p= 0.004) significantly increased the risk for ischaemic stroke, while physical activity (B= -0.39, SE= 0.19, p= 0.04) had a significant protective effect. Again, lower educational level was associated with increased risk of ischaemic stroke (B= -1.63, SE= 0.72, p= 0.03). Marital status, housing conditions, and occupation did not show any association with incidence of ischaemic stroke.
Advanced age (B= 0.09, SE= 0.01, p= $0.76x10^{-9}$), hypertension (B= 0.45, SE= 0.26, p= 0.08), and smoking (B= 0.55, SE= 0.25, p= 0.03) were significant risk factors for MI. Being female (B= -0.946, SE= 0.297, p= 0.001) and high HDL level were significantly protective (B= -0.025, SE= 0.009, p= 0.004). Educational attainment, marriage, cohousing as well as former or current occupational level had no significant association with suffering from MI.

Interpretation

Implementation of preventive strategies have proven highly effective at community level. A deepened health care education focusing on the revealed socioeconomic discrepancies in the INVADE cohort might lower incidence rates and the financial as well as health burden of vascular diseases in the administrative district of Ebersberg.
As research plays a fundamental role in reducing the strain of stroke and MI, combined

efforts of science and politics on target-orientated preventive programs in lower socioeconomic classes can contribute to a decline of overall costs in the German health care system.

Keywords

INVADE study, ischaemic stroke, transient ischaemic attack, myocardial infarction, socioeconomic impact, health care education

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Abbreviations

ABCD2 Age, Blood pressure, Clinical features, Duration of TIA, and presents of Diabetes score

ACS Acute coronary syndromes

AF Atrial fibrillation

AHA American Heart Association

AMI Acute myocardial infarction

AOK Allgemeine Ortskrankenkasse

APCSC Asia Pacific Cohort Studies Collaboration

ARIC Atherosclerosis Risk In Communities study

ASA American Stroke Association

AVAIL Adherence eValuation After Ischaemic stroke Longitudinal study

BMI Body mass index

BP Blood pressure

BRFSS Behavioural Risk Factor Surveillance System

CHA2DS2-VASc Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke or TIA or thromboembolism - Vascular disease, Age, Sex Category

CHD Coronary heart disease

CHS Cardiovascular Health Study

CI Confidence interval

COPD Chronic obstructive pulmonary disease

CVD Cardiovascular disease

DALY Disability-adjusted life year

DBP Diastolic blood pressure

DM Diabetes mellitus

e.g. exempli gratia, for example

ECG Electrocardiogram

EU European Union

FHS Framingham Heart Study

FRS Framingham Risk Scoring

GP General practitioner

HbA1c Hemoglobin A1c

HDL High-density lipoprotein

ICD-10 International Statistical Classification of Diseases and Related Health Problems, 10th revision

ICH Intracerebral haemorrhage

INVADE Intervention project on cerebrovascular diseases and dementia in the district of Ebersberg

IRR Incidence rate ratio

LDL Low-density lipoprotein

MI Myocardial infarction

MRFIT Multiple Risk Factor Intervention Trial

NOMASS Northern Manhattan Stroke Study

NSTEMI Non–ST-elevation myocardial infarction

OC Oral contraceptives

OR Odds ratio

PA Physical activity

QOL Quality of life

RR Relative risk

RSA Risikostrukturausgleich

SBP Systolic blood pressure

SED Socioeconomic deprivation

SEP Socioeconomic position

SES Socioeconomic status

STEMI ST-elevation myocardial infarction

TIA Transient ischaemic attack

UA Unstable angina

US United States

vs. versus

WARIS Warfarin, Aspirin Reinfarction Study

WHO World Health Organization

1 Introduction

1.1 Context of this thesis

This study investigates the association of selected socioeconomic variables, namely educational attainment, occupation, marital status, and cohousing, with the incidence of ischaemic stroke, ischaemic stroke including transient ischaemic attack (TIA), and myocardial infarction (MI) in the INVADE cohort (**In**tervention project on cerebro**va**scular diseases and **d**ementia in the district of **E**bersberg), after having adjusted for well-established risk factors. As ischaemic stroke and TIA are closely linked, the category of ischaemic stroke including TIA was enclosed to analyse potential differences by comparing the findings in both groups.

Consequently, chapter 1 defines ischaemic stroke, TIA as well as myocardial infarction and reports recent incidence, prevalence, and mortality rates. Chapters 2 and 3 give an overview of current literature regarding risk factors for ischaemic stroke including TIA, and myocardial infarction, respectively. This will explain the collection of risk factors applied in the present study. Furthermore, chapter 4 delves deeper into socioeconomic position and health, focusing on the variables chosen in the present study. Specific findings on socioeconomic circumstances in association with the risk of stroke or myocardial infarction are described in chapter 5. Based on the results reported in the previous chapters, chapter 6 underlines the importance and motivation of the study. This section leads over to the methods described in chapter 7, followed by the results in chapter 8. To conclude, chapter 9 discusses the stated findings, strengths, and limitations of this study. Finally, implications for prevention of ischaemic stroke including TIA and myocardial infarction are described.

As the generalization of epidemiological results on other countries or geographical regions has to be handled with care, the present study gives deeper insight into socioeconomic position and vascular diseases in the administrative district of Ebersberg. These findings enable a specific and medical need-orientated approach for the area in question.

1.2 Definition ischaemic stroke, transient ischaemic attack and myocardial infarction

The following section will provide a current definition of ischaemic stroke, transient ischaemic attack and myocardial infarction.

Classically, stroke is characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause. This encompasses cerebral infarction, intracerebral haemorrhage (ICH), and subarachnoid haemorrhage. Despite its worldwide impact, there is no consistent definition of the term “stroke” in assessments of the public health, in clinical practice, or in clinical research [1].

A recent definition of ischaemic stroke is an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction [1].

Furthermore, a TIA can be described as a brief episode of neurologic dysfunction caused by focal brain or retinal ischaemia [2]. It is not associated with lasting cerebral infarction [3]. The term “transient” indicates a lack of permanence.

In 2002, a research group of cerebrovascular physicians suggested a tissue-based, rather than time-based definition. They described a TIA as a brief episode of neurological dysfunction due to focal brain or retinal ischaemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction [2]. This proposed new definition has been well received and numerous cerebrovascular experts endorsed this further developed suggestion [3]. Defining TIA with a 24-hour maximum duration has the potential to delay the initiation of effective stroke interventions. A 24-hour limit for transiently symptomatic cerebral ischaemia is arbitrary. It is not representative for the usual duration of these events [3].

Based on the considerations mentioned above, the American Heart Association (AHA) writing committee found that the definition was well supported by the data in current literature. Nevertheless, the reference to a one-hour time point in the new definition was not supportive, as this point in time does not demarcate events with and without tissue infarction.

Accordingly, the following revised definition for TIA was proposed as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction [3].

In terms of MI, it can be stated that there was a continuous need for a better definition of this type of disease for epidemiological, diagnostic, and research purposes since the 1971 publication of the first standardized definition by the World Health Organization (WHO) [4].

The term myocardial infarction pathologically describes the death of cardiac myocytes, also known as cardiac muscle cells or muscle fibre, due to extended ischaemia. This may be caused by an increase in perfusion demand or a decrease in blood flow. An acute myocardial infarction (AMI) is categorized in the spectrum of acute coronary syndromes (ACS). Those include unstable angina (UA), non–ST-elevation myocardial infarction (NSTEMI) as well as ST-elevation myocardial infarction (STEMI) [5].

A persistent elevation of the ST-segment on an electrocardiogram (ECG) signifies a severe occlusion of a coronary artery, leading to a necrosis of the myocardial tissue. This condition is called STEMI. ACS without ST-segment elevation may either be attributed to NSTEMI or UA [5].

Atherosclerosis describes the buildup of fats, cholesterol and other substances in and on the artery walls resulting in plaques that can restrict the blood flow. These plaques can burst and launch a blood clot. The rupture of a high risk plaque in the coronary arteries is generally speaking a primary causative factor in the development of an acute myocardial infarction [5]. High-risk or vulnerable plaques are provided with a cover of a thin fibrous cap, which predisposes these plaques to rupture. Consequently, the rupture of the thin fibrous cap exposes blood to plaque constituents that add to the activation, adhesion, and aggregation of platelets and the production of thrombin. This process is causing subsequent thrombus formation, which occludes the vessels, impedes the blood flow, and subsequently leads to the development of AMI. It can be stated that more than 90% of patients with STEMI and approximately 35% to 75% of patients with NSTEMI or UA have been reported to have thrombus formation in their coronary arteries [5].

The detection of a rise and/or fall of cardiac biomarkers, along with at least one of the values being elevated (>99th percentile upper reference limit), is central to the third universal definition of MI suggested by the expert consensus of the American College of Cardiology Foundation. The highly sensitive and specific cardiac troponin can be seen as the preferred biomarker of myocardial necrosis. Additionally, one of the five following predefined criteria should be present to justify a diagnosis of MI [6]:

Table 1.1
Criteria for diagnosis of myocardial infarction

Signs for myocardial infarction
New or presumably new significant ST-segment/T-wave changes or left bundle branch block (cardiac conduction abnormality in ECG)
Development of pathological Q-waves on ECG (sign of previous myocardial infarction)
New loss of viable myocardium, which is the muscular tissue of the heart, or regional wall motion abnormality by imaging
Identification of intracoronary thrombus by angiography or autopsy

1.3 Incidence, prevalence and death rates of stroke, transient ischaemic attack and myocardial infarction

To understand the great significance and the fundamental need of current research in stroke and myocardial infarction, the current rates for incidence, prevalence and death will be discussed in the following chapter on a global, regional and Germany-specific level. Due to the neurological scientific and academic background this thesis is built on, this work will focus on cerebrovascular disease, namely stroke.

1.3.1 Stroke

Global overview

Currently, about 7.3 billion people populate the earth [7]. Over the past twenty years, the age-standardised rates of stroke mortality have declined globally. Nevertheless, the absolute number of people who have a stroke every year, stroke survivors, related deaths, and the overall global burden of stroke are immense and raising [8].

Based on the results of the Global Burden of Diseases study, stroke was the second most common cause of death [9] and globally the third most frequent source of disability-adjusted life years (DALY) in the year 2010 [10].

By 2030 there will be nearly 12 million deaths due to stroke, 70 million stroke survivors and above 200 million disability-adjusted life years lost worldwide, if these trends in stroke incidence, mortality, and DALYs continue [8]. By this time, an additional 3.4 million

adults will have had a stroke. This is an increase of 20.5% in prevalence compared to 2012 [11].

A systematic review on worldwide stroke incidence trends reported a decline in overall age-adjusted stroke incidence rates over the last four decades in developed countries [12].

In the same time, there is a huge trend in rejuvenation regarding the proportion of stroke in people $\leq$ 65 years. This can particularly be observed in low-income and middle-income countries.

The proportion of young people <20 years and young and middle-aged adults, which is 20 to 64 years, affected by stroke is raising [13]. In terms of even younger population groups, more than 83,000 children and youths aged 20 years and younger are afflicted with stroke per year [8]. Compared to older patients, young stroke patients show different etiologic subtype patterns [14].

From a social and public health point of view, any decrease in stroke incidence is a great achievement. Though, it has to be kept in mind that the reduced incidence in old age goes along with increased numbers in younger patients as mentioned above. Obviously, this leads to a crucial cut in quality and productivity of life corresponding with fundamental costs in the public health care system [15]. Further details will be discussed in chapter 6 on the motivation of this study.

To get a comprehensive picture, the ten leading causes of death in the world in 2012 are displayed in the figure 1.1, demonstrating affected individuals in millions. Stroke ranks with 6.7 million deaths worldwide on second place, following ischaemic heart disease on top rank leading to 7.4 million deceases [16].

In low-income and lower/upper-middle-income countries, stroke incidence seems to raise, while decreasing in high-income countries of 42% over the last forty years [12]. In this context, it clearly has to be stated that the main part of research and attention to stroke prevention and intervention measures takes place in high-income countries, whereas more than 85% of the cases of stroke occur in low-income and middle-income countries [17].

In the following, figures 1.2-1.5 compare the major causes of death in low, lower-middle, upper-middle and high-income countries per stroke deaths/100,000 residents. In low-income-countries, stroke accounts for 52 deaths/100,000 inhabitants and in lower-middle-countries for 78 deaths/100,000 inhabitants. Additionally, in upper-middle-countries, the

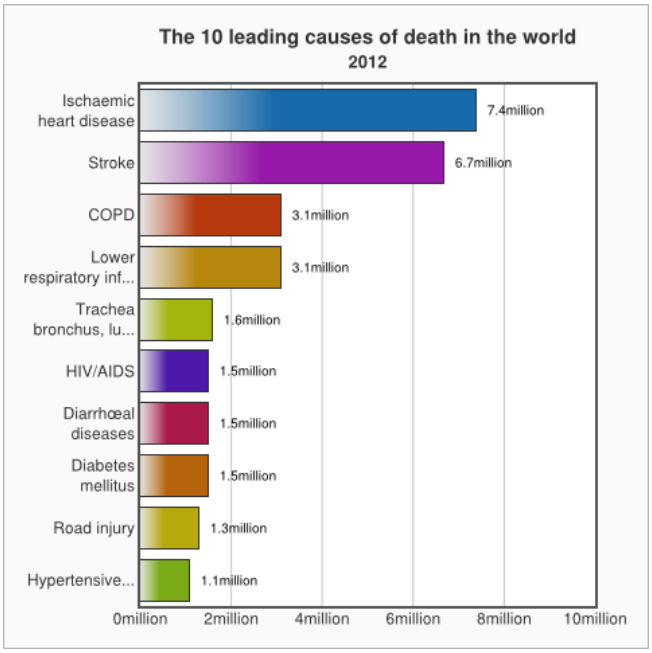

Figure 1.1
The 10 leading causes of death in the world in 2012;
legend to this overview: place 4: lower respiratory infections; place 5: trachea bronchus, lung cancers; place 10: hypertensive heart disease [16].

rate reaches 126 deaths/100,000 inhabitants, which is almost double compared to low-income-countries. Finally, in high-income countries 95 deaths/100,000 inhabitants were reported due to stroke [16], underlining the general trends described in the beginning of this section worldwide.

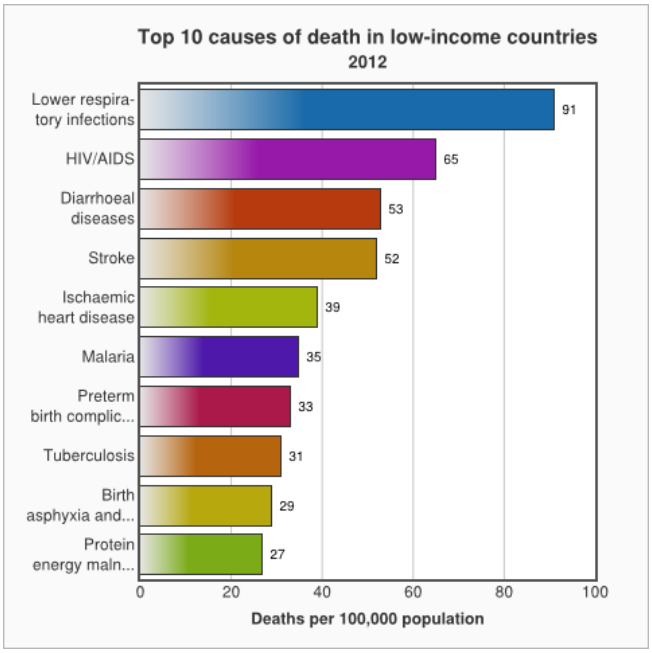

Figure 1.2
The 10 causes of death in low-income countries in 2012;
legend to this overview: place 7: preterm birth complications; place 9: birth asphyxia and birth trauma; place 10: protein energy malnutrition [16].

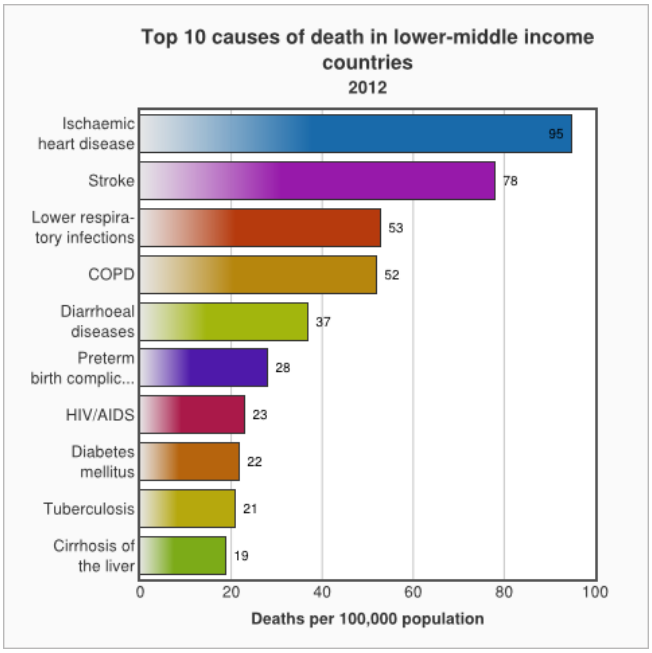

Figure 1.3
The 10 causes of death in lower-middle income countries in 2012;
legend to this overview: place 4: COPD (Chronic obstructive pulmonary disease); place 6: preterm birth complications [16].

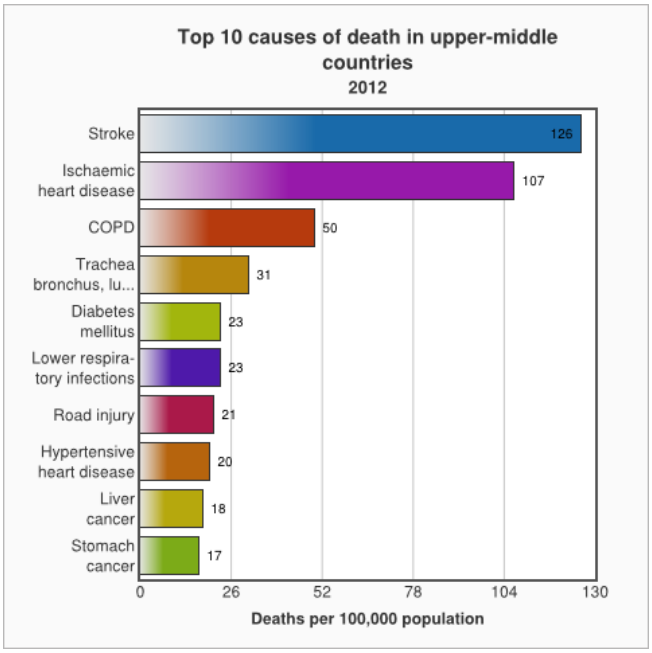

Figure 1.4
The 10 causes of death in upper-middle income countries in 2012;
legend to this overview: place 4: trachea bronchus, lung cancers [16].

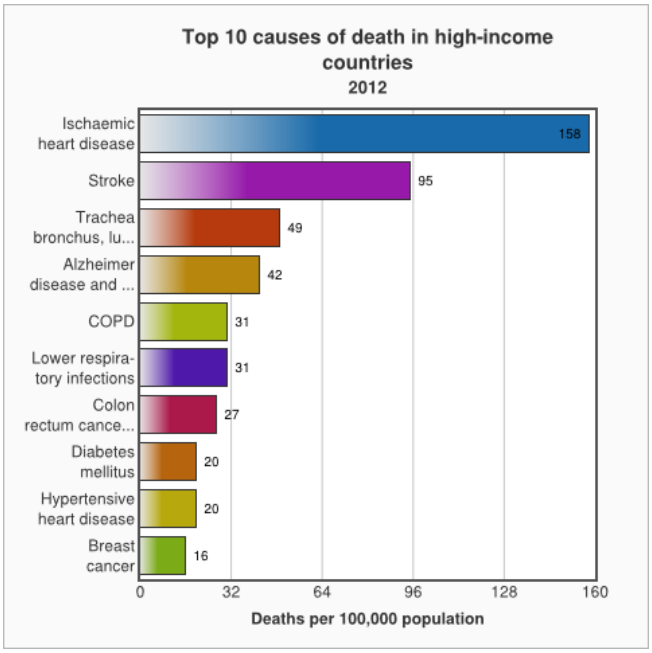

Figure 1.5
The 10 causes of death in high-income countries in 2012;
legend to this overview: place 3: trachea bronchus, lung cancers; place 4: Alzheimer disease and other dementias; place 7: colon rectum cancers [16].

At the end of this paragraph, figure 1.6 shows the stroke mortality rate on a global level [8].

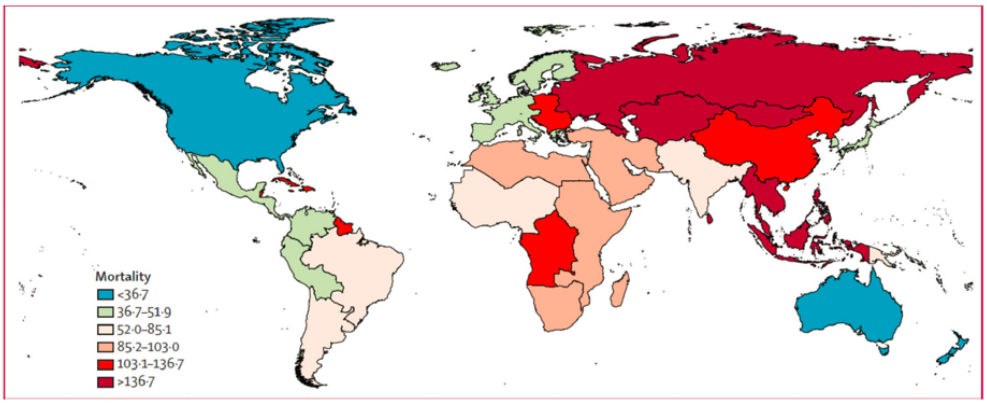

Figure 1.6
Age-standardized stroke mortality per 100,000 people in 2010 [8].

Overview of the situation in the United States

Based on this global overview, there will be an outline of the current situation in the United States of America.

As there is a huge data volume and a broad range of studies originated from the United States (US), those findings will be disused as a reference throughout this thesis.

On average, every 40 seconds, a person in the US has a stroke. Every four minutes, an individual dies of this condition [18]. In 2010, stroke accounted for approximately one of every 19 deaths in the US [18] which currently states a population of 321.3 million inhabitants [7].

When examined independently from other cardiovascular diseases (CVD), stroke reaches number four among all causes of death, behind diseases of the heart, cancer, and chronic lower respiratory disease. This is in contrast to data published by the WHO, naming stroke as second cause of death in high-income countries, indicating variations on country level. In the US, the number of deaths from stroke as an underlying cause was reported as a total number of 129,476 affected persons in the year 2010 [18].

Every year, about 795,000 people experience an incident or recurrent stroke in the US. Approximately 610,000 of these events are first attacks, and 185,000 are recurrent attacks. Of all stroke subtypes, 87% are ischaemic and 10% are intracerebral haemorrhage strokes, whereas only 3% can be attributed to subarachnoid haemorrhages.

Differences in gender

Women have a lower age-adjusted stroke incidence in comparison to men. Nevertheless, sex differences in stroke risk may be modified by age [19]. There have been gender differences reported in the onset of stroke. Women tend to be older at onset than men, with 75 years compared to 71 years respectively [20].

Data from the Framingham Heart Study (FHS), a long-term and ongoing trial on residents of the town of Framingham, Massachusetts, which was launched in 1948 with 5,209 adults and has now reached its third generation of subjects [21], reported that white women in the age of 45 to 84 had a lower risk of stroke compared to white men. However, this relation is reversed in older ages in women >85 years, who showed an increased risk [20]. The higher prevalence of stroke for females is probably linked with hormonal changes during the menopause. Lifetime risk of stroke among those 55 to 75 years of age was one in five for women (20%-21%) compared to approximately one in six for men (14%-17%) [22].

Additionally, the major part of these strokes were documented in women older than 70 years, who were more likely socially isolated, live alone, have fiscal restraints as well as higher rates of comorbid diseases. The increased rate of stroke deaths in females is anticipated to raise in the future based on population projections. An excess of 32,000 stroke deaths in women in 2000 compared to nearly 68,000 deaths by 2050 is predicted [19].

Results from the Austrian Stroke Unit Registry state that among patients submitted to acute stroke unit care, women were significantly older (median age 77.9 for females versus (vs.) 70.3 years for males), had higher pre-existing disability, and more severe strokes. After correction for age, no significant sex-related differences in quality of care were determined. Comparable onset-to-door times, times to and rates of neuroimaging as well as door-to-needle times and rates of intravenous thrombolysis were identified for both sexes. Nevertheless, despite the equal acute stroke care and a comparable rate of neurorehabilitation, women showed a worse functional outcome at three-month follow-up (modified Rankin scale 3–5: odds ratio (OR), 1.26; 95% confidence interval (CI) [1.17–1.36]). The modified Rankin scale is frequently applied to estimate the degree of disability or dependence in the daily activities of people who have suffered a stroke. However, a lower mortality rate (OR, 0.70; 95% CI [0.78–0.88]) after correcting for confounders was reported for women [23].

In the past 16 years, the German Erlanger Stroke Register reported that the total stroke

incidence decreased in men (incidence rate ratio (IRR) 1995 to 1996 vs. 2009 to 2010 0.78; 95% CI [0.58–0.90]), but not in women [24].

Differences in race and ethnicity

Over the past decade, stroke incidence has been diminished in the US in whites but not in blacks [25]. This indicates a worsening of the racial differences in stroke incidence [15]. In summary, stroke became the fourth-leading cause of death in whites and the fifth-leading cause of death in men while it persisted to be the second-leading cause of death in women and blacks [26].

Overview of the situation in the European Union

In the European Union (EU), which currently encompasses 504.6 million inhabitants, one million first ischaemic strokes are estimated each year [27], [28]. For the last ten years, data on temporal trends of age- and sex-adjusted stroke incidence in European communities is restricted [8]. Furthermore, the estimation of time-trends across different population-based registers can be compounded as these studies cannot be considered homogeneous in various aspects touching stroke incidence in the local population. Examples for this are ethnic group diversity, geographical region or risk factor distribution in the general population [24].

Current situation in Germany

Based on this, an overview of the situation in Germany will follow.

Derived from data published by the German Federal Statistical Office, 52.044 individuals, which is 5.8%, died of acute myocardial infarction (ICD-10 classification I21) whereas stroke (ICD-10 classification I64) attributed with 18.883 (2.1%) of deaths in 2013 [29]. Consequently, AMI ranked on place two, while stroke marked place seven on the list of the major ten causes of death in Germany (see table 1.2).

The aging of the population in Germany and whole Europe will further raise the socioeconomic burden of stroke and limit the medical and social resources accessible to support the needs of individuals affected by stroke and their kin. Based on the current Robert-Koch-Institut federal health report, the life expectancy in Germany is 81.6 years for women and 76.0 years for men [30].

Table 1.2
Top 10 causes of death in Germany, based on ICD10-classification in 2013 [29]

ICD-10 code	Causes for death	n	%
I25	chronic ischaemic heart disease	73,176	8.2
I21	acute myocardial infarction	52,044	5.8
I50	heart failure	45,815	5.1
C34	malignant neoplasm of bronchus and lung	44,813	5.0
J44	other chronic obstructive pulmonary disease	28,882	3.2
F03	unspecified dementia	24,738	2.8
I11	hypertensive heart disease	24,669	2.8
I64	stroke, not specified as haemorrhage or infarction	18,883	2.1
J18	pneumonia, unspecified organism	18,797	2.1
C50	malignant neoplasm of breast	18,009	2.1

To meet this challenge, the Helsingborg Declaration clearly stated the need for population-based monitoring of particular core indicators like stroke incidence and case fatality [31]. Based on this demand, in 1994, a community-based stroke register was established in Erlangen, Bavaria, Germany [32].

The Erlangen Stroke Project can be described as the first prospective community-based stroke register including all age groups in Germany. It underlined incidence rates of stroke similar to those reported from other population-based studies in western industrialized countries [33], [34], [35], [36], [37], [38]. In 1998, the annual incidence rate for Germany was 1.74 per 1,000, in detail 1.47 for men and 2.01 for women [32]. After having adjusted for age compared to the European population, the incidence rate was 1.34 per 1,000, which was 1.48 for men and 1.25 for women. Furthermore, the overall case fatality at 28 days was 19.4%, at three months 28.5%, and at one year 37.3%. Additionally, it was stated that 51.0% of all first strokes were recorded in individuals aged 75 years or older.

This rate was comparable to estimates also found in predominantly white populations in the Framingham study in the United States [39], [40] or Australia [41].
However, those incidence rates were lower than those reported in former East Germany and closer to the rates observed in other Eastern European countries [32]. As Germany has been separated for 45 years, both politically and socioeconomically, it remains to be seen to what extent and in which period of time reunification will diminish this gap in stroke incidence and fatality rates predominantly.

In addition to this, it was reported that more than 94% of those patients with stroke were

hospitalized. This is comparable with the proportion observed for the majority of other industrialized countries, particularly in urban areas [32]. The stated case-fatality rates at day 28 were also similar to those identified in other Western European countries [33], [35], [38].

Differences in gender in Germany

Recent data from the Erlangen Stroke Project recorded 3,243 patients with first-ever stroke over a period from January 1995 to December 2010 [24]. The median age was 75 years, 55% of all patients were females. In this context, it clearly has to be stated that the total stroke incidence decreased in male population over the study period of 16 years (IRR 1995–1996 vs. IRR 2009–2010 0.78; 95% CI [0.58–0.90]), but not in females. A decrease in ischaemic stroke incidence (IRR 0.73; 95% CI [0.57–0.93]) was reported in men and an increase of stroke due to small artery occlusion in women (IRR 2.33; 95% CI [1.39–3.90]). The discrepancies in time trends of pathological and etiological stroke subtypes that became obvious might be connected to gender differences in the development of major vascular risk factors [24].

Heuschmann et al. (2004) analysed predictors of in-hospital mortality and attributable risks of death after ischaemic stroke based on data retrieved from the German Stroke Registers [42]. An overall in-hospital mortality of 4.9% was stated. In women, higher age ($p<0.001$), the severity of stroke accounted by number of neurological disabilities ($p<0.001$) as well as atrial fibrillation (hazard ratio [HR], 1.3; 95% CI [1.0-1.6]) were independent predictors for death in the hospital. Furthermore, in the male population, diabetes (HR, 1.3; 95% CI [1.0-1.8]) and previous stroke (HR 1.4; 95% CI [1.0-1.9]) significantly influenced the early outcome in addition to the factors defined for females in a negative way. More than half of all in-hospital deaths derived from serious medical or neurological complications (54.4%; 95% CI [54.3-54.5]).

To visualize gender differences in the EU, figure 1.7 compares the age-standardized mortality rates for cerebrovascular diseases per 100,000 inhabitants in Germany, France, the Netherlands and the United Kingdom by sex [30].

1.3.2 Transient ischaemic attack

It clearly has to be stated that only few epidemiologic data are available in terms of incidence and prevalence of TIA. In Europe, the incidence rate was 0.52 to 2.37 and

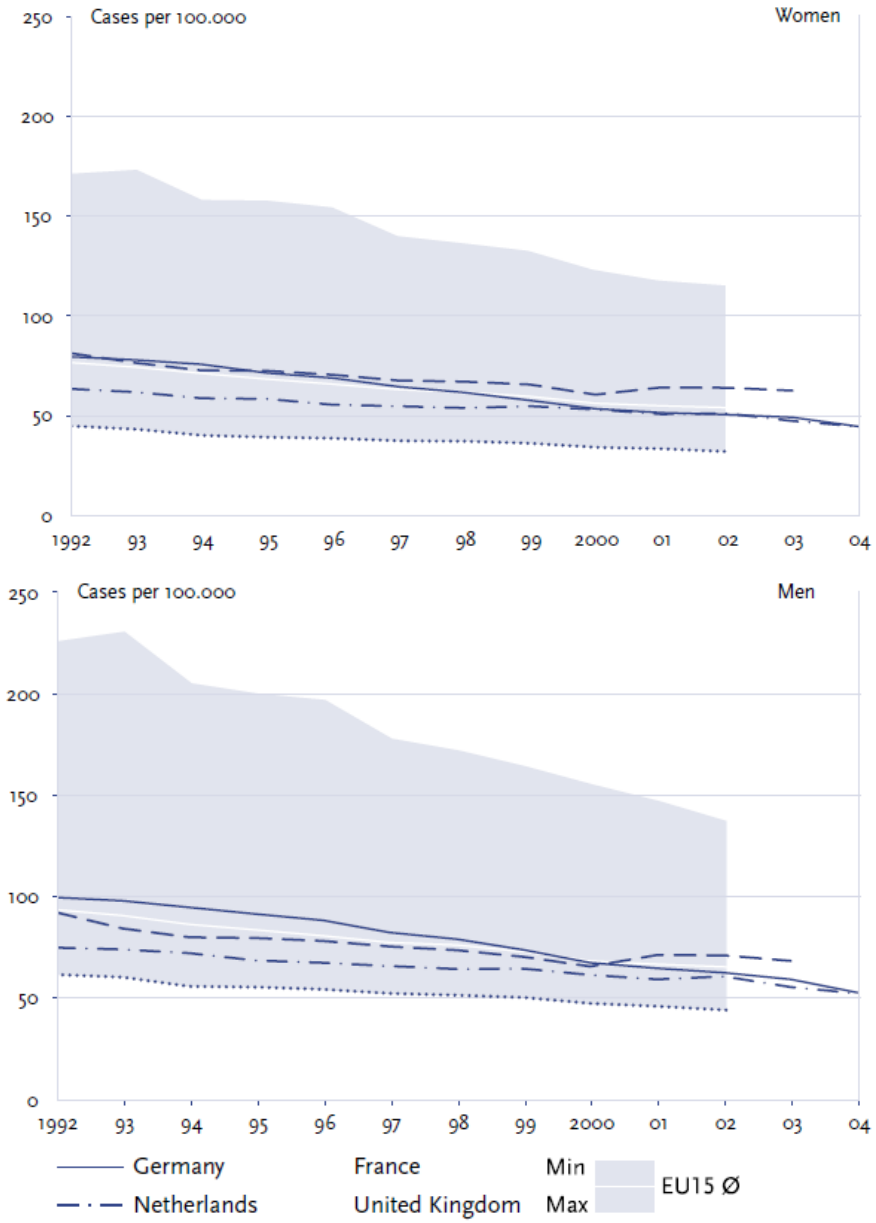

Figure 1.7
Comparison of age-standardized mortality rates for cerebrovascular diseases per 100,000 inhabitants in four European countries by sex [30].

0.05 to 1.14 in men and women aged 55 to 64, 0.94 to 3.39 and 0.71 to 1.47 in those aged 65 to 74, and 3.04 to 7.20 and 2.18 to 6.06 in those aged 75 to 84, respectively. In this context, it has to be mentioned that higher incidences were reported in men than in women [43]. Those variations in incidence might be due to the vague definition of TIA.

The corresponding incidences were comparable in the US. A nationwide survey of US adults showed that the estimated prevalence of self-reported physician-diagnosed TIA was 2.3%. This number corresponds with approximately five million people. The true prevalence of TIA is assumedly higher, as this medical information will not always reach the healthcare provider [44]. About 15% of all strokes are announced by a TIA [45].

Meta-analyses reported the short-term risk of stroke after TIA to be about 3% to 10% at two days and 9% to 17% at 90 days [46], [47]. Additionally, it can be stated that individuals who had a TIA and survive the initial high-risk period, have a ten-year stroke risk of approximately 19% and a combined ten-year risk of stroke, MI, or vascular death of 43%. This is 4% per year [48]. Within one year after TIA, approximately 12% of patients will perish [49]. Supposedly, one third of episodes registered as a TIA would be considered infarctions on the basis of diffusion-weighted magnetic resonance imaging results [50].

To facilitate health care planning and resource allocation, regular up-dating of stroke prevalence data is fundamental [51]. Further research is needed to enhance understanding of stroke and TIA determinants as well as the burden worldwide. Reasons behind discrepancies and changes in trends in strain of stroke between countries of different income levels need to be established [8].

1.3.3 Myocardial infarction

Current situation in the United States

In terms of incidence, about every 44 seconds, an US citizen will have a MI. The forecasted annual incidence of MI is 515,000 new attacks followed by 205,000 recurrent attacks. Around 600 in every 100,000 men and 200 in every 100,000 women have an AMI every year [5].

On average, a patient is 64.9 years old in males and 72.3 years in females at their first myocardial infarction [52]. An annual decline in the overall mortality rates among AMI

patients in the US can be observed [5]. Since the mid-1990s, the rate of hospitalization for MI and in-hospital case fatality rates have decreased continuously [53].

Current situation in Germany

Focusing on Germany, the lifetime prevalence of diagnosed myocardial infarction in those aged 40 to 79 years is 4.7% [54]. An increase was documented with advancing age, which is raising from 1.5% in 40 to 49 year olds to 10.2% in 70 to 79 year olds. In females, the prevalence is 2.5%, which is about half of the percentage for men (7.0%). People younger than 60 years show a prevalence of less than 1%.

For Germany, the incidence is approximately 300/100,000 inhabitants. Additionally, the mortality from myocardial infarction continues to fall (see figure 1.8). According to official statistics on causes of death, 29,550 women and 34,679 men died of acute myocardial infarction in 2003. In this regard, 6.5% of all deaths were documented in the female population and 8.7% in the male. Additionally, the age-adjusted mortality rate among women decreased from 48.0 to 32.4 deaths from infarction per 100,000 inhabitants. In the same period of time it declined from 127.6 to 71.4 per 100,000 male inhabitants [29].

According to the mentioned data published by the German Federal Statistical Office above, 52,044 individuals (5.8%) died of acute myocardial infarction in 2013 [29]. As a result, MI holds place two on the list of the top ten causes of death in Germany (see table 1.2).

The only increase in mortality from myocardial infarction has been reported in women over 90 years of age [30].
Data from the Augsburg myocardial infarction registry emphasizes that the proportion of patients with infarction who die before reaching the hospital or during their first days in hospital has fallen since 1985. This development is inseparably linked to improved emergency care. As a consequence, better acute treatment and rehabilitation have reduced the risk of men and women over 65 years experiencing another heart attack. Notwithstanding that 90% of all deaths following a MI still occur before the patient has reached the hospital or during the patient's first day of active treatment [30].

Differences in gender

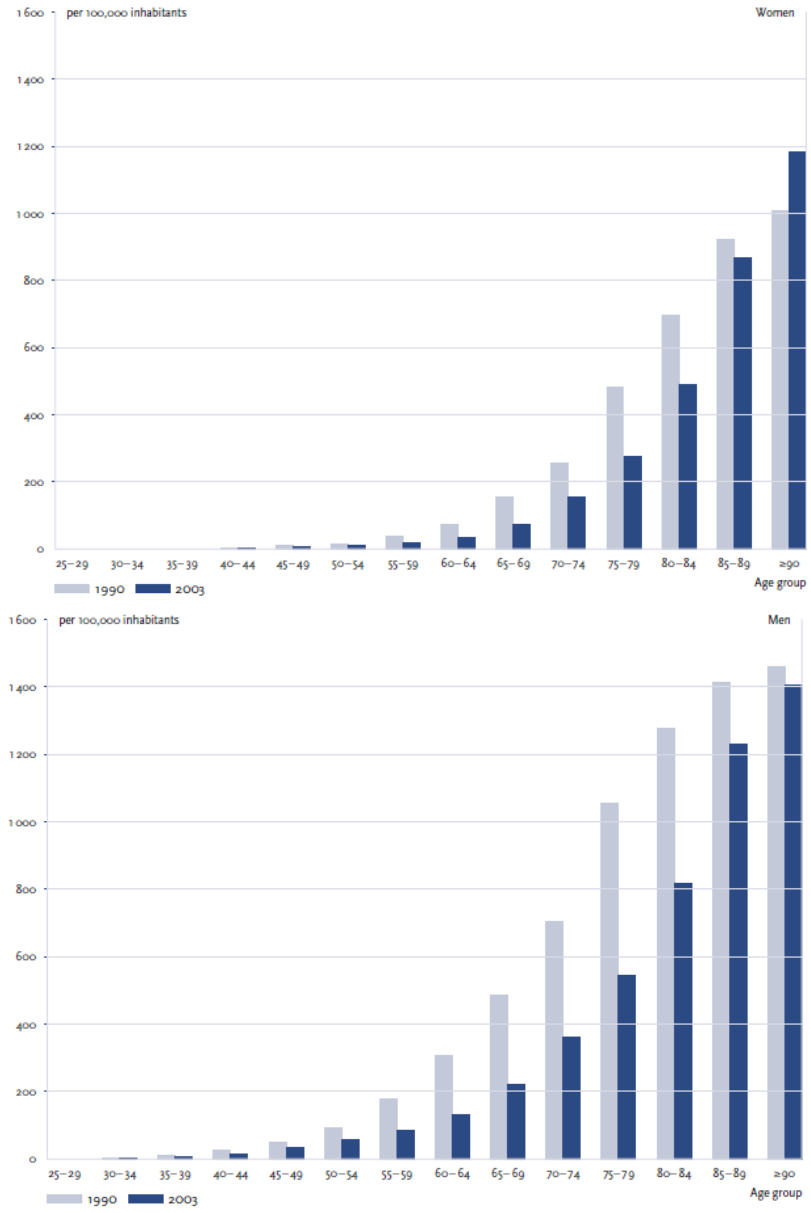

Figure 1.8
Mortality rate for acute myocardial infarction in Germany by sex [30].

A decline of the incidence rate can also be reported in women between the ages of 55 and 75, while the incidence in women between the ages of 25 and 54 is increasing. This raise is linked to higher cigarette consumption among the German female population and with women starting to smoke at an earlier age [55]. In young women, the thromboembolic events are mainly associated with the intake of hormones.

Nevertheless, males are primarily affected by heart attacks. In earlier years men are at an eight-fold higher risk to suffer from a myocardial infarction and nine times more likely

Table 1.3
Most frequent cause of death per 100,000 inhabitants in Germany by sex [30].

Women	Rank 2004	Mortality rate
I25 Chronic ishemic heart disease	1	114.7
I50 Cardiac insufficiency	2	78.6
I21 Acute myocardial infarctiont	3	67.3
I64 Stroke, not specified whether haemorrhage or infarction	4	50.0
C50 Malignant neoplasm of the mammary glands)	5	41.7
I11 Hypertensive heart disease	6	27.2
C34 Malignant neoplasm of the bronchia and lungs	7	26.1
J18 Pneumonia Cause not specified	8	24.7
C18 Malignant neoplasm of the colon	9	24.4
E14 Diabetes mellitus (no specification)	10	23.1

Men	Rank 2004	Mortality rate
I25 Chronic ishemic heart disease	1	88.8
I21 Acute myocardial infarction	2	82.6
C34 Malignant neoplasm of the bronchia and lungs	3	71.3
I50 Cardiac Insufficiency	4	37.3
J44 Other chronic obstructive pulmonary diseases	5	29.2
I64 Stroke, not specified whether haemorrhage or infarction	6	27.6
C61 Malignant neoplasm of the prostate	7	27.6
C18 Malignant neoplasm of the colon	8	22.7
J18 Pneumonia. Cause not specified	9	19.8
K70 Alcohol-related liver disease	10	18.5

to die from it than women of the same age. After the age of 65, the risk for men is three times higher than for the female population. From the age of 85, there is no longer any difference perceivable. Taken together, the age-standardized incidence and mortality rate is double for men compared to women (see figure 1.8) [30]. In females, oestrogen shows a protective effect.

The Federal Health Report announced by the Robert-Koch-Institut displays gender differences in table 1.3 [30]. For females, MI was on third rank, followed by stroke on fourth place. In contrast to this, MI was already on second place and stoke only on sixth rank in men.

2 Risk factors for stroke and transient ischaemic attack

To get a deeper understanding of variables attributed to risk of stroke and TIA, the following chapter will give an overview of established and upcoming risk factors. This insight in current scientific literature will underline the composition of risk factors chosen in the present study.

Risk factors that cannot be modified are composed of age, sex, low birth weight, race, and ethnicity as well as genetic predisposition. Well-documented and modifiable risk factors comprise of hypertension, dyslipidaemia, exposure to cigarette smoke, diabetes, postmenopausal hormone therapy, carotid artery stenosis, atrial fibrillation, other specific cardiac conditions, sickle cell disease, poor diet, physical inactivity, obesity as well as body fat distribution. Less well-documented or potentially modifiable risk factors are stated as the metabolic syndrome, drug abuse, excessive alcohol consumption, sleep-disordered breathing, use of oral contraceptives, hyperhomocysteinaemia, migraine, inflammation, hypercoagulability, and elevated lipoprotein(a) [56].

Extensive evidence allows determining a variety of specific variables that alter the risk of a first stroke. Consequently, this approach enables to find strategies for decreasing risk in stroke and TIA.

Generally non-modifiable risk factors are variables which cannot be modified. These risk factors identify subjects who are at altered risk of stroke. This group may profit from precise prevention or treatment of other modifiable risk factors [56].

2.1 Generally non-modifiable risk factors

2.1.1 Sex

As stated before, stroke is globally more common in men than in women [57]. Additionally, the male population generally has increased age-specific stroke incidence rates in terms of ischaemic and haemorrhagic stroke [58], [25]. An exception for these findings represent the age group 35 to 44 years and those aged >85 years [59]. Pregnancy and the intake of oral contraceptives (OC) add to the elevated risk of stroke in young women [60], [61], [62]. Stroke leads to death in one in six women [63]. General differences in gender are described in chapter 1.3.1 on incidence and prevalence of stroke.

There are some risk factor issues specific to women that need to be considered carefully. On average, women are older than men at stroke onset, which is approximately 75 years for females compared with 71 years for males [64]. Combined with atrial fibrillation, women have a significantly higher risk of stroke than men [65]. Results from the FHS supported that women with natural menopause before the age of 42 had twice the risk of ischaemic stroke compared to women with natural menopause [66].

A large body of studies has reported that hormone replacement therapy is associated with a higher risk of stroke in post-menopausal women [67]. This increase might have accounted to the unfavourable risk profile in female patients.

Additionally, low-oestrogen-dose oral contraceptives are linked to a 93% increased risk of ischaemic stroke. However, the absolute increased risk is small, namely 4.1 ischaemic strokes per 100,000 non-smoking, normotensive women [68]. Endogenous oestrogen seems to act protective, while hormone replacement therapy increases the risk.

In this context, migraine with aura is associated with ischaemic stroke in younger women. This is particularly true in combination with smoking or the use of oral contraceptives. If all three factors merge, the risk raises approximately nine-fold compared with women without any of these [69]. For further details see 2.2.11 on OCs.

Lastly, the risk of ischaemic stroke during pregnancy and the first six weeks after giving birth was reported to be 2.4 times higher compared to non-pregnant women of similar age and race [70].

The Framingham study investigated the gender differences in stroke incidence and post-stroke disability [64]. In summary, a consistent body of international studies stated higher

rates of dependency in women after stoke, including the China National Stroke Registry [71].

Moreover, more and more research support that women may receive suboptimal treatment of cardiovascular risk factors as the perception of risk by the treating physician might be lower than for male patients [72]. As a result, sex-based adaptions in risk factor profiles and stroke incidence rates are of special interest [73].

Furthermore, trends from the Rotterdam study have shown that although blood pressure levels were increased in both, in men and women, grade 2 hypertension (160-179 / 100-109) was much more frequent in women than men. This might also have had an impact on stroke incidence rates in females [73].

2.1.2 Age

Stroke is considered as a disease of the elderly people. As stroke risk factors can be described as variables which progress over life time, the risks of both, ischaemic stroke and for intracerebral hemorrhage, alter over time. This fact is further promoted by cumulative effects of age on the cardiovascular system [74].

Also in terms of people in their middle years, a decrease of mean age of stroke from 71.2 years to 69.2 years in only 13 years could be reported in some areas in the US. These results are based on an increase of stroke rates in individuals between 20 to 54 years [75]. Additionally, the North American Nationwide Inpatient Sample reported higher rates of hospitalization because of stroke for individuals between 25 and 34 years of age to a period of 35 and 44 years of age from 1998 to 2007 [76]. Recent findings from the Framingham Heart Study predicted the lifetime risk of stroke to be one in six or more in this target group [22]. This development of stroke onset in increasingly younger ages implements greater lifetime impairment and a considerable burden of disability. Further information is stated in chapter 1.3.1 on incidence and prevalence of stroke.

The risk to suffer an ischaemic stroke and ICH redoubles every ten years having passed the mark of 55 years [25], [58].

2.1.3 Others: low birth weight, race and ethnicity, genetic factors

Low birth weight

Numerous cohort studies underlined an association between low birth weight and risk of stroke in later life. In a population-based trial conducted in England and Wales, it could be confirmed that stroke mortality rates are higher among people with lower birth weights [77]. This can be explained as followed. Low-birth-weight babies were usually born in less wealthy families, given birth to by undernourished mothers with poor overall health status in a socially disadvantaged area [77]. Lackland et al. (2003) compared a group of South Carolina Medicaid beneficiaries who were 50 years or older and had suffered stroke with population controls [78]. The odds for stroke were more than twice in subjects, having had a birth weight of <2500 g in comparison to participants weighing 4000 g. For low-birthweight newborns compared to normal-birth-weight neonates an OR of 2.16 ($p<0.01$) for heart disease, MI and the risk of stroke by the age of 50 was emphasized in a nationally representative longitudinal investigation in the US [79].

It has to be kept in mind that there are regional differences in birth weight that could partly be based on geographic disparities in stroke-related mortality. This is also linked to a persons' birthplace [78]. Until today, potential reasons for these relationships remain unclear and statistical correlations alone do not prove causality [56].

Race and ethnicity

It is problematic to investigate race or ethnic effects on disease risk separately [80]. A vast number of epidemiological studies underline those differences in regards to the risk of stroke [81]. Blacks [59], [82] and some Hispanic/Latino Americans [83] show an increased occurrence of all types of stroke which also leads to an altered mortality rate. The risk of first ischaemic stroke raises dramatically from 88 per 100,000 in whites to 149 per 100,000 in Hispanics/Latinos and to 191 per 100,000 in Blacks [52]. Blacks and Hispanics/Latinos have two to four times the stroke rate, recurrence of stroke, and deaths related to stroke than whites [15]. Despite the fact that discrepancies are more pronounced in younger age groups, race and ethnicity differences remain within older age groups [15].

The Atherosclerosis Risk In Communities study (ARIC) reported an increase of 38% in terms of stroke incidence of all types in the white population (95% CI [1.01 to 1.89])

compared to blacks [84]. Until today, further investigations are needed in order to clarify, if these racial differences are based on genetic or environmental discrepancies, or if there is an interaction between these influencing factors [74]. The higher incidence and mortality rate of stroke in African Americans could be explained by increased prevalence of obesity, hypertension, diabetes mellitus, and prehypertension [85], [86], [87], [88].

In the period of 45 to 65 years, approximately half of the racial disparity in stroke risk derives from well-established risk factors, particularly high systolic blood pressure (see 2.2.1) [89]. These results in combination with socioeconomic variables mark a critical need to understand the differences in the development of traditional risk factors.

However, altered occurrence of these variables does not clarify all of the excess risk [86], [90]. Several studies have discussed that differences based on ethnicity and race could find their roots in social deciding factors like nativity [91], geographical background [90], linguistics, access to and make use of health care systems [81] as well as neighborhood determinants [92], [93]. Such socioeconomic factors will further be discussed under chapters 4 and 5 on socioeconomic position in life and regarding stroke, respectively.

Genetic Factors

Familial history of stroke has been hypothesized as a risk factor for stroke [94], [95]. Taking into account the process of the disease, it seems reasonable that a positive parental history of stroke may especially lead to an increased risk of stroke events. This process might be triggered through a number of aspects.
Firstly, through genetic heritability of stroke risk factors like higher blood pressure (see 2.2.1), elevated serum cholesterol (see 2.2.4) or diabetes (see 2.2.2). Secondly, the inheritance of susceptibility to the effects of such risk factors or thirdly, familial sharing of cultural/environmental and lifestyle factors might play a decisive role. Examples for shared life style variables are higher sodium and fat diet, little physical activity as well as lower socioeconomic status. The interaction between genetic and environmental factors can be crucial [95].

In not less than 35% of patients, the origin of ischaemic stroke cannot be determined. Lately, there have been encouraging findings from techniques using DNA sequence data in combination with clinical information which might improve our knowledge of stroke origin. In this context, it has to be clearly stated that no implementations for preventive therapy could be made so far [74].

Looking into recently operated clinical trials, Flossmann et al. (2004) conducted a meta-analysis underlining that a positive family history of stroke alters risk of stroke by approximately 30% (OR, 1.3; 95% CI [1.2-1.5], p=0.00001) [96].

The FHS stated that parental stroke by the age of 65 was linked with a three-fold increase in risk of offspring stroke. After adjusting for conventional stroke risk factors, this increased risk persisted, hence parental stroke history could be used as a helpful risk marker of the tendency to develop stroke over life time [97]. The assessment of stroke heritability diverges with variables like the subtype of stroke, sex, and age [98], [99].

Cardioembolic stroke appears to be the least heritable type of stroke in comparison with other ischaemic stroke subtypes [98]. A heritability for cardioembolic disease of 32.6% was found based on genome-wide common variant single-nucleotide polymorphism analysis [100]. A parental history of stroke is more present in women [99]. In addition to this, Schulz et al. (2004) reported that younger stroke patients tend to have a first-degree relative who suffered from stroke [98].

Frequent genetic variants for these risk factors have been investigated in genome-wide association trials. There is a rising number of studies which focus on the influence of the accumulative burden of risk alleles of risk factors for stroke [74]. It still has to be seen if the development of a genetic risk score will contribute to clinically helpful information beyond the knowledge that can be taken from clinical risk factors. So far, only a small number of loci affecting stroke susceptibility or risk factors for stroke could have been determined [74].

A great number of well-established and rising risk factors are discussed in the following sections. Those variables show genetic as well as environmental and behavioural aspects. Additionally, a number of uncommon genetic disorders can be linked to stroke, such as cerebral autosomal dominant arteriopathy with subcortical infarcts, leukoencephalopathy, Marfan syndrome, Fabry disease, and neurofibromatosis which go beyond the scope of this thesis. Personalized medicine, applying genetic testing, is able to enhance the safety in terms of primary prevention based on pharmacotherapies [56].

To conclude, it could be conceivable to classify genetic factors as potentially modifiable. Currently, no gene specific therapeutic approaches are accessible for the main part of medical conditions apart from treatments for some rare illness, such as Fabry disease and sickle cell disease [74]. Consequently, genetic factors have been classified as non-modifiable in this thesis.

2.2 Well-documented modifiable risk factors

The following section shall delve deeper into the field of well-known risk factors that can be influenced and handled to some degree.

2.2.1 Hypertension

Hypertension can be seen as a leading risk factor for cerebral infarction [74]. Following the Seventh Joint National Committee, hypertension can be defined as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg [101]. The correlation between stroke risk and blood pressure (BP) is stable, predictive, continuous, persistent, graded, autonomous, and etiologically significant [101]. As a fundamental rule it can be stated that a higher BP, including the non-hypertensive range, leads to an increased risk of stroke [102].

In Germany, hypertension is a wide spread illness. Approximately half of all adults show clear evidence of hypertension and one in four individuals with diagnosed hypertension is on medication. High blood pressure is more prevalent in Germany compared to most other industrialized countries (see table 2.1 men and women aged 35 to 64) [103]. Only half as many individuals suffer from high blood pressure in the US and Canada.

Table 2.1
International comparison of occurrence rate of hypertension and anti-hypertension therapy [103].

Country	Prevalence Rate			Anti-hypertensive therapy
	Total	Women	Men	
North America	27.6%	24.8%	30.4%	44.4%
USA	27.8%	25.8%	29.8%	52.2%
Canada	27.4%	23.8%	31.0%	36.3%
Europe	44.2%	38.6%	49.7%	26.8%
Italy	37.7%	30.6%	44.8%	32.0%
Sweden	38.4%	32.0%	44.8%	26.2%
England	41.7%	36.5%	46.9%	24.8%
Spain	46.8%	44.6%	49.0%	26.8%
Finland	48.7%	41.6%	55.7%	25.0%
Germany	55.3%	50.3%	60.2%	26.0%

A large number of clinical studies have analysed various risk factors and markers for development of hypertension. Those included among others, family history of hypertension

and genetic factors, age, ethnicity, greater weight, lower physical activity, consummation of tobacco, psychosocial stressors, and dietary factors such as dietary fats, higher sodium and lower potassium intake as well as excessive alcohol level. Furthermore, socioeconomic variables also revealed their fundamental influence. A general lower socioeconomic status and low education were significantly associated with hypertension [52]. The influence of socioeconomic position in life will be reviewed under chapter 4.

Overwhelming evidence from studies conducted over the last 40 years depict the prevention of stroke by pharmacological treatment of hypertension [101]. This statement was underlined in a meta-analysis referring to 23 randomized trials with stroke outcomes. The risk of stroke was decreased by 32% due to antihypertensive drug treatment in comparison with no drug treatment. (95% CI [24-39]; p=0.004) [104].

This effect could be replicated for the European population as well. 4,695 patients with isolated systolic hypertension were addressed in the Systolic Hypertension in Europe study. Subjects were randomized to active treatment with a calcium channel blocker or placebo. A 42% risk reduction (95% CI [18-60]; p=0.02) could be stated in the actively treated group [105].

In accordance to recent US data, 72% of hypertensive patients were aware of their diagnosis, 61% were treated due to this diagnosis, and 35% had their BP supervised. Until today, in minority and elderly populations a lack of diagnosis and inadequate treatment are present [101].

Another study stated that BP control can be accomplished for the larger part of individuals. In this matter, the patients' treatment usually consists of $\geq$2 drugs [106].

Hypertension prevails as the most important, well-documented modifiable stroke risk factor. The treatment of this condition can be contributed to the most efficient approaches to prevent ischaemic stroke [74]. However, to this day, hypertension remains still undertreated and replenished projects to refine treatment compliance are needed to be developed, evaluated, and implemented into clinical routine [56].

2.2.2 Diabetes mellitus

Diabetes is perceptibly linked to hypertension, an increased prevalence of atherosclerotic risk factors as well as abnormal blood lipids (see 2.2.4) [56], [74].

Globally, the prevalence of Diabetes mellitus (DM) for all age groups was estimated at 2.8% in 2000. By 2013, it is projected to be 4.4%. The total number of people with DM worldwide is forecasted to rise from 171 million in 2000 to 366 million in 2030 [107]. In 2010, a total of 1.9 million new cases of type 1 or type 2 DM were diagnosed in US adults $\geq$20 years [108]. In the Multi-Ethnic Study of Atherosclerosis, the incidence of DM varies considerably by race. The incidence is reported to be highest in Hispanics with 11.3%, followed by black with 9.5%, then Chinese with 7.7%, and lastly, by white participants with 6.3% [109].

In Germany, there are approximately four million people with diabetes. 80% to 90% of them are suffering from type 2 diabetes. This type of diabetes becomes more frequent with advancing age. Based on the growing proportion of elderly in the global including the German population, the number of diabetics raised significantly in the last few decades. Overweight, physical inactivity, and poor social conditions have an impact on development of type 2 diabetes [30].

In terms of attributed conditions, DM increases the risk of Atrial fibrillation (AF). On the basis of a meta-analysis including more than 1.6 million participants, DM was crudely associated with a 40% increased risk for AF (RR, 1.39; 95% CI [1.10–1.75]) [110]. To control the risk factors mentioned above, an aggressive treatment of hypertension and the decrease of glycated hemoglobin A1c (HbA1c) are recommended to prevent cardiovascular complications [111], [112].

Diabetes mellitus can be considered as an independent risk factor for stroke. Each year, the risk is raising by 3% and triples with present diabetes of over 10 years [113]. Approximately 20% of all patients suffering from diabetes mellitus will die due to stroke [74].

2.2.3 Relation of diabetes mellitus and hypertension

Obviously, in some patients a number of adverse medical conditions come together. In terms of type 2 diabetes mellitus, two current meta-analyses analysed the effect of BP lowering in affected patients.
The first meta-analysis randomized a total number of 73,913 patients with diabetes mellitus in 31 intervention trials. The group of investigators around Reboldi et al. (2011) stated that an aggressive treatment decreased the incidence of stroke by 9% (p=0.006). Additionally, a lower as opposed to a less aggressive BP control diminished the stroke

risk by 31% (RR, 0.61; 95% CI [0.48–0.79]). Following the meta-regression analysis, the risk of stroke was reduced by 13% (95% CI [0.05–0.20); p=0.002) for each 5-mmHg reduction in SBP and by 11.5% (95% CI [0.05–0.17]; p<0.001) for each 2-mmHg reduction in DBP respectively [114].

In the second meta-analyses, Bangalore et al. (2011) investigated 37,760 patients with type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance with achieved SBP of $\leq$135 mmHg versus $\leq$140 mmHg. It could be underlined that intensive BP control was linked with a decrease of 17% in stroke and 10% in all-cause mortality (OR, 0.90; 95% CI [0.83–0.98]). A constant risk reduction for stroke to a SBP of <120 mmHg was observed. Nonetheless, a rise of 40% regarding serious adverse events with no benefit for other outcomes was visible at levels of <130 mmHg [115].

2.2.4 Dyslipidaemia

Total Cholesterol

Hypercholesterolaemia is defined as a total cholesterol level $\geq$240 mg/dL and a risk factor for heart disease (see 3.2.3) as well as stroke [116].

One man in three and one women in three show clear evidence of hypercholesterolaemia in Germany. The most frequently affected subjects are females aged 60 to 69 years. Hypercholesterolaemia tends to manifest earlier in males, already affecting around 25% in the age of 30 to 39 years [30].

An association between higher cholesterol levels and a raised risk of ischaemic stroke is reported in the majority of epidemiological studies.

The Multiple Risk Factor Intervention Trial (MRFIT) in more than 350,000 men already stated that the relative risk of death from non-haemorrhagic stroke raised linearly with increasing level of cholesterol [117]. The Asia Pacific Cohort Studies Collaboration (APCSC) (n=352,033 participants) reported an increase by 25% (95% CI [13-40]) in ischaemic stroke rates for every 1 mmol/L rise in total cholesterol [118].

In both, the Women's Pooling Project (n=24,343 US women <55 years, no previous cardiovascular disease) and in the Women's Health Study, a prospective cohort study (n=27,937 US women $\geq$45 years) higher cholesterol levels were also linked to increased risk of ischaemic stroke [119].

In contrast to this, some investigations could not reveal a clear connection between cholesterol and stroke risk [74].

In the ARIC study (n=14,175 middle-aged men and women, no previous CVD), the association between lipid values and incident ischaemic stroke was not strong [120]. Additionally, no connection between cholesterol and cerebral infarction could be underlined in the Eurostroke Project (n=22,183) [121].

All in all, epidemiological trials tend to emphasize a competing stroke risk associated with total cholesterol levels in the general population [56]. Considering the complexity of the association between total cholesterol and stroke, it should be underlined that there seems to be no positive relation between stroke mortality and total cholesterol [122].

High-density lipoprotein

The main part of all epidemiological studies report an inverse association between high-density lipoprotein (HDL) and stroke [123], [124], [125], [126]. Increased concentrations of HDL are significantly associated with a decreased accumulation of atherosclerosis (see also 3.2.3) within the arterial walls [127]. It removes fat molecules from macrophages, white blood cells engulfing and digesting cellular debris, in the wall of arteries.

In the Copenhagen City Heart Study, the Oyabe Study as well as in the Israeli Ischaemic Heart Disease Study, HDL cholesterol was also constistently inversely linked to ischaemic stroke [128], [124], [126]. The Northern Manhattan Stroke Study (NOMASS) revealed higher HDL cholesterol levels linked to decreased risk of ischaemic stroke [123]. In the Cardiovascular Health Study (CHS), high HDL cholesterol was related to a reduced risk of ischaemic stroke in males but not in females [129].

In contrast to this, the ARIC study reported no significant association between HDL cholesterol and ischaemic stroke [120]. A decreased risk of stroke ranging from 11% to 15% for each 10 mg/dL increase in HDL cholesterol was documented in a systematic review [130].

Low-density lipoprotein

Low-density lipoprotein (LDL) particles transport their content of fat molecules into artery walls and attract macrophages, thus increasing the risk of atherosclerosis [131].

In a pooled cohort analysis of the ARIC study and the CHS, lower levels of LDL cholesterol were inversely related to incident intracranial haemorrhage [58].

A meta-analysis of 22 trials including 134,537 patients analysed the association of LDL cholesterol lowered with statin therapy and major cardiovascular events including stroke [132]. The risk of major vascular events was decreased by 21% (95% CI [23–29]) for each 39 mg/dL reduction in LDL cholesterol. In accordance with these findings, for every 39 mg/dL decrease in LDL, there was a 24% (95% CI [5–39]) reduction in the risk of stroke.
Furthermore, another meta-analysis, including 14 trials reporting on stroke outcomes, found that the relative risk (RR) of stroke was significantly lower among statin recipients compared to the control group (RR, 0.83; 95% CI [0.74–0.94]) [133].

2.2.5 Atrial fibrillation

Atrial fibrillation is related to a four- to five-fold increased risk of ischaemic stroke due to embolism of stasis-induced thrombi formed in the left atrial appendage of the heart [134]. Treating AF is therefore a major major potential to prevent primary stroke [74].

On average, the absolute stroke rate ranges at 3.5% per year in 70 year-old subjects diagnosed with AF but the risk differs 20-fold among patients based on age and other clinical features [135], [136]. Additionally, AF can be seen as an independent predictor of increased mortality [137].

Until today, a significant minority of stroke related to atrial fibrillation can be seen without a prior diagnosis of the condition. There is a great number of studies concerning active screening for AF in patients >65 years of age in primary care surroundings. Those investigations state that pulse assessment by trained personnel helps to detect undiagnosed atrial fibrillation [138]. In addition to this, systematic pulse measurement in the course of routine clinic examinations combined with a 12-lead ECG in patients, who showed an irregular pulse, lead to a 60% increase of diagnosis [138].

Stroke risk stratification in atrial fibrillation patients

As soon as there is a set diagnosis of AF, an estimation of an individual's risk for cardioembolic stroke and for haemorrhagic complications of antithrombotic therapy is needed. In order to be able to estimate risk of AF-related cardioembolic stroke, more

than a dozen risk stratification schemes have been published based on numerous combinations of clinical and echocardiographic predictors [136]. Finding the balance between advantages and risks of long-term antithrombotic therapy in primary stroke prevention is crucial [74].

As the treatment of choice for patients at high risk of cardioembolic stroke and acceptably low risk of haemorrhagic complications, dose-adjusted warfarin was commonly chosen. It can be stated that treatment with dose-adjusted warfarin strongly protects against stroke (RR reduction, 64%; 95% CI [49–74]). Essentially, this leads to an elimination of the immense risk of ischaemic stroke linked with AF if the intensity of anticoagulation is sufficient. Additionally, this approach resulted in a reduction of all-cause mortality by 26% (95% CI [3–23]) [139]. Furthermore, anticoagulation decreased stroke severity and post-stroke mortality [140]. In comparison to aspirin, dose-adjusted warfarin reduced stroke by 39% (95% CI [22–52]) [139].

2.2.6 Physical activity

For Germany, figure 2.1 shows the proportion of men and women who practise sport for two and more hours a week. According to the 2003 Telephone Health Survey, 37.4% of males and 38.4% of females above the age of 18 practised no sports at all. An additional 20.9% of men and 28.4% of women were active in some kind of sports for less than two hours a week. The remaining 41.7% (male) and 33.2% (female) announced that they are physically active for two or more hours a week. The proportion of such relatively highly active persons was highest in early adulthood, whereas only little fluctuation could be stated for middle-aged people. Participation rates fell quite rapidly after the age of 70 at the latest [141].

In this connection, a recent study to inactivity among US adults stated that every hour per day of increased television watching was associated with 0.15 kg of greater weight gain every four years. This was also true the other way around. Every hour per day of decreased television watching was linked with a similar amount of relative weight loss [142].

An enormous amount of adverse health effects are linked to physical inactivity. In this line, an increased risk of total as well as specific cardiovascular mortality and morbidity due to stroke was published. A number of meta-analyses underline that physically active people tended to show a 25% to 30% decreased risk of stroke or death compared to

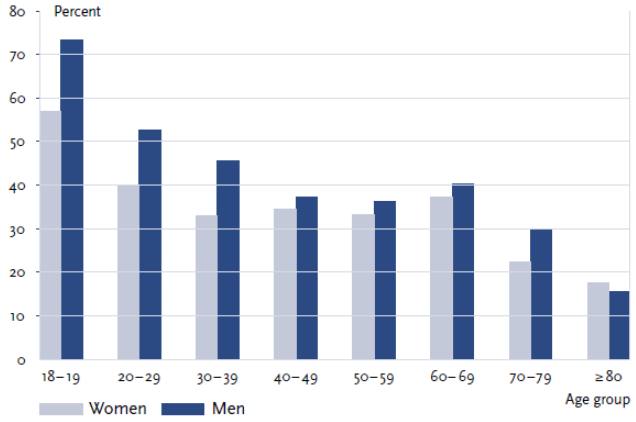

Figure 2.1
Proportion of men and women who practise sports for two and more hours a week in Germany [30].

the least active men and women [143]. A meta-analysis of 23 studies on the association of physical activity (PA) with stroke, for instance, reported that high (RR, 0.79; 95% CI [0.69–0.91]) and moderate (RR, 0.91; 95% CI [0.80–1.05]) levels of activity compared with low levels of movement were inversely associated with the likelihood of developing stroke. This included both, ischaemic and haemorrhagic stroke [144].

The major gains seem to derive from diverse types of activity which include occupational activity, leisure time physical activity as well as fast walking. Until today, studies are rare regarding race and ethnicity [145].

It remains unclear, how the intensity as well as amount of physical activity affects stroke risk. A gender interaction can be assumed. An increased gain in women following greater intensity was reported in the Physical Activity Guidelines Advisory Committee Report. The median RR was 0.82 for all stroke types for moderate-intensity activity versus no or light activity. By comparison, the RR for high-intensity versus no or light activity was 0.72. In the male population, no apparent benefit of greater intensity with median RR 0.65 for moderate-intensity versus no or light activity and a RR 0.72 for high-intensity versus no or light activity was stated [146].

It is assumed that the protective effect of physical activity is partially driven by its impact on diminishing risk factors for CVD [147], including diabetes [148] and excessive body weight. Additionally, anti-inflammatory elevations in plasma tissue plasminogen activator activity and HDL cholesterol concentrations as well as decreased plasma fibrinogen and platelet activity have also been discussed [149].

In summary, overwhelming evidence from prospective observational studies underlined that routine physical activity can prevent stroke. Regarding the Physical Activity Guidelines for Americans, at least 150 minutes per week of moderate intensity or 75 minutes per week of aerobic physical activity with vigorous intensity, or an equivalent combination are recommended. In this context, it has to be emphasized that some physical activity is better than none, as any extent of physical activity leads to health benefits [146].

2.2.7 Diet and nutrition

An individual's energy balance, or consumption of total calories appropriate for needs, is determined by the balance of average calories consumed versus expended. This balance is driven by multiple factors. Those include the calories consumed, age (see 2.1.2), sex (see 2.1.1), physical activity (see 2.2.6), body size, and underlying basal metabolic rate.

Table 2.2 summarizes the consumption of selected groups of food and beverages in inhabitants aged 18 to 79 years in Germany [150].

Changes in intake of different foods and beverages were associated with weight gain on the long-term in divergent ways. Refined grains, starches, and sugars as well as red and processed meats are most positively associated with weight gain. By contrast to this, increased consumption of whole grains, fruits, vegetables, nuts, and yogurt, was linked to relative weight loss over time. Those findings suggested to focus on dietary quality, not simply counting total calories, as crucial for a healthy energy balance [142]. Additional weight gain involved greater television watching including greater snacking in front of the television due to the influence of advertising on poor food choices and the lack of physical activity [142]. Additionally, lower average sleep duration had a significant negative impact on an individual's energy balance [142], [151].

A US national survey from 2008 stated that energy-dense snack foods and beverages were present in 96% of pharmacies, 94% of gas stations, 22% of furniture stores, 16% of apparel stores, and 29% to 65% of other types of investigated stores [152].

In the context of energy balance, the size of a meal played an important role. Preferences for portion size were associated with the socioeconomic status, body mass index (BMI), eating in fast food restaurants, and television watching [153]. In Germany, the turnover per year in fast food rose from €2 billion to almost €6 billion during the 1990s. In

Table 2.2
Consumption of selected groups of foods in grams per day in Germany [150].

	Men		Women	
	Median	Percentile 25–75	Median	Percentile 25–75
Food				
Bread	168	121–224	121	89–160
Cereal/grain	45	23–81	39	21–68
Pastries	28	12–53	23	10–42
Leaf vegetables	26	10–51	29	14–54
Cabbage vegetables	38	21–60	39	23–61
Other vegetables	139	95–204	140	93–207
Potatoes	130	85–181	98	63–136
Fruit	145	71–238	177	107–281
Cakes	20	5–45	21	7–42
Confectionery	38	19–67	31	17–52
Dairy products	229	133–401	219	138–352
Eggs	19	10–31	16	8–26
Meat	102	68–145	69	45–99
Poultry	13	6–26	13	6–22
Sausage & sausage products	54	30–82	27	13–44
Fish	16	7–28	14	5–24
Animal fats	10	5–20	8	4–15
Vegetable fats	15	10–23	12	8–18
Beverages				
Beer	143	18–429	0	0–29
Wine	8	0–56	11	0–41
Coffee	340	121–600	340	150–534
Juices and squashes	54	0–232	61	1–195
Lemonade and pop	161	0–471	146	0–396
Drinking water	500	150–986	595	293–1000

comparison, the amount spent on meals in restaurants remained constant at €50 billion [154].

In industrialized countries, dietary supplements gain more and more popularity. In 2010, approximately half of US adults used $\geq$1 dietary supplement. The most common supplements were multivitamin-multimineral products. The intake of supplements was linked to older age, higher education, greater physical activity, lower BMI, moderate alcohol consumption, and restraint from smoking [155].

In a pooled analysis of 25 randomized trials in a study population with and without hypercholesterolaemia, nut consumption led to significantly improved blood lipid levels [156]. A mean consumption of 67 g of nuts per day reduced the total cholesterol by 10.9 mg/dL (5.1%), LDL cholesterol by 10.2 mg/dL (7.4%), and the ratio of total cholesterol to HDL cholesterol by 0.24 (5.6% change; $p<0.001$ for each). Interestingly, different types of nuts showed comparable effects.

The following section shall delve deeper into the association of diet and risk of stroke.
A high BP can be seen as one of the most dominant modifiable risk factor for ischaemic stroke as discussed above (see 2.2.1). A large body of studies underlined the association between aspects of diet and the pathogenesis of high BP [56].

A scientific statement issued by the AHA showed an increased BP following high alcohol consumption, excess salt intake, low potassium intake, suboptimal dietary pattern as well as excess weight [157]. It was emphasized that blacks are especially sensitive to elevated BP effects resulting from low potassium and high salt intake as well as suboptimal diet. A major decrease of these racial disparities in BP and stroke can be achieved by dietary modifications [157].

Fruits and vegetables

Figure 2.2 illustrates the consumption of fruit and vegetables by 18 to 79 year olds in Germany. The proportion of persons consuming more than 400 grams of fruit and vegetables per day, excluding juices, are displayed below [150].

Observational studies reported multiple relationships between diet and the risk of stroke. A strong inverse association between servings of vegetables, fruits, and consecutive stroke were stated [158]. Servings of fruits and vegetables less than three times per day were compared to people who consumed three to five servings. It could be shown that the relative risk of ischaemic stroke was less in the second group (RR, 0.88; 95% CI

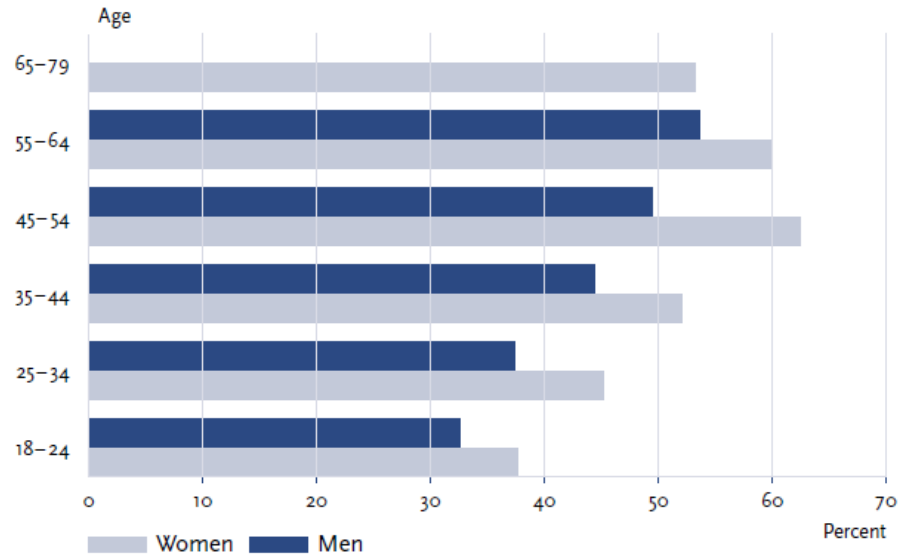

Figure 2.2
Consumption of >400 grams fruit and vegetables in Germany [150].

[0.79 to 0.98]) and even more pregnant in those consuming more than five servings per day (RR, 0.72; 95% CI [0.66-0.79]) [159].

The relative risk of incident stroke was 0.69 (95% CI [0.52-0.92]) for participants in the highest versus lowest quintile of vegetable and fruit intake published in analyses of the Nurses' Health Study and the Health Professionals' Follow-Up Study [159].

In this context, it has to be kept in mind that the recommended daily consumption of fruits and vegetables is at an average intake of >5 servings per day [160].

Sodium and potassium intake

As mentioned above, the level of sodium intake should be considered as well. Following the Dietary Guidelines for Americans report, a sodium intake of <100 mmol/d for the general population is indicated.

Epidemiological [161] and prospective studies [162] underlined the association between a raised sodium intake and an elevated risk of stroke.

Additionally, a potassium intake of at least 120 mmol/d is recommended. An increased level of potassium intake led to a reduced risk of stroke in prospective studies [163]. Regarding those results, the context of the mentioned studies has to be kept in mind. A

large number of methodological limitations, followed by difficulties in estimating dietary electrolyte intake as well as inhibited risk assessment could result in false-negative or even paradoxical findings in observational studies. It can be assumed that the impact of potassium and sodium on stroke elevation may be influenced by both, direct effects on BP and independent aspects of BP [164].
Especially in dose-response clinical trials, the association between sodium intake and BP was described as a direct and progressive relation without an apparent threshold [165]. A higher sensitivity of BP-decreasing effects by less sodium consumption were apparent in middle- and older-aged adults, blacks, and people diagnosed with hypertension [166].

Dairy products

Having had a closer look at milk products, a higher consumption of this kind of merchandise is associated with lower incidence of diabetes mellitus and trends toward lower risk of stroke [156], [167]. Some evidence suggests that these associations are stronger for low-fat dairy or milk than for other dairy products but these results have to be considered as still limited [52].

It is evident that low-fat dairy products, a diet rich in fruits and vegetables, and decreased in saturated as well as total fat diminishes the BP [168].

2.2.8 Overweight and obesity

In Germany, approximately 50% of all men and 33% of women adults are overweight. In addition to this, a further 17% of men and 20% of women suffer from obesity [30]. The total number of overweight and obese inhabitants is increasing since the mid-1980s.

Forecasts for 2030 suggest that 51% of the Northern American population will be obese, with 11% of severe obesity, marking an increase of 33% for obesity and 130% for severe obesity [169].

The traditional but also more and more criticized classification of weight status can be defined by the body mass index. It is calculated by weight in kilograms divided by the square of an individual's height in meters. Following the general classification, a BMI of 25 to 29.9 kg/m^2 indicates overweight, people revealing a BMI $\geq$30 kg/m^2 are registered as obese [170]. Specifications include the measurement of abdominal obesity by either waist circumference or the waist-to-hip ratio.

A waist circumference >102 cm in men and >88 cm in women is clinically defined as abdominal obesity. Until today, the prevalence rates of obesity and overweight are raising alarmingly in developed countries, affecting children as well as adults [171].

In a collaborative analysis of data from 57 prospective studies which mainly refer to Western Europe and North America, overall mortality was lowest at a BMI of approximately 22.5 to 25 kg/m^2 in both sexes and at all ages, after having adjusted for smoking status. Above this range, each higher BMI by 5 kg/m^2 was associated with a 30% higher all-cause mortality [172].

In a meta-analysis of 1.46 million white adults, all-cause mortality was stated to be lowest at BMI levels of 20.0 to 24.9 kg/m^2 over a mean follow-up period of ten years [173]. Obesity was correlated with significantly increased mortality caused by CVD and DM. An association of 13% of CVD deaths could be revealed in 2004 [174].

Recent estimates suggest that reductions in smoking, cholesterol, BP, and physical inactivity levels resulted in a gain of 2,770,500 life-years. In contrast to this, these gains were diminished by a loss of 715,000 life-years caused by the increased prevalence of obesity and DM [175].

Focusing on the association between weight and incident stroke, a meta-analysis published a nonlinear relation between BMI and mortality [172]. In the BMI range of 25 to 50 kg/m^2, each 5 kg/m^2 increase in BMI was linked to a 40% heightened risk of stroke mortality. No relationship between BMI and stroke mortality in the lower BMI range (15-25 kg/m^2) could be detected.

Studies that investigated the effects of BMI and abdominal body fat showed that abdominal body fat predicted stroke risk more efficiently than the BMI [176], [177].

Usually, the direct relationship of BMI and stroke has been endured in multivariable analyses, controlling other cardiovascular risk factors as blood lipids, BP, and diabetes/insulin resistance. It has to be mentioned that the strength of the association is decreased in general. This leads to the conclusion that the effect of BMI on stroke risk is partly mediated by the impact of adiposity on other stroke risk factors [56].

A great number of studies have investigated the mechanisms of weight reduction on BP in non-hypertensive as well as hypertensive subjects. A mean decrease of 4.4 mmHg in SBP and 3.6 mmHg in DBP could be stated due to an average weight loss of 5.1 kg [178].

2.2.9 Cigarette smoking

In Germany, approximately 33% of all inhabitants aged ≥18 years do smoke, with 25.4% smoking daily and 7.1% occasionally. A further 26.9% reported to be former smokers. Taken together, nearly 60 percent of the German population smoke or used to smoke [179]. Table 2.3 gives an overview by gender and age.

Table 2.3
Percentage of regular smokers, occasional smokers, former smokers, and persons who have never smoked in Germany [179].

	Women					Men				
	18–29	30–44	45–64	65+	Gesamt	18–29	30–44	45–64	65+	Gesamt
Regular smoker	33.6	29.3	22.0	5.1	21.9	39.3	36.0	26.1	11.8	29.2
Occasional smoker	11.0	7.4	5.3	2.4	6.1	14.4	8.3	6.9	3.8	8.1
Former smoker	14.6	24.1	25.5	21.2	22.3	14.7	23.9	38.2	52.1	31.8
Never smoked	40.8	39.2	47.2	71.3	49.7	31.5	31.8	28.8	32.4	30.9

Short exposures to second-hand smoke can lead to blood platelets becoming stickier, a decrease of coronary flow velocity reserves, and a damage of the lining of blood vessels. All those factors can potentially increase the risk of an acute myocardial infarction.

In this context, it has to be emphasized that pooled data from 17 studies in Europe, North America, and Australasia suggested that a smoke-free legislation can diminish the incidence of acute coronary events by 10% [180].

Virtually every multivariable investigation of stroke risk factors, e.g. the Framingham heart study [20], the Cardiovascular Health Study [181], and the Honolulu Heart Study [182], stated smoking as a major risk factor for ischaemic stroke. Worldwide, tobacco smoking, including secondhand smoke, was one of the top three leading risk factors for disease in 2010 [183], doubling the risk for ischaemic stroke. Smoking was estimated to contribute to 6.2 million deaths [183], causing approximately 467,000 adult deaths (19.1%) in the United States. It is assumed that one third of these deaths were related to CVD [184].
Stroke risk is altered through acute impact on the risk of thrombus generation in atherosclerotic arteries and chronic effects associated with increased atherosclerosis [185].

Overall, the risk for smokers to suffer from stroke during their life span is twice as high compared to individuals who never smoked [186], [187]. Recent estimates indicate that approximately 19% of the burden of stroke is based on current smoking [188].

A meta-analysis composed of 32 studies estimated the relative risk for ischaemic stroke to be 1.9 (95% CI [1.7-2.2]), for ICH 0.74 (95% CI [0.56-0.98]), and for SAH 2.9 (95% CI [2.5-3.5]) for smokers versus non-smokers [189].

A reliable association between cigarette smoking and ischaemic or haemorrhagic stroke respectively was observed in the younger population. In the United States, smoking seemed to contribute to 12% to 14% of all stroke deaths [190].

Furthermore, smoking can potentiate the influence of other stroke risk factors, such as SBP [191], oral contraceptives [192], and vital exhaustion [191].

Apart from active smoking, the exposure to environmental tobacco smoke can be seen as an established risk factor for heart disease [193]. The major extend of risk related to environmental tobacco smoke seems unexpected, as this dose is considerably lower than for active smoking. Physiological studies assume that there is a tobacco smoke exposure threshold rather than a linear dose-effect association [194].

The most effective prevention is evidently to never smoke and to minimize exposure. Being a smoker, risk is decreased with smoking cessation. This measure is associated with a rapid reduction in risk of stroke and other cardiovascular events. Although, the risk is diminished, it does not reach the level of those who never touched a cigarette [185]. Generally, smokers quitting smoking at 25 to 34 years of age gained ten years of life compared with those who continued to smoke. Additionally, those aged 35 to 44 years aquired on average nine years and those aged 45 to 54 years attained six years of life [186].

A large number of efficient programs aiming at smoking cessation are available. To date, studies documenting the relation between the participation in these projects and a long-term reduction in stroke are still pending [56].

Tobacco control policies that aim at smoking cessation should be a key feature of stroke primary prevention programs. This is especially fundamental in low- and middle-income countries, as those regions carry the greatest dual burden of tobacco exposure and increasing stroke rates [195].

2.2.10 Acute myocardial infarction

A meta-analysis reviewing population-based studies issued between 1970 and 2004 reported that the risk of ischaemic stroke after AMI was 11.1 per 1,000 (95% CI [10.7–11.5])

during the index hospitalization, 12.2 per 1,000 (95% CI [10.4–14.0]) at 30 days, and 21.4 (95% CI [14.1–28.7]) at one year after AMI [196]. The following risk factors were found to be associated with an increased stroke risk: advanced age (see 2.1.2), hypertension (see 2.2.1), diabetes mellitus (see 2.2.2), AF (see 2.2.5), and congestive heart failure.

The Warfarin, Aspirin Reinfarction Study (WARIS) showed that warfarin in combination with aspirin or given alone, compared with aspirin alone, led to a reduction of the risk of thromboembolic stroke. However, at the same time, it was associated with a greater risk of bleeding [197].

A meta-analysis analysing data of ten randomised trials that focused on the efficacy of warfarin after AMI evaluated a stroke incidence over five years of 2.4%. Furthermore, warfarin decreased the risk of stroke (OR, 0.75; 95% CI [0.63–0.89]) but again increased the risk of bleeding [198]. Clinically, the CHA2DS2-VASc score (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke or TIA or thromboembolism - Vascular disease, Age, Sex Category) will enable a decision on a therapy with warfarin.

2.2.11 Others: oral contraceptives

The association of risk of stroke, particularly ischaemic stroke, with the use of OCs continues to be controversial. The current guidelines for the primary prevention of stroke issued by the American Heart Association/American Stroke Association (ASA) do not go into detail any more [74]. The previous version summarizes that the risk of stroke in association with use of OCs is low [56]. The combination of certain factors, like older age, smoking cigarettes, obesity, hypertension, diabetes, and hypercholesterolaemia are supposed to lead to higher relative and absolute risk. The controversial nature bases on estimates that primarily derive from case-control and a smaller number of cohort studies. Consequently, those trials are limited by a small numbers of females with stroke events. In women without additional risk factors, the incremental risk of stroke related to the use of low-dose OCs, if one exists, appears to be low [199].

Other risk factors like the sickle cell disease or asymptomatic carotid artery stenosis will not be further discussed, as those variables are not relevant in the context of this thesis.

2.3 Less well-documented or potentially modifiable risk factor

The last text section gives an overview of less well-documented or potentially modifiable risk factors such as alcohol intake. This variable is also included in the present study.

2.3.1 Alcohol consumption

In 2003, the general alcohol consumption rate in Germany was 147 l, or in other words 10.2 l of pure alcohol, more than 50% of which was consumed in beer. Wine and spirits each made up a fifth of total consumption [200]. Per capita consumption, which is estimated in terms of pure alcohol consumption, nearly quadrupled over the period of the 1950s to the early 1990s. In comparison to many other EU countries, like the United Kingdom or the Netherlands, Germany has ranked as one of the countries with the highest alcohol consumption for years [30].

It is evident that excessive alcohol consumption can result in various medical complications. Obviously, this also includes the occurrence of stroke [56]. A conclusive body of literature documents the association of intensive alcohol consumption and an increase in blood pressure [201].

A great number of studies underlined that heavy consumption of alcohol can be seen as a risk factor for all subtypes of stroke [202]. In this context, a J-shaped relationship between alcohol and the risk of total as well as ischaemic stroke is reported. This pattern attributes that light to moderate drinkers have less risk than abstainers, while heavy drinkers are at the highest risk. Few or moderate drinks, particularly in the form of wine, showed a protective effect whereas the risk was fundamentally raised by heavy alcohol consumption [203]. Contrarily, a linear connection between alcohol consumption and risk of haemorrhagic stroke was stated [204].

An effect of light to moderate consumption of alcohol was linked to lower fibrinogen concentrations [205], increased insulin sensitivity, and glucose metabolism [206], greater levels of HDL cholesterol [207] as well as reduced platelet aggregation [208]. Hypercoagulability, reduced cerebral blood flow, hypertension, and increased risk of atrial fibrillation can be the consequence of heavy alcohol consumption [205].

A meta-analysis including 35 observational studies [204] stated that a consumption of 60 g of alcohol per day led to a 64% rise of stroke risk (RR, 1.64; 95% CI [1.39-1.93]), a 69% increase in ischaemic stroke (RR, 1.69; 95% CI [1.34-2.15]), and a risk twice as high of haemorrhagic stroke (RR, 2.18; 95% CI [1.48-3.20]). In contrast to this, drinking <12 g of alcohol per day showed a reduced risk of total stroke (RR, 0.83; 95% CI [0.75-0.91]) and ischaemic stroke (RR, 0.80; 95% CI [0.67-0.96]), with consumption of 12 g to 24 g per day associated with a decreased risk of ischaemic stroke (RR, 0.72; 95% CI [0.57-0.91]).

A Finnish study described a strong association between the frequency of alcohol consumption and stroke mortality. This finding was independent of total amount of alcohol consumption. The risk of stroke death was the most pronounced in males who consumed alcohol >2.5 times per week [209].

The performance of prospective clinical studies investigating the diminished risk by reduction of heavy alcohol consumption or the benefits by light alcohol consumption are not feasible as it is well established that alcohol dependence can be considered as a major health problem [74].

In this context, it clearly had to be mentioned that data on alcohol consumption are generally based on questionnaire information. This approach, which is also applied in the present study, may lead to misclassification of exposure status, which should not be neglected. This incorrect classification may have induced biased estimates of the association between alcohol consumption and risk of stroke. Bots et al. (2002) therefore consider an underestimation of the true magnitude of the association [201]. An alternative approach to questionnaires could be the measure of the serum level of gamma-glutamyl transferase as an unbiased although not perfect marker [210].

2.3.2 Others: drug abuse, migraine

Drug abuse

Social and health-related problems often occur in the context of drug addiction as a chronic, relapsing condition [211].

An association between cocaine, heroin, amphetamines, and elevated stroke risk was reported [212]. These drugs can lead to a great number of threatening conditions including acute and severe BP elevation, vasculitis, cerebral vasospasm, haematologic,

and haemostatic abnormalities. They contribute to raised blood viscosity and platelet aggregation, embolization caused by infective endocarditis as well as ICH [213], [214].

Insights regarding stroke-related drug abuse are based on epidemiological studies in urban populations. An elevation in the risk of both ischaemic and haemorrhagic stroke was reported [215]. A cross-sectional study of hospitalized patients showed that amphetamine abuse was linked to haemorrhagic stroke (adjusted OR, 4.95; 95% CI [3.24-7.55]) but not to ischaemic stroke. Additionally, cocaine abuse was found to be associated with haemorrhagic stroke (OR, 2.33; 95% CI [1.74-3.11]) and ischaemic stroke (OR, 2.03; 95% CI [1.48-2.79]). Only amphetamine abuse could be linked to an increased risk of death after haemorrhagic stroke (OR, 2.63; 95% CI [1.07-6.50]) [215].

The evaluation of the clinical utility of screening tests for drug abuse in primary care settings, like toxicology tests of blood or urine, the application of standardized questionnaires to screen for drug use or misuse are still unsatisfactory. Until today, studies are needed to address the independent risk of stroke in association with specific drugs of abuse. No controlled trials exist revealing a decrease in risk of stroke following abstinence [56].

Migraine

Most consistently, migraine headache has been associated with stroke in young women. This was particularly observed in those female patients suffering from migraine with aura [216]. A meta-analysis of 13 case-control and eight cohort studies stated an overall pooled RR of 2.04 (95% CI [1.72–2.43]) [217]. Additionally, an increased risk of ischaemic stroke was reported in migraine with aura (pooled adjusted OR for seven studies, 2.51; 95% CI [1.52–4.14]) compared with migraine without aura (pooled adjusted OR for six studies, 1.29; 95% CI [0.81–2.06]). Furthermore, another meta-analysis of nine studies, including six case-control and three cohort studies, stated a pooled RR of 1.73 (95% CI [1.31–2.29]) between any migraine and ischaemic stroke [69]. Again, the researchers reported a significantly increased risk of stroke among individuals with migraine with aura (RR, 2.16; 95% CI [1.53–3.03]) compared with no aura (RR, 1.23; 95% CI [0.90–1.69]; meta-regression for aura status, p=0.02).
It has to be clearly underlined that the significant risk affecting women (RR, 2.08, 95% CI [1.13–3.84]) but not men (RR, 1.37; 95% CI [0.89–2.11]) was reported. Females younger than 45 years (RR, 3.65; 95% CI [2.21–6.04]), who smoked (RR, 9.03; 95% CI [4.22–19.34]) and used OC (RR, 7.02; 95% CI [1.51–32.68]) showed a further increased

risk [69]. The two mentioned meta-analyses are in general agreement with studies published earlier [218].

A huge amount of research has been conducted over the last decade to enlighten the association between ischaemic stroke subtypes and the numerous risk factors described above. Nevertheless, further studies are required to clarify the interaction of modifiable variables alone and in combination with non-modifiable risk factors, and the discrepancies in ischaemic stroke incidence. More and more concise research indicates that approximately 80% of stroke events could be reduced by making simple lifestyle modifications [219]. A more in-depth understanding of these distinctions will enable and bring forward more effective stroke prevention programs in high-risk groups.

The population-based cohort Rotterdam study found that in the investigated cohort about half of all strokes are attributable to established causal and modifiable factors. This finding reassures not only to conduct intervention on established etiological factors but also to carry out further study on less well-established factors [220].

2.4 Early risk assessment in stroke by the Framingham Stroke Risk Profile

A major contribution of the Framingham study involves the application of a number of statistical developments to support and facilitate risk prediction in creating a quantitative scale. This scale helps to calculate the probability of developing a stroke during a specific time period. The so-called Framingham Stroke Risk Profile has been widely implicated as a clinical tool for estimating stroke likelihood by applying patient data available to an office-based health care professional. Recent trends in the prevalence and impact of risk factors as well as current findings such as familial occurrence of stroke are incorporated into an updated modification of the Framingham Stroke Risk Profile on an ongoing basis [221]. In Europe, the CHA2DS2-VASc Score is mainly used for clinical assessment.

2.5 Risk factors for transient ischaemic attack

Until today, the evidence of risk factors for TIA excluding ischaemic strokes is very limited [43]. The ABCD2 score (Age, Blood pressure, Clinical features, Duration of TIA,

and presents of Diabetes) was developed to estimate individual risk and to determine potential patients on the first presentation (see figure 2.3 [222]). The US National Stroke Association indicates that the score is optimized to predict the risk of stroke within two and 90 days after TIA. The score is calculated by summing up points for five independent factors, namely age, blood pressure, clinical features, duration of TIA, and presence of diabetes [223].

Risk Factor	Points	Score
Age		
≥ 60 years	1	☐
Blood pressure		
Systolic BP ≥ 140 mm Hg *OR* Diastolic BP ≥ 90 mm Hg	1	☐
Clinical features of TIA (*choose one*)		
Unilateral weakness with or without speech impairment *OR*	2	☐
Speech impairment without unilateral weakness	1	
Duration		
TIA duration ≥ 60 minutes	2	☐
TIA duration 10-59 minutes	1	
Diabetes	1	☐
Total ABCD ^{2} **score**	0-7	☐

Figure 2.3
ABCD2 score [222].

In a current review on prognostic TIA, the crude rate of stroke risk for the general population was 1.7% at day two, 4.8% at week one, 6.6% at one month, 8.5% at three month, and 11.4% at six months. By comparison, for hospital patients was 13.7% at one month and 12.4% at three months, respectively [43].

There is very limited evidence regarding an association between family history of stroke and the incidence of stroke after TIA. This leads to the assumption that a positive family anamnesis of stroke does not conclusively predict the risk of ischaemic stroke after TIA [43].

3 Risk factors for coronary heart disease focusing on myocardial infarction

Following the chapter on risk factors for stroke, the upcoming section will provide an overview of distinct differences and similarities regarding an increased risk for MI. This review of current literature enables a deeper understanding of the selection of risk factors for myocardial infarction in the INVADE study (see chapter 7).

As also seen in the outline of stroke risk factors, there are numerous well-established risk factors leading to atherosclerosis and plaque formation resulting in MI. These include male gender (see 3.1.1), age (see 3.1.2), family history (see 3.1.3), hypertension (see 3.2.1), diabetes (see 3.2.2), dyslipidaemia (see 3.2.3), and smoking (see 3.2.4). Furthermore, the list of less well-established factors contains obesity (see 3.3.2), metabolic syndrome, and chronic kidney disease.

In addition to this, potential triggers for AMI comprise of extreme physical inactivity (see 3.3.3), excessive alcohol intake (see 3.3.4), psychosocial conditions, the use of illicit drugs such as cocaine, amphethamines, and nonsteroidal drugs [5].

The percentage of patients with a first MI, who will experience stroke within five years is 2% of men and 6% of women at 45 to 64 years of age and 5% of men and 8% of women at $\geq$65 years of age [224]. In the following, crucial disparities and connections in risk factors for MI regarding stroke will be stated, where applicable.

The term coronary heart disease (CHD) encompasses the following conditions: stable angina, unstable angina, myocardial infarction, and sudden coronary death. As those conditions are commonly discussed together in literature and not always clearly separated, a general overview of CHD focusing on MI will be given in the following section.

Based on pooled data from 1986 to 2007 reported in the FHS, ARIC, and CHS, 19% of men and 26% of women at $\geq$45 years of age were reported to die within one year after they had their first MI [224]. Additionally, within five years after a first MI, 36% of males and 47% of females were documented to die aged $\geq$45.

The Behavioural Risk Factor Surveillance System (BRFSS) analysed data from 14 US states regarding the alertness of warning signs for heart attack. Only 27% of all participants (n= 71,994) were aware of five warning signs and symptoms. Addressed was firstly, pain in jaw, neck, or back, secondly, weakness, light-headedness, or faint, thirdly, chest pain or discomfort, fourthly, pain or discomfort in arms or shoulder and lastly, shortness of breath. Significant variation in the percentage of subjects being aware of all five heart attack warning signs and symptoms, and calling the ambulance as their initial action varied by educational status [225].

The following chapter will delve deeper into the field of risk factors which are protective determinants for cardiovascular health. The well supported concept of ideal cardiovascular health is defined by the presence of firstly, ideal health behaviours, namely not smoking, body mass index <25 kg/m^2, physical activity at goal levels described below (see 3.3.3), and following a diet consistent with current guideline recommendations (see 3.3.1). Secondly, ideal health factors, which are untreated total cholesterol <200 mg/dL (see 3.2.3), untreated blood pressure <120/<80 mmHg (see 3.2.1), and fasting blood glucose <100 mg/dL (see 3.2.2) [226] should be focussed.

3.1 Generally non-modifiable risk factors

3.1.1 Sex

Coronary heart disease was stated to be the leading cause of death among women in both developed and developing countries [227]. The incidence of CHD is significantly lower among women than men prior to the age of 50 years. After this time the risk for CHD among women raises and approaches the risk reported among men by the age of 80 [228]. Women have their first acute MI approximately nine years later than men. Despite the fact that the Framingham study described risk factors for CHD in women, the study population was limited to white Caucasians living in the US. The authors could not thoroughly explain the observed later age of first occurrence of MI among women [229]. The measurement of only a limited number of risk factor can have led to this restraint. It

is widely believed that the advanced age in female MI incidence is based on protective effects of female sex hormones. Additionally, different habits in diet and smoking may also play a fundamental role [230].

The INTERHEART study, a global case–control study including 52 countries, found nine modifiable risk factors that explained more than 90% of acute MI across all major ethnic groups in both young and older individuals. This was reported for both, men and women [231]. Smoking (OR 2.87 for current vs. never having smoked), history of hypertension (OR 1.91), diabetes (OR 2.37), abdominal obesity (OR 1.12 for top vs. lowest tertile and OR 1.62 for middle vs. lowest tertile), psychosocial factors (OR 2.67), daily consumption of fruits and vegetables (OR 0.70), regular alcohol intake (OR 0.91), and routine physical activity (OR 0.86) were all significantly related to acute myocardial infarction with $p<0.0001$ for all risk factors and $p=0.03$ for alcohol. The authors concluded that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, low consumption of fruits and vegetables, high alcohol intake, and rare physical activity explain most of the worldwide risk of myocardial infarction in both sexes and at all ages in all regions. As a result, methods of prevention can be based on similar principles globally. This has a huge potential in preventing a large number of premature cases of myocardial infarction [231].

A sub-sequent analysis of those nine risk factors, which were more strongly associated with MI in women, were comprised of diabetes, hypertension, alcohol consumption, and physical activity. In contrast to this, only former smoking was more strongly associated with MI in the male population. On the other hand, the association of current smoking, psychosocial factors, consumption of a high-risk diet, and abdominal obesity with MI did not reveal any significant gender difference. Generally speaking, the listed risk factors were more strongly associated with acute MI in subjects <60 years by comparison to older individuals, aged $\geq$60 years. Delving deeper into the specifics among women, hypertension, current smoking as well as diabetes were more strongly associated with MI in younger compared to older ages. In the male population, abdominal obesity, current and former smoking, hypertension but not diabetes were more strongly linked to MI in younger compared to older men. In this connection, Anand et al. (2008) found that the beneficial and protective effects of physical activity as well as regular alcohol consumption and MI were stronger among older versus younger men [232].

These findings are consistent with previous investigations stating that the determinants of CHD among women are relatively similar to those among men [233], [234]. Specifics regarding the listed potential risk factors will be stated below.

3.1.2 Age

Increasing age is regarded as the most significant risk factor for CHD. Individuals aged older than 45 years have a greater risk for AMI, which is considered to be eight times higher compared to younger individuals. In this context, it has to be kept in mind that less than 10% of patients who have AMI are aged younger than 45 years [235].

As women have MIs at older ages than men, they are more likely to die of MI within a few weeks [224], as described in the section regarding gender differences above (see 3.1.1).

3.1.3 Genetic factors and family history

It can be stated that individuals with a family history of ischaemic heart disease in a first-degree relative have a higher risk for AMI [5]. Familial accumulation of CVD may be allied with the aggregation of specific behaviours such as smoking and consumption of alcohol or specific risk factors like hypertension, DM, and obesity. Those factors themselves may have genetic and environmental contributors [236]. The presence of paternal history of a heart attack has been reported to almost double the risk of a heart attack in men and raise the risk in women by approximately 70% [237].

Family history of CVD plays an important role in the understanding of the disease complex as well. Among a huge number of large-scale prospective epidemiology trials, the Framingham Heart Study emphasized a strong and significant relation of a reported family history of premature parental CHD with incident MI or CHD in its descendants [237]. Additionally, family history of premature MI is also an independent risk factor in other multivariable risk models that contain traditional risk factors. This has been reported in large female [238] and male cohorts [239].

Apart from family history, genetics are more and more explored. In the European-derived populations, the most consistently reported genetic marker for heart disease is located at 9p21.3. It can be stated, that at this single-nucleotide polymorphism, approximately 27% of the white population is estimated to have zero risk alleles. Furthermore, 50% are supposed to have one risk allele and the remaining 23% are predicted to have two risk alleles [240].

The same 9p21.3 region has also been associated with ischaemic stroke (see 2.1.3) [241].

3.2 Well-documented modifiable risk factors

The following passage will describe well-known risk factors for MI, which can be modified.

3.2.1 Hypertension

Recent results from the Harvard Alumni Health Study stated that higher BP in early adulthood was associated several decades later with higher risk for all-cause mortality, CHD, and CVD mortality [242].

Focusing on myocardial infarction, about 69% of people who experienced a first heart attack had a BP >140/90 mmHg. The same condition was observed for 77% of those who had a first stroke [52].

Several trials addressed the awareness of a patient's hypertensive condition, which is an essential part in the prevention of AMI. Data from NHANES (2007 to 2010) revealed that 81.5% of all subjects were aware of their condition, 74.9% were under current treatment, 52.5% had their hypertension under control, and 47.5% did not have it controlled. Awareness of hypertension was lower in the age group 18 to 39 years than among those aged 40 to 59 years or $\geq$60 years of age [243].

Finally, to get a better understanding of the future impact, it may be advisable to check on upcoming expenses. For 2010, the estimated direct and indirect expenses of HBP were $46.4 billion. By 2030, the total cost of HBP could increase to an estimated $274 billion based on methodology stated in Heidenreich et al., 2011 [244].

3.2.2 Diabetes mellitus

Diabetes mellitus is another major risk factor for CVD and stroke [245]. Consequently, it is also associated with a higher risk of AMI [5]. Following AHA guidelines, identified untreated fasting blood glucose levels of <100 mg/dL for adults can be attributed to one of the seven components of ideal cardiovascular health [226].

Diabetic subjects are at higher risk of suffering from myocardial infarction and have worse outcomes compared to individuals without diabetes. The underlying pathophysiology of the atherosclerotic process is comparable to non-diabetic subjects. Nevertheless, the prothrombotic and procoagulant state with which diabetes is accompanied is assumed

to add to the increased incidence of and worse prognosis after MI [246]. Type 2 diabetes is present in 10% to 30% of patients presenting with MI [247].

Finally, a look at the resulting cost is appropriate. The expenditures of DM were estimated up from $174 billion in 2007 at $245 billion in the year 2012. Of these costs, $176 billion were direct medical costs, while $69 billion resulted from individual's diminished productivity. Inpatient care attributed to 43% of these expenses [248]. In general, the medical costs for patients with DM were 2.3 times higher than for those without DM after having adjusted for age and sex [108].

3.2.3 Dyslipidaemia

Dyslipidaemia can clearly be attributed to one of the most important risk factors of AMI. This is based on the fact that elevated serum levels of LDL cholesterol and non–HDL cholesterol significantly raise the risk of AMI. HDL value of less than 40 mg/dL is a risk factor for atherosclerosis, too [235].

High cholesterol is consistently repeated as a major risk factor for CVD and stroke [116]. The AHA has identified untreated total cholesterol <200 mg/dL as one of the seven components of ideal cardiovascular health for adults (see also 2.2.4) [226]. More detailed information on dietary cholesterol and other factors that affect blood cholesterol levels can be found in the chapter on diet and nutrition regarding MI (see 3.3.1).

It can be stated that treatments aiming at lowering LDL levels in dyslipidaemic patients are effective in preventing AMI. Beneficial LDL levels are 80 mg/dL or less in patients with atherosclerosis and 100 mg/dL or less in asymptomatic patients with high risk for CHD. According to the 2007 American College of Cardiology/American Heart Association guideline for management of patients with STEMI, the recommended LDL cholesterol level should be substantially less than 70 mg/dL [249].

3.2.4 Cigarette smoking

Cigarette smoking can be seen as a major risk factor for atherosclerosis and therefore for AMI. The resulting risk is directly proportional to the number of cigarettes smoked per day [235].

There are several preventive measures supported by the American College of Cardiology and the American Heart Association. Lifestyle modifications such as smoking cessation are stated as one of the most essential preventive measures of AMI. To quit smoking for six months has already been found to reduce the dysfunction of coronary endothelium in AMI patients. Two years after cessation, the risk of AMI drops by remarkable 50% [235].

There is a sex differential in the burden of smoke which may further expand as the detrimental effects of smoking are stronger for women in some diseases. This encompasses lung cancer and CHD [250]. A recent overview underlined the excess risk of smoking-related CHD to be 25% higher in women than in men [251].

It stands to reason that some of the pathways mediating the relation between smoking and coronary risk are more sensitive to the anti-oestrogenic effect of smoking than those controlling the connection between smoking and stroke risk. For instance, decreased oestrogen levels in smokers are considered to have a negative impact on components of the lipid profile, which is a major risk factor for CHD and, to a lesser extent, for stroke. This results in elevations in total cholesterol and triglycerides while lowering levels of HDL cholesterol [252].

In this line, atherosclerosis and plaque formation shall be only mentioned, as these risk factors are not actively considered in the present study.

3.3 Less well-documented or potentially modifiable risk factors

The following section leads to less well-documented or potentially modifiable risk factors like for example obesity (see 3.3.2), the amount and type of physical activity (see 3.3.3), or alcohol consumption (see 3.3.4). Additional variables such as metabolic syndrome, psychosocial conditions, and chronic kidney disease shall just be mentioned here.

3.3.1 Diet and nutrition

As dietary habits affect a broad range of established and recently discovered risk factors [52], they shall be described in the following.

A large number of meta-analyses underlined that each daily serving of fruits or vegetables was associated with a 4% lower risk of CHD (RR, 0.96; 95% CI [0.93–0.99]) and a 5% lower risk of stroke (RR, 0.95; 95% CI [0.92–0.97]) [253]. Additionally, greater whole grain intake (2.5 compared with 0.2 servings per day) was linked with a 21% lower risk of CVD events (RR, 0.79; 95% CI [0.73–0.85]). Similar estimates in men and women were reported for various outcomes including CHD and stroke [254].

Furthermore, regularly consumption of nuts was associated with significantly lower incidence of CHD (comparing higher to low intake: RR, 0.70; 95% CI [0.57–0.82]) [255].

In addition to these findings, refined grain intake was not associated with lower risk of CVD (RR, 1.07; 95% CI [0.94–1.22]) [256]. In a meta-analysis analysing data of 16 prospective cohort studies including 326,572 generally healthy individuals in Europe, the United States, Japan, and China, fish consumption led to a significantly lower risk of CHD mortality [254]. Contrasted with no consumption, an estimated 250 mg of long-chain omega-3 fatty acids per day was linked with 35% lower risk of CHD death ($p<0.001$).

In regards of the consumption of meat, unprocessed red meat was not significantly associated with incidence of CHD. By contrast, each 50 g serving per day of processed meat, which is sausage, bacon or deli meats, correlated with a higher incidence of CHD (RR, 1.42; 95% CI [1.07–1.89]) [257]. In a meta-analysis including 442,101 participants and 28,228 DM cases, unprocessed red meat consumption was linked with a higher risk of DM (RR, 1.19; 95% CI [1.04–1.37], per 100 g/d) [258]. For associations between DM and MI see 3.2.2.

Having had a closer look at dairy products, no significant higher or lower risk of CHD was reported [255]. There was an independent association between the regular consumption of sugar-sweetened beverages and higher incidence of CHD, with 23% and 35% increased risk with 1 and $\geq$2 servings per day, respectively, compared with an intake of <1 per month [259].

As already stated in the section about nutrition and stroke (see 2.2.7), a meta-analysis of 15 prospective cohort samples revealed that each 1.64 g/day higher potassium intake was linked with a 21% lower risk of stroke (RR, 0.79; 95% CI [0.68–0.90]) and trends toward lower risk of CHD and total CVD [260].

In summary, societal and environmental factors are independently associated with energy imbalance in terms of weight gain. This is driven through either increased intake of calories or decreased expenditure. Education, income, race/ethnicity, and local conditions in the environment like the availability and types of grocery stores, types of restaurants,

safety, parks and open spaces, and walking or biking paths are closely linked with this aspect [261].

Taken together, most of those findings combined in one dietary pattern, namely the Mediterranean diet, characterized by higher intakes of vegetables, legumes, nuts, fruits, whole grains, fish, and unsaturated fat as well as lower intakes of red and processed meat, was associated with a 22% lower cardiovascular mortality (RR, 0.78; 95% CI [0.69–0.87]) [262], risk of weight gain, continued CHD, and stroke [263].

How fundamentally important the focus on nutrition in relation to vascular health is, becomes obvious when underlining the impact on mortality. In the year of 2010, a total of 678,000 deaths of all causes were attributable to suboptimal diet [52].

An overview of the costs of miscellaneous strategies for primary prevention of CVD emphasized that the estimated costs per year of life gained were between $20 to $900 for population-based healthy eating and approximately $1,500 for lifestyle advice [264]. More than $33 billion in medical costs and $9 billion in lost productivity resulting from heart disease, stroke (see 6.1.5), cancer, and diabetes mellitus were assigned to poor nutrition [265].

3.3.2 Overweight and obesity

Overweight and obesity attribute to the major risk factors for CVD and stroke (see 2.2.8) [266], [267], [268]. Patients with a BMI of $\geq$30 have a higher risk of AMI [235]. The AHA has identified <25 kg/m^2 for adults aged $\geq$20 years as one of the seven components of ideal cardiovascular health as mentioned above [226].

Those observations have a crucial impact on future generation's morbidity. Overweight children and adolescents are at increased risk for developing adverse health effects over their life span. Those include a higher prevalence of traditional cardiovascular risk factors such as hypertension (see 3.2.1), DM (see 3.2.2), and hyperlipidaemia (see 3.2.3) and result in associated health conditions like AMI and stroke [269]. Additionally, this could lead to poorer school performance, tobacco smoking (see 3.2.4), alcohol use (see 3.3.4), poor diet (see 3.3.1), as well as premature sexual behaviour.

If this current trend in weight gain continues, total healthcare costs attributable to obesity could reach up to $957 billion by 2030. This would account for 16% to 18% of all US health expenses [270]. The total excess expenditures due to the current prevalence

of adolescent overweight and obesity are approximately $254 billion. This estimated amount is composed of $208 billion in lost productivity secondary to premature morbidity and mortality as well as $46 billion in direct medical costs [271].

3.3.3 Physical activity

Another of the major risk factors for CVD is physical inactivity [272]. Leisure-time physical activity has been associated with a lower risk of AMI among lean, normal-weight, and overweight patients (BMI 25-25.9), respectively [235]. Light to moderate leisure time activities performed regularly, like working in the garden and intensive walking, are recommended.

Physical activity has been stated to decrease the risk of CHD by lowering haemostatic and inflammatory biomarkers such as C-reactive protein. Additionally, decreasing blood pressure, lipid levels as well as increasing insulin sensitivity are essential [5].

In terms of morbidity and mortality, physical inactivity is responsible for 12.2% of the global burden of MI after accounting for other CVD risk factors such as abdominal obesity (see 3.3.2), cigarette smoking (see 3.2.4), diabetes mellitus (see 3.2.2), hypertension (see 3.2.1), psychosocial factors, lipid profile (see 3.2.3), and no alcohol intake (see 3.3.4) [231].

In summary, a large number of longitudinal studies stated a graded and inverse association of PA amount and duration with incident CHD and stroke [273]. The economic consequences of physical inactivity are fundamental. Concise WHO data sources concluded that the expenses of physical inactivity account for 1.5% to 3.0% of total direct healthcare expenditures in developed countries [274].

3.3.4 Alcohol consumption

Alcohol moderation and prevention of illicit drug use are important in the prevention of cardiac conditions [235]. Currently issued European guidelines on cardiovascular disease prevention in clinical practice recommend to limit the consumption of alcoholic beverages to two glasses per day (20 g/day of alcohol) for men and one glass per day (10 g/day of alcohol) for women [275].

Considerable epidemiologic evidence linked moderate alcohol consumption to a reduced risk of CHD and stroke. Especially red wine seems to be protective for cardiovascular diseases [276].

It has to be kept in mind that alcohol consumption is associated with many potentially confounding factors [277]. As a result, it is difficult to address the causal effect of alcohol consumption on CVD risk in observational studies. Long-term randomized controlled trials assessing the impact of regular alcohol consumption on hard cardiovascular endpoints are unlikely to be ever conducted.

3.4 Early risk assessment in myocardial infarction

A person's overall risk for CHD can be evaluated for example by administering his or her cardiac risk factors in specific equations based on large cohort series as reported in the Framingham study.

The US Preventive Services Task Force does not recommend routine screenings for CHD in patients with low or even moderately increased risk. This recommendation includes the routine use of methods like resting ECG or exercise treadmill test to screen for evidence of coronary atherosclerosis or prediction of CHD events in persons without significantly increased risk [278].

There are additional methods to detect CVD. Carotid intima-media thickness is considered to be one of the most widely used and well-validated subclinical CVD measures. This approach has also been implemented in the present study. Ultrasound is applied to quantify the thickness of the intimal and medial layers of the carotid artery and quantify plaque in the carotid artery, as applied in the present study. Both, plaque ultrasound and carotid intima-media thickness measures are highly reproducible and significantly associated with later CVD events. This connection was even observed among low-risk populations [279].

3.4.1 Framingham scoring

The Framingham Risk Scoring (FRS) is based on the patient's age, sex, smoking history, blood pressure, and total and HDL cholesterol [280] (see figure 3.1).

Age:	Years
Gender:	Female Male
Total cholesterol:	mmol/L
HDL cholesterol:	mmol/L
Smoker:	Yes No
Diabetes:	Yes No
Systolic blood pressure:	mm Hg
Is the patient being treated for high blood pressure?	Yes No

Figure 3.1
Framingham Risk Scoring [281].

Until today, it has been validated in various samples [282], [283]. The scoring serves an estimate of the ten-year risk for CHD [284], [283]. Additionally, it is incorporated into current cholesterol treatment guidelines [280]. In this context, it clearly has to be considered to involve an individual's socioeconomic status (SES) in the risk assessment. Omission of socioeconomic position (SEP) involvement might bias CHD risk assessment of patients with lower SES [285]. Based on FRS alone, individuals of higher and lower SES had a predicted CHD risk of 3.7% and 3.9%, respectively. The observed risks for each group were 3.2% and 5.6%. After having added SES to the model, the predicted risk estimates became 3.1% for those with higher and 5.2% with lower SES. As a result, inclusion of SES in the model resulted in upgrading of the risk classification for 15.1% of low-SES participants (95% CI [13.9-29.4]). This integration would consequently contribute to reduce the bias.

3.4.2 Prevention of myocardial infarction

Measures for preventing AMI can be compared with those generally recommended for preventing the development of CHD. Consequently, they embrace lifestyle modifications such as quitting smoking, being engaged in regular exercise, and making dietary adjustments. As described above, the control of comorbidities like hypertension, diabetes mellitus, and hypercholesterolemia are crucial in addition to this. Lastly, an appropriate patient education is fundamental (see 9).

3.4.3 Population at risk

Physicians can by instance identify the population at risk based on the ten-year risk of CHD occurrence related to the FRS. The risk should be calculated in all patients with two or more revealed risk factors. Individuals showing $\geq$2 risk factors, who are found to have high ten-year risk, would benefit the most from primary prevention [235]. In this context, it is decisive to determine patients with CHD and those with risk equivalents to launch secondary prevention schemes [235]. Patients, their relatives, and the public should be educated properly, especially on how to detect and respond to an episode of AMI [235].

4 Influence of socioeconomic position in life

This chapter presents a broad list of indicators of a person's socioeconomic position included in this study and discusses their origins. The present overview will give a description of what the factors intend to measure as well as how data are commonly elicited in health research. This will help to better understand and adequately categorizes the reported results in chapter 5 on the specific impact of a person's SES on stroke and MI.

Additionally, strengths, limitations, and a life course approach of these variables will be discussed.

4.1 Preliminary considerations

The term socioeconomic position is a frequently used concept in epidemiological and health research. Even though researchers have an intuitive sense of what factors SEP involve, the various ways of measurement reveal the complexity of the construct. A huge variety of other terms, such as social or socioeconomic status, social class, and social stratification are commonly used interchangeably [286]. Nevertheless, it has to be kept in mind that their theoretical bases and, therefore, interpretations might defer significantly [287].
A person's socioeconomic position describes the social and economic factors that have an influence on the kind of positions an individual or groups hold within the structure of a society [287], [288]. These concepts enclose divergent historical and disciplinary origins, which will briefly be discussed here. SEP is linked to various resources, exposures, and susceptibilities that may have an effect on health [286].

It has to be clearly stated that there is no single best indicator of SEP applicable for all study aims and appropriate at every time point in all clinical trials. Each indicator is based on particular measures and may be more or less relevant to diverse health outcomes. Additionally, it might vary at different stages in a person's life course.

Ideally, the choice of SEP measure should therefore be based on consideration of the specific research question and the proposed mechanisms associating SEP with the outcome. This is the case, when SEP is assumed to be a confounding or mediating variable and the exposure of interest. On the other hand, if the aim of the study is to investigate the existence of a socioeconomic gradient in a specific health outcome then the choice of indicator may not be decisive [286]. If an isolated measure of SEP shows an association with an addressed health outcome, it will not encompass by default the completeness of the effect of SEP on health. It clearly has to be kept in mind that this aspect is of particular importance in case SEP is considered a potential confounding factor. To address this issue, multiple SEP indicators, by preference collected across the course of life, could attribute to avoid residual confounding by unmeasured socioeconomic circumstances [289].

The following chapter delves deeper into the theoretical basis, measurement, and interpretation. Additionally, strengths and limitations of each indicator considered in this study will be discussed. Figure 4.1 displays examples of indicators measuring life course socioeconomic position [290].

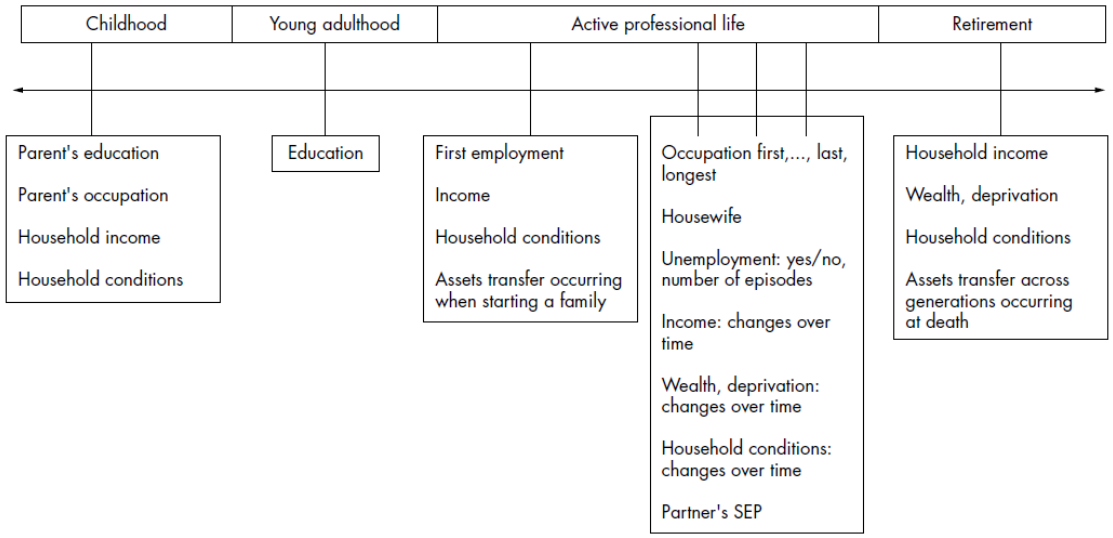

Figure 4.1
Examples of indicators measuring life course socioeconomic position [290].

4.2 Theoretical origins

A large number of the concepts underlying the use of SEP in epidemiological research are based on the understanding of two formative social theorists, namely Karl Marx and Max Weber. In Marx's work, SEP was exclusively determined by "social class", in which individuals were defined by their relation to the "means of production" (e.g. land and factories). The social class and class relations were typified by the inherent conflict between exploited workers and the exploiting capitalists, who controlled the means of production. Regardless of the fundamental political weight of Marxist ideology in the 20th century, there are only two classifications employed in epidemiological research that are based on Marx's theory of social class [291]. The first is the Erik Olin Wright's classification [292]. The second refers to categorizations developed in South America [293].

As opposed to Marx, who was convinced that social stratification in capitalist societies were both, source and outcome of the conflict between two necessarily opposed social groups, Weber's theory followed the approach that society is hierarchically stratified along numerous dimensions. This assumption led to the creation of groups whose members share a common market position, resulting in shared "life chances". In Weber's concept, market position is not inevitably singularly defined by Marx's class relations [291].

In summary, theories about the association between health and socioeconomic status substantially focus on three mechanisms [294]. The first approach is a materialist one, basically stating that those with higher incomes are able to purchase higher quality of nutrition, better housing, live in safer environments, and also have better access to health care. The second underlines behavioural or so called lifestyle factors. In this category alcohol consumption, smoking, dietary habits, and appropriate use of and admission to health care can be stated. Those factors may vary with cognitive skill and access to information. The third approach supports the idea of impact of psychosocial factors such as empowerment as well as relative social integration and social status. Those aspects subsume the exposure to stresses that may derive from low status and little autonomy in important areas of life, such as work or housing environment [295]. Behavioural concepts generally relate more closely to education, while occupational characteristics or measures of relative deprivation might be applied to reveal psychosocial links between socioeconomic status and health [295].
In this connection, it clearly has to be kept in mind that all these indicators are interrelated.

None of them gathers completely the domains identified as fundamental in the theoretical literature. In other words, such an approach may be over simplistic. In practical application, all three approaches, taken together with others discussed below, are commonly utilized in analyses of health inequalities [296]. In a large number of studies, these highly correlated measures are practically applied interchangeably, despite the fact that this may hamper efforts to comprehend how social position influences health [297]. One aspect the majority of the studies have in common, is the fact that their use for analyzing older populations is troublesome [295].

4.3 Education

4.3.1 Theoretical basics

Education is a commonly used marker in epidemiologic studies. The employment of education as an SEP indicator historically goes back to the status domain of the Weberian theory [298] and its endeavor to capture the knowledge related to the property of an individual [288]. In this context, it has to be kept in mind that formal education is usually completed in young adulthood and can be conceptualized within a life course framework as an index that partly measures early life SEP [299], [294]. Additionally, it is strongly influenced by parental characteristics.
Education and therefore the ability to make an informed choice has been used as a reliable measurement of socioeconomic status based on the following advantages. Firstly, it is stable and becomes established in early adulthood as mentioned above. Secondly, it is not modified by chronic illness in later adulthood and lastly, it is easy to measure [300].

4.3.2 Measurement

There are several possible approaches how to measure a person's educational level. It can be addressed as a continuous variable, in terms of years of completed education, or as a categorical factor by assessing educational achievements such as completion of primary or high school, higher education diplomas or degrees, as in this study. The continuous measure is based on the assumption that every year of education contributes similarly to a person's attained SEP and that time spent in education has greater importance

than educational landmarks. In contrast to this, the categorical approach understands that specific achievements are crucial in identifying the individual SEP [298].

4.3.3 Interpretation

Although education is commonly involved as a generic measure of SEP, there are particular interpretations to clarify its association with health outcomes [301], [298], [302].

Firstly, education captures the transition from parents' received SEP to the own adulthood SEP. It can also be seen as a significant predictor of future employment and income [294],[288], [303]. Consequently, educational level displays intellectual, material, and other resources derived from the family of origin.
Secondly, the knowledge and skills developed through educational procedures and experiences may affect a person's cognitive functioning. It could make an individual increasingly receptive to health related education messages or enable a facilitated communication with and access to adequate health care services as well as a better compliance.
Measuring of knowledge in terms of "cultural literacy" and assessing its role in the association between education and health might result in substantial difficulties in analysing specific effects of education and knowledge on health [304], [305].
Thirdly, poor health in childhood can lead to reduced educational attendance and/or achievement and predispose to adult disease. This might provoke a health selection impact on health inequalities [306].

4.3.4 Strengths and limitations

Comparatively, education can be straightforward captured in self-administered questionnaires and usually leads to a high response rate. Additionally, it is pertinent to people disregarding their age or working conditions, unlike many other SEP indicators [298]. Moreover, the age leaving full-time education is unaffected by poor health in adulthood [290]. Educational attainment can be reliably recalled and is easily quantified.
The meaning of educational position differs for different birth cohorts. Along with secular trends in improving educational attainment, there have been substantial changes in educational opportunities for women, as in this study, and some minority groups over the last decades. Such cohort effects can be crucial but are often not taken into account in epidemiological trials. Consequently, the findings from studies that include years of

education or educational qualifications that incorporate participants from numerous birth cohorts may be biased if cohort effects are not considered. Older cohorts will therefore be over-represented among those classified with lower education [307].

Additionally, education must be seen in a culturally specific context. A further limitation of educational levels exists if individuals have obtained their education outside the country of residence [286]. This circumstance has no relevance in the present study, as the addressed cohort has mainly attained its education in the area of Ebersberg.

Lastly, measuring the number of years of education or levels of attainment does not always contain information about the quality of the educational experience. This is decisive if conceptualizing the role of education in health outcomes particularly related to cognitive skills, knowledge, and analytical capacities. It may be of less importance when considering education as a broad indicator of SEP [286].

4.4 Marital status

A wealth of evidence underlined a protective effect of marital status and/or cohabitation on long-term mortality and other health outcomes in a large body of trials in general populations [308]. In general, mortality rates were increased among unmarried individuals even after adjusting for registered socioeconomic and health variables which are assumedly selecting people into and out of marriage [309].

4.4.1 Theoretical basics

Marriage has been hypothesised to have protective effects for longevity through a variety of interconnected variables, with a greater overall marriage advantage for men compared to women [308].
Influencing pathways might be financial resources, social integration, support and control, as well as social role attainment [308]. Social integration into the family, community, educational facilities like schools, and religious institutions through marriage has contributed and continues to create a sense of meaning, obligations regarding others, purpose, and belonging [310]. A stable relationship adds to socioemotional support, establishing a greater resilience to stress and physiological strain [311]. In addition to this, a solid partner may assist in the monitoring of health, adherence to treatment, health-related

behaviours, and lifestyle adaptions [312].
In the financial point of view, marriage might contribute to a greater family income and general wealth, allowing advances in medical care and higher quality of diet [310].

4.4.2 Measurement

Data usually derives from official sources, such as a country's census bureau, survey interviews or self-administered questionnaires. These investigations usually apply data in which marital status and other covariates are documented in cross-sectional surveys up to a decade before mortality exposure. Another option is the usage of data from panel surveys with much smaller sample sizes [308].

4.4.3 Interpretation

A tendency to a decreasing influence of marital status has been suggested as the institution of marriage becomes less prevalent in more and more societies. In some areas it has been superseded by unmarried cohabitation [313]. In contrast to this, a recent review stated, persistent with cross-national comparative findings, a widening mortality difference between married and unmarried individuals in high-income countries over recent decades [308]. The replacement of marital status with cohabitation bears a comparable strata-specific beneficial effect [314].

4.4.4 Strengths and limitations

In such a complex system as marriage, involving and influencing that many facets of life, additional impact of unobserved characteristics cannot be precluded as at least a partial explanation. Future efforts to model such selection are warranted. Another limitation is the fact that prospective studies of mortality tend to use household survey data. This might lead to biased findings by the omission of older individuals in institutions such as nursing homes [308]. To summarise, effects of marital status on health may not only be specific to time, culture, and region, but may also depend on the disease. Generalizability of previous findings must therefore be considered with caution. To get a deeper understanding, disease- and region-specific investigations are needed [314], as in the present study.

4.5 Housing conditions and social environment

4.5.1 Theoretical basics

Housing characteristics measure material features of socioeconomic circumstances. Generally speaking, housing based indicators are applied in industrialized and non- industrialized countries. The characteristics assessed might diverge significantly based on the addressed setting and be exceedingly specific to the area where they were developed. Howden-Chapman et al. (2004) investigated housing standards and their association with health [315]. Houses and neighborhood can be seen as an exceedingly practical setting for public health action. By their nature, they integrate both, private and public interests [315]. The following aspects are more directly linked with SEP.

4.5.2 Measurement

The most widely collected characteristic is housing tenure. This factor describes if the house is owner occupied, in terms of owned outright, being bought with a mortgage, rented from a private or social landlord. Ownership might be more present in rural areas [316].
Additionally, household amenities can be taken into account as well. Those commonly include owning a telephone, refrigerator or washing machine, access to hot and cold water and central heating, sole use of bathrooms and toilets and whether the toilet is inside or outside the home. These amenities serve as markers of material circumstances in different cohorts and geographical areas. They may also go along with specific mechanisms of disease. An example for this would be that the lack of running water and no toilet might be related to an increased risk of infection indicating low standards of hygiene [316].
In this study, the focus was on the number of people living together in one household.

4.5.3 Interpretation

Housing related factors are primarily markers of material conditions. Housing characteristics are commonly the key component of most people's wealth. They mainly attribute to expenses issued from a person's income. Generally, this factor is an essential, multidimensional

indicator of SEP, and is in some cases difficult to interpret. As mentioned above, some housing circumstances may be direct exposures or markers of exposures for specific diseases.

4.5.4 Strengths and limitations

Defined characteristics of a cohort's housing and amenities are extensively used as measures of SEP. Those factors are relatively easy to collect and may also lead to indications of special mechanisms relating SEP to specific health outcome. Their main restraint is that, although addressing the same basic concept, these indicators may be specific to the temporal and geographical background where they have been created. As a consequence, it is challenging to compare them across trials [286].

4.6 Occupation based measures

4.6.1 Theoretical basics

Occupation based indicators of SEP are also widely used in epidemiological research.
Occupation can be seen in accordance with Weber's notion of SEP as a reflection of a person's place in society, related to their social standing, capability of mind, and earnings (see 4.2) [291]. In this study, the former occupation as well as current employment status were addressed.
Furthermore, it describes working relations between an employer and his employees. There is also the possibility of a characterization of an individual as exploiters or exploited in class relations [286].

4.6.2 Measurement

The majority of studies consider the current or longest held occupation of a person to characterize their adult SEP. This study approaches the occupational level in the same way.
Nevertheless, with increasing interest in the role of SEP across the life course, some trials encompass parental occupation as an indicator of childhood SEP in conjunction

with individuals' occupations at different stages in the person's adult life [317]. In some cases, the occupational measures can be expanded and transferred. The measures from one person or the combinations of several individuals can be used to describe the SEP of others connected to them. For instance, "highest status occupation in the household" or the occupation of the "head of the household" can serve as an indicator of the SEP of dependents, as children, spouse or the household as a unit [286].

4.6.3 Interpretation

Specific aspects of SEP measure different occupational classification schemes. Admittedly, it might be demanding to detach those specific effects of individual indicators. In the following, a number of more general mechanisms that may explain the association between occupation and health related outcomes are addressed.
First, the occupation, may it be parental or own adult, is strongly associated with income. Consequently, a relation with health might be one of a direct relation between material resources, meaning the monetary and other tangible compensations for work that influences material living standards, and an individual's health condition. Next, the occupational status represents social standing and may be linked with health outcomes due to certain benefits and privileges that are provided by higher standing. Examples for this could be an easier admission to better health care, access to education as well as more beneficial residential facilities. In this line, a higher educational level enables a wider range of career opportunities going along with a greater understanding of health related behaviour.
Thirdly, occupation can reflect social networks, work based stress levels, work-related control, and autonomy. Through this, health outcomes may also be influenced by psychosocial processes [286].
Finally, occupation may also involve specific toxic environmental or work task exposures such as physical demands (e.g. laborer or transport driver), benefits, or disadvantages going along with particular occupational groups [286].

4.6.4 Strengths and limitations

A substantial strength of these measures is their availability in many routine data sources. This includes census data and death certificates. Occupation can be used as an indicator of social status, power, education, and income [290]. In this study, it was also addressed

using a self-administered questionnaire.
The potential subjectivity and inconsistency of these ranking systems has always to be kept in mind. Occupation may be affected and determined by poor health in adulthood [290].
One major limitation of occupational indicators is that they cannot readily be assigned to individuals who are momentarily unemployed. If used as the only source of information on SEP, socioeconomic differentials may be underestimated through the exclusion of a number of participants [318]. Overgeneralization can easily lead to a rejection of retired people, people whose work is at home, which is mainly affecting women/housewives, students, unemployed people as well as individuals working in informal, unpaid or illegal jobs [286]. In the present study, there is a large group of housewives, whose occupational level has to be considered accordingly.
Furthermore, there are groups that might be less readily defined or willing to disclose their occupation [286].

4.7 Life course socioeconomic position

As described above, there is strong and further increasing evidence that unfavourable SEP in early years, independently of adult SEP, is a strong predictor of adult illness [299], [317]. A large number of prospective trials suggest a higher mortality among those who undergo adverse socioeconomic position at different periods of life. A huge variety of mechanisms have been discussed to explain these associations [319]. Coronary heart disease and ischaemic stroke seem to be affected by components acting across the entire life span, resulting in a rather cumulative risk model [294], [320].

In summary, figure 4.2 shows a model of the causal paths through which the socioeconomic level could influence risk and outcomes.

4.8 Concluding remarks

An individual's SEP can be seen as the key to delve deeper into and to better understand inequalities in health. It is best considered as an umbrella term for a range of indicators and co-dependent approaches. Across the life course, time and place, based on an

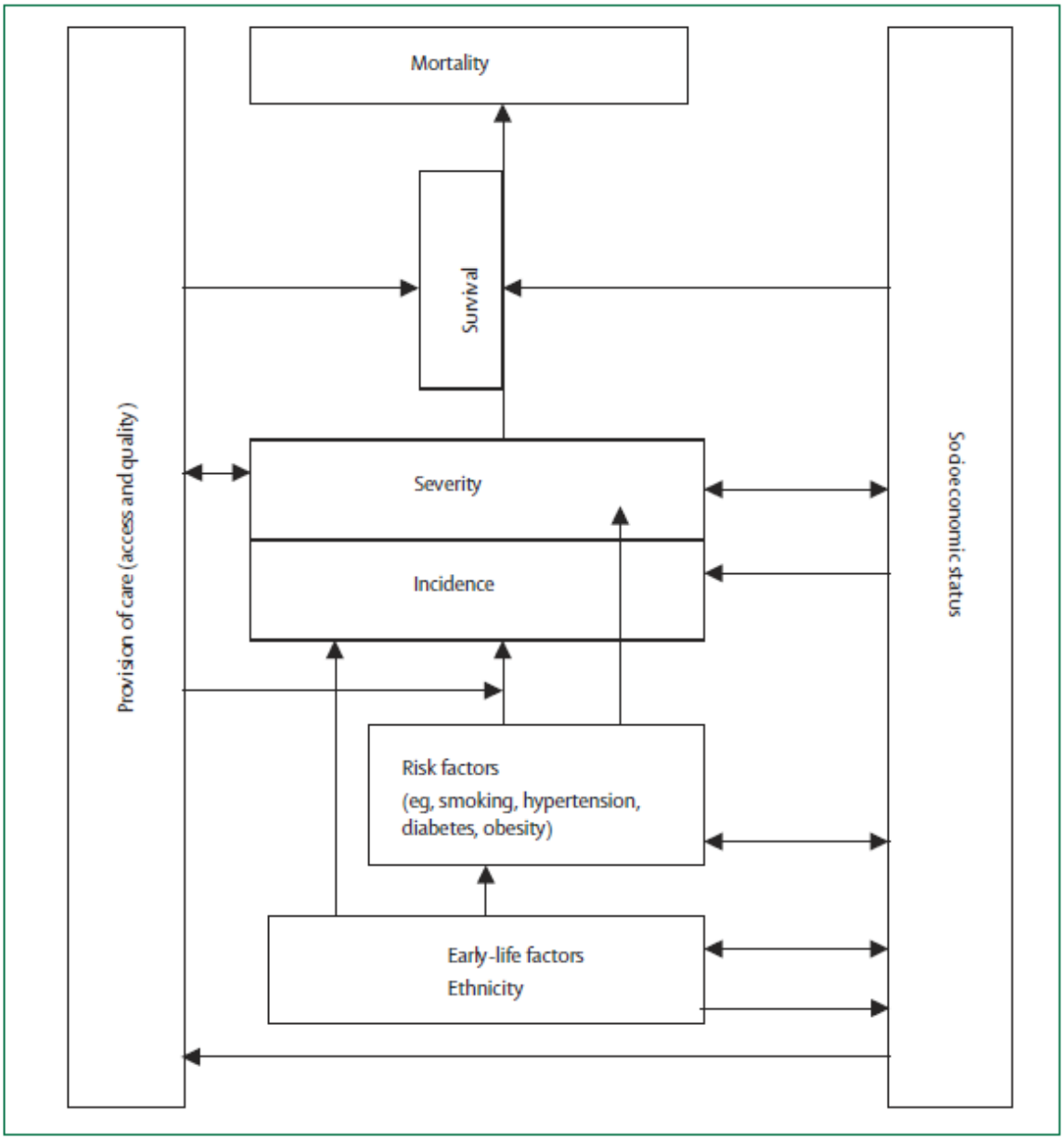

Figure 4.2
Model of the causal pathways of socioeconomic status affecting risk and outcomes [290].

individual and on the whole, numerous studies have shown how socioeconomic disadvantage is related to poorer health outcome [321].

Most work on inequalities in health related context has been conducted in developed countries, leading to indicators appropriate in this environment. Further research is necessary to develop indexes that might be more applicable in clinical settings in developing countries [286].

The starting point for a more complete etiological insight of socioeconomic health differentials should consequently be based on mechanistic specificity of relations between particular SEP indicators, as discussed above, and diverse health outcomes. As a result, this approach enables us to get a deeper understanding of the mechanisms of educational background, marital status, housing conditions, and occupational group that generate socioeconomic inequalities in the incidence of ischaemic stroke, ischaemic stroke including TIA as well as myocardial infarction in the community-based cohort in Ebersberg, Germany.

After having discussed the extensive impact of SES on an individual's health and wellbeing in general, the following chapter will focus on the specific influence of a person's socioeconomic position on stroke and MI, describing active mechanisms. This overview of current literature will provide a basis for discussion in chapter 9.

5 Socioeconomic position in stroke and myocardial infarction

The following chapter will describe current findings regarding the association of socioeconomic status, stroke, and myocardial infarction. As little is known about the impact of SEP on transient ischaemic attack specifically, this shall be subsumed under stroke itself.

5.1 Association of stroke and socioeconomic position

5.1.1 General socioeconomic position

People in low socioeconomic groups have an elevated risk of stroke [290], even in egalitarian European countries [322]. For Germany, Helmert et al. (1993) found increased numbers of cardio-cerebrovascular diseases in lower social classes [323]. It can clearly be stated that the social disparity in stroke has persisted over time, regardless of the overall decline in the stroke mortality rate [324] (see 1.3).

The majority of clinical studies attempting to explain the basis for the socioeconomic gradient in stroke state that risk of stroke is reduced after taking account of conventional stroke risk factors [325], [326], [327], [328]. Even though, a significant excess risk in the lower socioeconomic classes frequently endures [329], [328].

Studies focusing on incidence of stroke and socioeconomic status can be described as heterogeneous in design and outcome measures applied [330], [326], [328], [331], [332]. Some studies did not meet the criteria for the gold standard for comparable stroke-incidence studies. Notwithstanding that all studies support an inverse association between socioeconomic status and stroke incidence [290], [333]. A person's socioeconomic status measured in middle or old age may mirror influencing factors on later stages of pre-clinical stroke and stroke triggers [334].

A current updated review conducted by Addo et al. (2012) brings large evidence related to associations between SES and stroke [335] as well as underlining a generally increased impact of stroke among lower socioeconomic groups in different populations with 30% higher incidence rates [336]. Both, men and women from low socioeconomic groups experienced higher rates of stroke than individuals from high socioeconomic levels. The strength of this association was more pronounced for ischaemic stroke [337].

There is a strong and independent association between living in a socioeconomically disadvantaged neighborhood and risk of ischaemic stroke [338], [339], [340], [341] as well as coronary heart disease [334], [342]. This association was globally stable even after adjustment for individual socioeconomic position [343].

A follow-up study on neighborhood environment and stroke in Sweden stated that specific potentially health-damaging neighborhood resources involve higher odds on stroke [344]. There was a statistically significant increased risk for those subjects with residence in neighborhoods with greater availability of fast food restaurants [344].

Meta-analysis conducted overseas, namely in Australia and New Zealand, also confirmed that people living in socioeconomically more deprived areas experience higher incidence rates of stroke. Again, this may be explained by a increased prevalence of risk factors, such as diabetes, hypertension, and cigarette smoking among those individuals [345].

5.1.2 Socioeconomic influences in early life

A large body of studies suggested that socioeconomic deprivation in early years is associated with increased risk of stroke in adulthood [77], [346], [347], [348]. Low socioeconomic status, educational attainment, and cognitive performance seem to be powerful predictors of stroke early in life [337], [336], [328].

The so called “fetal origins hypothesis" assumes that stroke in later years is related to responses to malnutrition in utero and infancy. Studies have shown that people with low birth weight (for further details see 2.1.3), smaller length at birth, and short adult stature are at higher risk of suffering from stroke in adulthood [77], [346]. This can be explained, as the mentioned factors are known indicators of insufficient maternal nutrition and poor growth in utero. As a result, they are associated with increased plasma fibrinogen concentrations and the development of hypertension in later life. The mechanism of these variables are still debatable but might include a permanent change in vascular structure based on malnutrition [77], [346].

In a review of childhood socioeconomic circumstances and adult mortality, the majority of studies stated a high overall risk of stroke in participants with poor socioeconomic circumstances in their early life [347]. A prospective cohort study in Scotland identified paternal social class as the most stable association with risk of stroke [349]. In this context, it has to be underlined that the revealed risk persisted after adjusting for risk factors and did not improve with beneficial changes in socioeconomic status in later life.

Liu and colleagues (2013) reported a combined effect of socioeconomic position and chronic conditions, like diabetes mellitus, hypertension, and heart problems in regards to stroke risk. Moreover, a potential cumulative effect of childhood and adulthood social circumstances as well as adult chronic conditions on risk of stroke was proposed [350]. As both, the prevalence and the effect of smoking and hypertension are socially biased, a decrease in smoking in lower socioeconomic groups and in those with hypertension might lead to a decline in social inequality regarding the risk of stroke [333].

Furthermore, a 33-year follow-up study assessed the risk factors in adolescence in relation to the later risk of stroke in Swedish men. Strong independent risk factors (all $p<1.0x10^{-6}$) for ischaemic stroke involved low aerobic fitness (HR 0.84 per SD increase), high BMI (HR, 1.15 per SD increase), diabetes (HR 2.85), alcohol intoxication (HR 1.93), and low annual income (HR 0.85 per SD decrease) [351]. All those risk factors for stroke have been discussed in chapter 2.

5.1.3 Risk factors for stroke

Studies of general populations conducted in developed countries also underline a higher prevalence of various traditional stroke risk factors in the low socioeconomic groups [352], [337], [353], [327]. A study of patients with stroke and transient ischaemic attack reported a higher proportion of smokers in the lowest SES quartile for instance [354].

As people belonging to lower socioeconomic groups are repeatedly exposed to various risk factors, it can be assumed that the effect of one of these factors on risk of stroke is supposedly stronger. Individuals from lower SEP can be considered more vulnerable [355]. The mechanisms driving social disparity in stroke have been described as partially resulting from differential exposure to well-established risk factors, such as smoking and hypertension, over the course of a life time [325], [345], [336], [327].

There are overall consistent findings regarding inverse associations for smoking, diabetes, blood pressure, physical inactivity as well as obesity. The latter would specifically apply for women [356], [357].

In the European Rotterdam study, older women with stroke were reported to show inconsistent patterns of risk-factor prevalence [331]. In this trial, a relation was stated between lower socioeconomic status and higher blood pressure. Nonetheless, smoking and diabetes were more frequent in lower socioeconomic classes. Furthermore, alcohol consumption and BMI were significantly associated with lower socioeconomic status.

In a pooled cohort study of 68,643 participants in Denmark, the combined effect of low education and current smoking was more than expected by the sum of their separate effects on ischaemic stroke incidence. This was especially observed in males, suggesting that men in lower socioeconomic groups could be more vulnerable to the effect of smoking. Furthermore, the combined effect of current smoking and hypertension was more than expected by the sum of their separate effects on ischaemic stroke incidence as well. This impact was most pronounced among women [333].

Assumptions differ as to how much of the observed dissimilarities in incidence and outcome of stroke can be assigned to disparities in risk factor prevalence. As much as risk factor profiles for different countries have altered over the last years, this is not necessarily matched with a corresponding change in mortality rates [358].

The US National Health and Nutrition Examination Surveys were conducted at different time points over a period of time from 1971 to 2002. The results revealed a decline in the prevalence of high blood pressure and cholesterol in all socioeconomic groups going along with widening socioeconomic disparities in smoking [359]. A broadening of the discrepancies in the prevalence of risk factors for stroke among different socioeconomic groups might to some extend be based on any widening in the socioeconomic disparities in mortality from cerebro-cardiovascular diseases [360]. Although, effective interventions and strategies for preventing stroke have been established, a substantially low uptake remains in some populations on a global level [361], [362].

These associations have also been found in Germany. Table 5.1 gives an overview of the prevalence of behaviour-related risk factors categorized by lower, middle, and upper social class among 18 to 79 year olds [30].

Table 5.1
Prevalence of behaviour-related risk factors according to social class in Germany [30].

	Men			Women		
	Lower class	Middle class	Upper class	Lower class	Middle class	Upper class
Smoking	47.4 %	37.8 %	29.0 %	30.1 %	29.5 %	25.0 %
Extreme overweight[1]	22.3 %	18.9 %	16.2 %	31.4 %	20.3 %	9.9 %
Hypercholesterolemia	33.1 %	30.9 %	35.7 %	39.9 %	33.0 %	32.5 %
No physical sports	67.9 %	61.4 %	51.9 %	78.5 %	62.5 %	51.4 %
Hypertension	22.1 %	24.8 %	25.6 %	26.8 %	20.2 %	16.8 %

1 Body Mass Index (BMI) > 30 kg/m2

5.2 Risk of stroke and selected socioeconomic variables

As this study will investigate the association of stroke and educational attainment, occupation, marital status, and cohousing in an elderly cohort, a topical overview is given in the next section.

5.2.1 Educational influences

A large body of studies agree that low compared to high educational levels are associated with greater ischaemic but not with haemorrhagic stroke incidence and that stroke risk factors are more prevalent in low educational groups [335], [203], [327], [363]. Furthermore, behaviours and conditions, such as smoking and frequent consumption of alcohol, which increase the risk of stroke, are more common among groups with low SES and educational level, as mentioned above [201], [333]. Additionally, hypertension was more prevalent among those with low education [333]. A 33-year follow-up study assessing risk factors in adolescence compared to stroke risk in later life stated that systolic blood pressure and alcohol intoxication showed a stronger association with haemorrhagic strokes, whereas low education and diabetes indicated a stronger link to ischaemic strokes [351].

This is also described in section 5.1.1 on the general risk factors for stroke in the context of an individual's socioeconomic position.

The Women's Lifestyle and Health Cohort Study including 49,259 women from Sweden showed that the risk of stroke was significantly and inversely related to completed years of education. The hazard ratio comparing lowest with highest education group was 2.1 (95% CI [1.4-2.9], p<0.001). This association was diminished after adjustment for established risk factors, although remaining significant (HR 1.5; 95% CI [1.0-2.2], p= 0.04).

As stroke risk increased with decreasing education level, school-leaving age was linearly associated with stroke risk. Women who left at a younger age had higher levels of stroke risk [364].

Avendano et al. (2004) addressed stroke mortality by educational level in ten European countries, namely England/Wales, Switzerland, Austria, Italy (Turin), Spain (Barcelona and Madrid), Belgium, Finland, Norway and Denmark [365]. For all age groups in all investigated countries, higher mortality rates were stated in groups with an education below upper secondary level or country-specific equivalent. This was consistent for both, men (RR 1.27; 95% CI [1.24–1.30]) and women (RR 1.29; 95% CI [1.27–1.32]) [365].

In the EU based Rotterdam Study, risk was reduced in women from households in which the head was classified professional. This effect was not mediated by traditional risk factors. Nevertheless, the number of cases was small and the follow-up period was short [331]. In a larger Danish cohort followed-up over 12 years, low education and small income were associated with increased risk of stroke [366]. In European cohorts of men, the majority of studies [94], [346] but not all trials [331] underlined an inverse association between education or income and stroke.

Observations in the Swedish Stroke Register underlined a social stratification in reperfusion therapy. This was partly explained by individual patient characteristics and the specialization level of the respective local hospital [367]. Patients with university-level education were more likely to receive perfusion therapy (5.5%) than patients with secondary (4.6%) or primary education (3.6%; $p<0.001$). This discrepancy linked with education was still perceivable after controlling for patient characteristics.

Educational impact on obesity

Based on data from the Centers for Disease and Prevention, the overall obesity prevalence in the US was inversely associated with education level. College graduates showed a 20.8% rate of obesity, whereas those who attained less than a high school education were attributed with an obesity prevalence of 32.9% [368]. Childhood sociodemographic factors might have added to sex disparities in obesity prevalence. The sex gap was largest in those with low parental education (16.7% of men compared with 45.4% of women were obese). By contrast, it was smallest in those with high parental education (28.5% of men compared with 31.4% of women were obese) [369]. Obesity rates were disproportionally more excessive in children living in low-education, low-income, and

higher-unemployment households [370]. In 2006, 39% of rural versus 32% of urban children were obese [371].

Educational impact on physical activity

For Germany, figure 5.1 illustrates the extent of sporting activity by socioeconomic status. The picture emerges that a larger proportion of people from the lower classes, both men and women, do not practise any sports. Consecutively, individuals belonging to middle class do less sports than those in higher classes [30]. Those discrepancies might be partly explained by the fact that individuals in the higher social classes spend their working day in a predominantly sitting position. Those subjects do specifically sports to compensate for the lack of movement during the day. Additionally, some kinds of sports involve a considerable amount of money to practice.

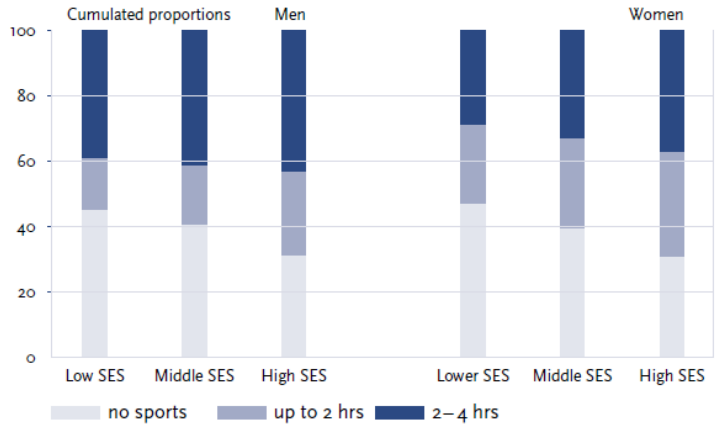

Figure 5.1
Extent of sporting activity by socioeconomic status in Germany [30].

In the US, an inverse association of adults $\geq$25 years not meeting the full aerobic and muscle-strengthening federal PA guidelines with educational level was stated. In detail, 66.4% of all participants with no high school diploma, 57.6% of those with a high school diploma or a high school equivalency credential, 46.8% of those with some college, and 33.2% of those with a bachelor's degree or higher did not comply with the full federal PA guidelines [372].

For Germany, data from the 2003 Telephone Health Survey revealed that overweight and obesity occurred significantly more often among men and women with a lower secondary-school leaving qualification compared to those with the higher education

entrance qualification (“Abitur”). The educational factor had a slightly higher impact on females [373]. Figure 5.2 displays the prevalence of overweight in light blue and obesity in darker blue by school education and sex.

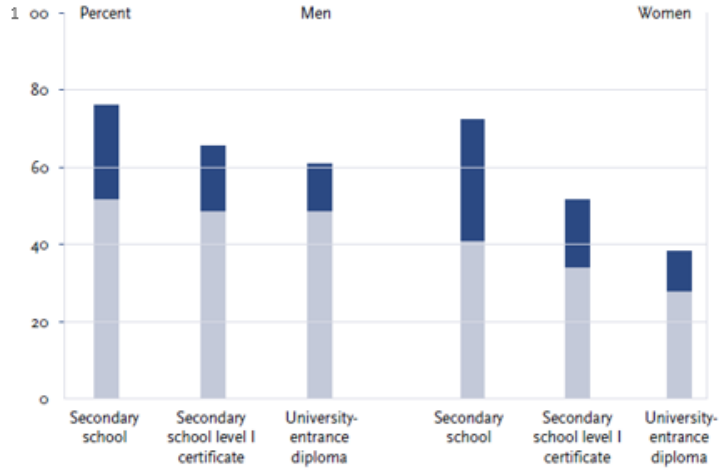

Figure 5.2
Prevalence of overweight and obesity by school education and sex in Germany [30].

5.2.2 Underlying mechanism for the association between educational attainment and cardiovascular diseases

Until today, the underlying mechanism of the relation of lower educational attainment and higher risk for cardiovascular diseases is not completely understood. As discussed above, low educational level is a crucial risk factor for cigarette smoking and the development of adverse factors, like obesity, hypertension, or high levels of serum cholesterol [328]. Several studies reported an increased risk of CVD, subsuming CHD and stroke, independent of other cardiovascular risk factors [328]. Furthermore, there is evidence that cardiovascular disease risk might also be independent of socioeconomic status, as already stated.

There are a number of aspects that help to understand basic mechanisms. Firstly, individuals of lower SES are substantially less likely to have access to health care [374]. This might also have an impact on the risk of cardiovascular diseases. Next, the frequency of physician visit can be decisive. Hinkle et al. (1968) suggested that reported discrepancies in cardiovascular disease risks were not a result of the educational process itself but rather a consequence of biological diversities in acquired habits. Those differences

can become obvious in diet patterns as well as the level and kind of activity, which are formed during childhood and youth and continue into adulthood [375]. It has been reported that the effect of educational attainment on myocardial infarction and stroke was more prominent in persons $\leq$50 years. Consequently, it can be assumed that adverse influences of low educational attainment tend to manifest in younger age groups. In contrast to this, in older people, the classical risk factors might have a bigger influence in determining an individual's risk for cardiovascular diseases [328].

Finally, in another European multicenter study, a higher level of education had a positive impact on motor and functional recovery during the inpatient rehabilitation period after stroke [376]. The rate of compliance might be decisive. Low socioeconomic status and educational attainment can also be related to less access to preventive and therapeutic health care and health information [330].

5.2.3 Occupation

Globally, differentials between occupational groups increased over time [290].

In the US and northern Europe, high stroke mortality in people among manual occupations was reported. This overview of socioeconomic discrepancies in stroke mortality found a lower mortality in the non-manual class in comparisons to national mortality rates [377].

Additionally, in an international review for the European Union Working Group on Socioeconomic Inequalities in Health, manual classes had higher stroke mortality rates compared with non-manual working conditions. This difference was reported to be relatively large in England and Wales, Ireland, and Finland. In contrast to this, it was observed to be rather small in Italy, Spain, Sweden, Norway and Denmark. Intermediate discrepancies were found in the United States, France, and Switzerland. In the majority of countries, diversities were much larger for stroke mortality than for ischaemic heart disease mortality [377].

Furthermore, manual occupation of an individual's father, which falls under indicator of childhood socioeconomic status, predicted adult stroke mortality in a cohort of employed men independent of their adult socioeconomic status [378]. Langagergaard et al. (2011) reported a higher risk of death after stroke in unemployed subjects compared with employed patients in Denmark [379].

5.2.4 Marital status

Among persons with acute stroke symptoms, earlier medical-seeking behaviour was reported in married patients compared to singles. This was especially true for married men [380]. Additionally, the incidence of stroke seems to be increased in divorced and widowed individuals [381].

The US Health and Retirement Study included 22,818 subjects born between 1900 and 1947, aged 50 and older, without stroke at baseline [382]. Based on possessions, behavioural risk factors, and cardiovascular conditions, stroke incident was estimated. This status was diversified as follows: married, widowed, divorced or separated, or never married. It could be stated that women were less likely to be married compared to men. Additionally, the distribution of risk factors differed according to sex and marital status, meaning that males had higher incident stroke rates after having controlled for risk factors (HR, 1.22; 95% CI [1.11-1.34]). In both sexes, never having experienced marriage or widowhood predicted greater risk. It has to be mentioned in this context that associations were diminished after adjustment for financial possessions. Additionally, widowed men had the highest risk compared to married women (HR, 1.40, 95% CI [1.12-1.74]). Lower income and wealth were linked to comparable high risk across subgroups, even though this risk factor particularly affected unmarried women, as in this group the lowest income and wealth levels were documented.

The authors concluded that the incidence of stroke and stroke risk factors differ largely in terms of sex and marital status. It can be assumed that social experiences differentiated according to gender, such as marriage and socioeconomic deprivation, mediating pathways, which interconnect sex and stroke.

5.2.5 Cohousing

Japan and German both face growing issues of an aging society, which are comparable. A recent Japanese study investigated the influence of life and family background on delayed presentation to hospital in acute stroke [383]. A classification into three categories, namely one- or two-person households, and patients living with three or more persons was conducted, as present in this study. It was stated that one-person (OR, 2.980, 95% CI [1.108-8.011]) and two-person households with individuals $\geq$65 years (OR, 3.059, 95% CI [1.297-7.217]) were significant independent factors for delayed presentation, in addition to stroke subtype, time of stroke onset, and route of admission. Significant delay

was demonstrated in two-person households with two individuals 65 years and older in comparison to individuals living with three or more persons (p=0.038). In conclusion, these results underlined that delayed hospitalisation was more likely in elderly couples, particularly in those patients who experienced an evening onset of stroke.

Additionally, data from 11 Ontario hospitals including 10,048 patients with acute stroke (87% ischaemic, 13% haemorrhagic) living at home were analysed [384]. Overall, 22.8% of all subjects were living alone at home before stroke. It was found that participants living on their own were more likely to be women (61.5% versus 41.4%), widowed (53.7% versus 12.3%), or single (21.5% versus 3.8%) and significantly older (mean, 74.6 versus 71.5 years). Individuals living alone were less likely to arrive within a time frame of 2.5 hours (28.3% versus 40.0%; OR 0.54; 95% CI [0.48-0.60]), to receive thrombolysis (8.0% versus 14.0%; OR 0.52; 95% CI [0.43-0.63]), or to be released home (46.0% versus 54.7%; OR 0.65; 95% CI [0.58-0.73]).

5.3 Outcomes of stroke and socioeconomic position

Socioeconomic status was reported to be associated with an increased risk of death, both, at 30 days and one year post-stroke [385], [386]. Additionally, poor survival in those with less than eight years of education and those in the lowest quartiles of the poverty index was stated [330]. A recent nationwide hospital-based study in Denmark showed that the survival of patients with low income was reduced by 30% compared to those with high earnings [387]. A recent trial analyzing data from hospitals in Luxembourg found that approximately 50% of survivors had low education and lower income [388].

In the Swedish stroke register, high income, university level education, and being cohabitant were independently associated with improved survival after first stroke [389]. It can be assumed that an explanation for this association is multifactorial. Previous research underlined that individuals with lower SEP suffer from a greater burden of vascular risk factors and comorbidities as already mentioned above [353], [336], [354] and experience more severe strokes [354], [390]. Low socioeconomic status is closely related with a lower likelihood of receiving optimal acute care after stroke [391].

In contrast to this, there have also been publications revealing either no or a weak association between socioeconomic status and survival [338], [392].

5.3.1 Stroke severity

Globally, there is some evidence for a connection between low socioeconomic status and more severe stroke [393], [354], [392]. This was specifically observed in those aged 65 years or older [338]. There were also associations of low socioeconomic status and the dependency of activities of everyday living at 28 days post-stroke [386], higher levels of longer term handicap as well as disability [394], [393]. In this context, it has to be considered that some of these studies were hospital based or had limited recruitment criteria and restricted potential for adjusting for confounding variables.

On a country level, the Berlin Stroke Register showed that older individuals or female patients were more likely to have socioeconomic deprivation (SED) and functional impairment after stroke compared to their male control groups [395]. Additionally, the results revealed that patients with lower education level had lower rates of functional recovery three months after stroke.

In this line, the South London Stroke Register emphasized that the effect of SED on poor functional recovery was predominant among individuals, who were older, female, and had suffered from an ischaemic stroke. The comprehensive impact on functional impairment was stronger than that on mortality after stroke [396].

The Swedish stroke register reported an independent association of living alone, low income, primary school education, and higher case fatality after the acute phase [389].

In addition to this, findings from the Adherence eValuation After Ischaemic stroke Longitudinal (AVAIL) registry focused on the disability stage after stroke. The results indicated, after controlling for demographic and clinical factors, that stroke survivors, who were unemployed or housewives, less educated, disabled, and currently not working, retired or reported to have inadequate income prior to their stroke, had significantly higher odds of post-stroke disability [397].

Furthermore, a number of studies underlined an inverse relation between low socioeconomic status and institutional care after stroke [386], [385], [393], affecting rehabilitation and general recovery. Structures in residential outcome could display cultural as well as local differences or material disadvantage in the domestic environment [398].

In summary, patients with lower socioeconomic status seem to have significantly worse health outcomes in terms of disability and handicap after stroke [399], [290], [354]. The higher disease burden led to a phenomenon called “double suffering”. This term describes that lower socioeconomic groups have not only a higher incidence of stroke

and a worse risk profile but are also more sensitive towards functional impairments [393].

5.3.2 Quality of life after stroke

Following the ten leading causes of death in the world in 2012, stroke ranked on place two [400], as described in chapter 1.3. As a result, increasing alertness should focus on improving the quality of life (QOL) for stroke survivors as a rising group in our society. Several studies stated that specific patient factors, including socioeconomic status, stroke severity, age, mood, and sex in terms of particularly societal roles, may have an influence on QOL after stroke [401], [394]. Various trials, but not all, reported worse QOL after stroke for women than men [402], [403]. This was specifically stated regarding mental and physical function [403].

The AVAIL registry, a US national, multicenter, longitudinal registry of ischaemic stroke and TIA patients aimed to determine the incremental impact of demographic, socioeconomic, clinical, and stroke-specific effects on longitudinal QOL. The results reinforce that women had worse QOL than men up to 12 months after stroke. This remained stable even after adjusting for important sociodemographic variables, stroke severity, and disability [404].

5.3.3 Stroke mortality

Generally speaking, stroke mortality rates are related to survivorship after acute events and incidence rates. Both influencing factors may be affected by socioeconomic status [330].

There are alterations in patterns of all-cause mortality regarding the socioeconomic status. In terms of disease-specific mortality rates, stroke shows one of the strongest inverse relations with socioeconomic status in Western Europe, the US, and Japan, increasing with age [405], [406], [407].

A large number of studies confirmed this association between low socioeconomic position and higher mortality after stroke [408], [389]. In contrast to this, other trials found no [337], [345] or only a partial association [409], [379]. These discrepancies can originate from demography, stroke severity, measures of socioeconomic position, study design, healthcare system organization, and comorbidity [387].

In a study using World Health Organization data from 35 countries in Europe and Central Asia, there was an overall decrease of stroke mortality rates between 1990 and 2006 in countries with the highest economic standard of living. Stroke mortality was considerably increasing in countries with lower economic standards of living over the same period of time [410].

The WHO MONICA, which is the Multinational Monitoring of Determinants and Trends in Cardiovascular Disease Project, can be considered as one of the world's largest prospective studies on cardiovascular disorders. In the stroke component, 34,715 stroke events were registered in 14 populations in Europe, China, and Siberia. The results suggested that up to 68% of the variation in mortality rates in European countries could be interpreted by diversities in nations' gross domestic product. Based on this assumption, stroke mortality in low income countries such as Russia and Latvia were more than twice as that of more prosperous countries like Switzerland and France [411].

Trends in stroke mortality rates have been published over the last decades. Mortality distinctions between socioeconomic groups broadened in the US between 1984 and 1997, despite this overall decrease in mortality. In this regard, the highest socioeconomic quartile showed the lowest rates [407]. Comparable schemes were reported in Australia, where the mortality rate declined by 66% to 69% among professional and administrative workers but only by 38% to 42% among manual workers and farmers between 1969 and 1996 [412]. Further findings on occupational level are stated in 5.2.3.

Cesaroni et al. (2009) found that in both stroke subtypes, ischaemic and haemorrhagic, deaths out of hospital occurred more frequently in women [337]. This is consistent with other studies reporting gender differences in recognizing symptoms of both myocardial infarction and stroke. This often leads to a late referral to the hospital among women [413] and a higher probability of dying prior to hospitalization [337].

Globally, higher incidence of stroke, stroke risk factors, and rates of stroke mortality are observed in low compared with high socioeconomic groups within and between populations [335]. For further details see chapter 1.3 on incidence and mortality rates in stroke.

In the following, the association of SEP and CHD will be discussed. The focus will be on MI.

5.4 General socioeconomic position in coronary heart disease focusing on myocardial infarction

Cumulative exposure to socioeconomic disadvantage across the life course seems to be inversely associated with coronary heart disease. Until today, these mechanisms are not fully understood [414]. Low socio-economic status, lack of social support, stress at work and in family life along with depression, anxiety, and hostility add to the risk of developing a CHD. Additionally, the worsening of clinical course and prognosis of CHD are affected.

In the Framingham Offspring study, cumulative SEP was also associated with incident CHD after adjustment for age and sex [414]. Overall, low SES is associated with risk for coronary heart disease independent of traditional CHD risk factors [415].

Socioeconomic influences in early life

As chronic diseases have long induction times, the period between exposure to risk factors and CHD mortality can extend over decades [416]. The following section will give an overview on how socioeconomic circumstances are crucial determinants of coronary heart disease, partly because of their associations with risk factors in adult life. Thus, it is a logical conclusion that the socioeconomic environment a child grows up in, may also be decisive to clinically recognized disease in later life [317].

In this line, the majority of prospective studies showed that indicators of less favorable socioeconomic conditions during childhood were associated with a greater risk for developing or dying of CHD.

5.5 Risk of coronary heart disease and selected socioeconomic variables

In this study, the association of MI and education, occupational level, marital status, and cohousing is investigated. Therefore, the following section will provide deeper insights into recent findings from international trials.

5.5.1 Educational and occupational influences

A study by Avendano and colleagues (2005) analyzed longitudinal data from six European countries from 1981 to 1995 to calculate stroke mortality rates. The status was obtained for England/Wales, Turin (Italy), Finland, Norway, Denmark and Sweden. The researchers compared these rates with rate ratios for ischaemic heart disease mortality [324]. Socioeconomic status was described based on occupational class as well as educational level. A comparable drop in age-standardized stroke mortality was reported for both, low and high socioeconomic groups in most countries. This was evident in relative and also absolute terms. Socioeconomic discrepancies in ischaemic heart disease mortality expanded in the majority of countries during the observational period.

Additionally, a higher risk of myocardial infarction associated with less than 12 years of education was reported [328]. The increased risk was independent of age, sex, race and ethnicity, cigarette smoking, systolic blood pressure, diabetes mellitus, serum cholesterol level, BMI, and socioeconomic status. Furthermore, the effect of education on myocardial infarction and stroke seemed to be more striking in persons who were 50 years of age or younger [328].

In a randomized case control study conducted in Greece, in both, patients and controls, education status was related to economic and occupation status, smoking habits, physical inactivity, alcohol consumption, and non-compliance to treatment. After controlling for these and other traditional risk factors as well as for age and sex, an increased coronary risk of 82% (OR, 1.82, $p<0.05$) for individuals with a lower level of education was reported. The risk was enhanced by 65% (OR, 1.65, $p<0.05$) for participants with an average education, compared to those with an academic career. Even though the least educated subjects developed a more adverse lifestyle than those with higher educational level, the inverse association between education and coronary risk was independent from such factors. The authors suggested that this inverse association may be a result of psychosocial differences [417].

Based on analyses of data from a statutory health insurance, an advanced risk for acute myocardial infarction in men with lower educational level was reported for Germany [418], [419]. Further studies exclusively focusing on Germany could confirm this relation for West Germany [420] and the former German Democratic Republic [421]. Bormann and Schroeder (1994) emphasized an increased MI risk of 32.5% for individuals with at least 12 years of education, whereas people with nine years of educational attainment or less revealed a risk of already 48% [422].

As concluding remark, the uneven distribution of strains and stresses in different industrial sectors and job profiles results in raising rates of early retirement due to diseases, like MI, or accidents in Germany. The current Report on Poverty and Wealth revealed that men without completed vocational education had a 5.6-fold risk of early retirement compared to those with higher education received from technical college or university. Low-qualified females showed a 2.8-fold risk [423].

5.5.2 Marital status

Within the West German population, modifications in gender roles, social and cultural norms during the post-war era have resulted in an altered weight of marriage or cohabitation on health and mortality over time [424].

Trials investigating all-cause mortality among AMI survivors stated a protective effect of marital status or cohabitation, leading to a negative impact of being single, divorced, or widowed on long-term [425].

The population-based MONICA and KORA (Cooperative Health Research in the Region of Augsburg) myocardial infarction registry encompasses data from the city of Augsburg and two adjoining districts situated in southern Bavaria, Germany. In order to investigate the effects of marital status on long-term mortality after the first acute myocardial infarction, a total of 3,766 men and women in the age of 28 to 74 years post 28 days were included. 2,854 participants, which is 75.8%, were married. It could be revealed that marital status had a strong protective effect in patients with diagnosed hyperlipidaemia, decreasing with advanced age. However, specific treatments or recommended alterations in lifestyle adjusted to hyperlipidaemia might have been influenced by the social interference and contribution of an individual's spouse [314].

A follow-up study aimed to clarify if statin treatments during the last week prior to AMI might explain this finding [426]. In fact, prior statin therapy seemed to be an underlying variable for long-term mortality reduction in married survivors after AMI with hypercholesterolemia. The authors assumed that, in marriage or cohabitation, beneficial effects of treatment and/or diet might had a larger impact on patients with diagnosed hyperlipidaemia.

The INTER-HEART China case-control study found that being single was significantly associated with an increased risk for AMI, especially in women (OR, 2.95; 95% CI [1.99-4.37]) [427]. However, after adjusting for potential risk factors, the protective effect of marriage did not persist for men.

In summary, an increasing number of studies found that total and cardiovascular disease mortality was higher among those individuals who never married [428]. Older age groups seem to have a smaller relative risk compared to their younger counterparts.

5.5.3 Cohousing

A prospective register study investigated 302,885 Finnish men and women, aged 40 to 60 years over a period from 1995 until 2007 [429]. Men, who were married, had a lower risk of MI incidence even after adjusting for socioeconomic factors, namely education, occupation, income, wealth, and employment status. In this line, the effects of living arrangements on incidence were fully related to the same socioeconomic factors for females. It clearly has to be stated that these results revealed that living arrangements were strong determinants for survival after MI independent of other socio-demographic variables. These findings underline higher fatality associated with living alone in men. The social support and regulation provided by marital relationship may especially protect from MI fatality.

Patients living alone have been reported with poorer clinical outcomes after AMI [430]. Living in a one-person household and/or being unmarried increased the risk of experiencing a heart attack, deteriorating the prognosis. This was observed for both, men and women regardless of age [431].

In a prospective cohort study in Denmark, it could be revealed that living in a single household doubled the risk of death. After controlling for potential confounding factors, living single was an independent predictor of death (HR 2.55; 95% CI [1.52-4.30]).

Additionally, it was confirmed that patients who live alone had higher long-term all-cause mortality following AMI (HR, 7.60; 95% CI [1.99-29.08]) [432].

5.5.4 Coronary heart disease mortality and socioeconomic position

Further investigations on mortality showed discrepancies in hospital specific 30 day risk-stratified mortality rates for patients with AMI. The patient's socioeconomic status profile was significantly associated with mortality rates [433].

In the Health Survey for England, both, psychological distress and low SES were associated with increased mortality from coronary heart disease after adjustment for demographic and clinical variables [434].

To conclude, individuals in low socioeconomic position were more vulnerable to the adverse effect of psychological distress. It has been suggested that persons belonging to higher SES implement more effective management strategies and take advantage of larger support networks as well as greater material possessions to cope with the potentially stressful situations [435], leading to decreased mortality rates.

5.6 General implications of socioeconomic position on the risk of stroke and myocardial infarction

Despite the fact that numerous trials have researched associations between socioeconomic status and cardiovascular disease, comparatively few studies have investigated socioeconomic status and stroke specifically. In terms of an association between SEP and AMI, there is also a lack of conclusive studies for Germany [436]. The gap regarding socioeconomic survival after stroke and CHD has remained predominantly unchanged during the 2000s. Socially underprivileged individuals represent a target group for advanced stroke as well as MI care and support during or after their hospital stay [389]. All those findings lead to the conclusion that individuals with a low level of education are relatively unprotected against acute coronary risk [417] and stroke.

This comparative neglect in research may also mirror past assumptions of homogeneity in the older population to some extend [437]. As measuring the socioeconomic status of elderly holds specific complications (see chapter 4), this aspect itself may discourage research and might lead to hampering in some cases [295]. Innovative acute and long-term stroke care strategies aiming at people with SED are needed. Those should specifically target older subjects, as in the present study, and female patients [438].

As a result, public health policy-makers should aim to inform this target group about the consequences of suboptimal lifestyle in enhancing the risk of developing acute coronary events. There is a persisting need for gathering of carefully designed research that will enable the development and testing of new conceptual and empirical models of the causal pathways through which socioeconomic status affects stroke risk and its

outcomes [335]. In the course of time, this will simplify and speed up the expansion of suitably targeted interventions [290].

Throughout Germany, a range of initiatives have been launched aiming at implementing this policy [439]. As there is an association between socioeconomic status and use of health services [440], administrators and providers of health care services also need information on social inequalities at national and regional level [295]. At this point, the INVADE study wants to contribute to a deepened understanding of local necessities and socioeconomic differences.

Ideally, any system of measuring socioeconomic status should be based on theoretical assumptions and rely on data that can be collected rather easily and reliably [441]. Consequently, the present study focuses on well-defined and consistently measured socioeconomic variables as educational level, marital status, occupational group, and housing conditions in a rural community based cohort in Ebersberg, southern Bavaria, Germany. Detailed knowledge about differences in risk factors is fundamental in order to define targeted and effective stroke prevention and management strategies for the area in question [335]. The reported results from one country cannot identically be applied to another country or even area [436]. As the population characteristics of the study cohort are highly individual, an overgeneralization should be handled carefully.

So far, a description of the diseases focused on in the present study was given, namely ischaemic stroke, ischaemic stroke including TIA, and myocardial infarction. In order to evaluate the global impact of those conditions, prevalence, incidence, and death rates were displayed (see chapter 1.3). A current review of literature has emphasized the broad range of risk factors for stroke (see chapter 2) and MI (see chapter 3) leading to these rates. Differences and similarities between those variables increasing the risk for stroke and MI have been provided. This will help to understand the choice of risk factors used in the present study. The association between the mentioned risk factors and specific socioeconomic aspects will be investigated in the INVADE cohort. Consequently, an overview of the general socioeconomic circumstances in life and their impact on health was underlined (see chapter 4). Subsequently, the specific association of educational level, occupation, marital status, and cohousing with stroke or MI was discussed in the present chapter. These findings provide the opportunity to compare the results stated in this study (see chapter 8) with conclusions drawn from current literature. This will enable to deduce implementations of the reported findings (see chapter 9).

6 Motivation

The present chapter will summarize the immense burden of disease and will give an insight in the complex and various mechanisms which come into force after having suffered from stroke.

6.1 Burden of stroke

Stroke has a comprehensive tragic personal impact on patients and their families. Moreover, it shows overwhelming financial strain on the economy [11]. The following chapter will delve deeper into the facets of the burden of stroke.

6.1.1 Global burden of risk factors for stroke

The Global Burden of Diseases 2010 studies identified three general major risk factors for disease burden, namely high blood pressure, smoking of tobacco involving second-hand smoke as well and the consummation of alcohol [183]. Furthermore, these three risk factors were rated in the top three for numerous low- to middle-income regions, including Central and Eastern Europe, Central Asia, and Southern Latin America. Nearly 70% of all incident stroke occur in low- to middle-income countries [8]. Additionally, lifestyle factors, such as poor fruit intake and low physical activity as well as high sodium intake made 10% of disability-adjusted life years (DALY) in 2010. These risk factors substantially contribute, along with non-modifiable variables like sex, age, and race/ethnicity, to the incidence of stroke [188]. Those variables and their impact have been be discussed in detail in chapter 2.

6.1.2 Psychological burden in patient

It can be stated that depression is the most frequent psychiatric disorder which exerts an immense impact on patients with stroke. Depressive symptoms following stroke could add to post-stroke morbidity and mortality [442]. Based on cohort characteristics and diagnostic criteria, the prevalence of post-stroke depression varies substantially across studies. Nevertheless, it can be underlined that it is considerably higher compared to control populations after having controlled for sex and age [443]. In general, younger age, poor functional outcome, previous diagnosed depression, and not being able to fulfil a profession three months after stroke are linked with post-stroke depression at 12 months [444], [443]. The annual incidence of depression post-stroke was estimated from 7% up to 21% [445].

Skolarus et al. (2014) found that depressive and anxiety symptoms were independently associated with participation restrictions within patient's family and friends as well as religious communities. Additionally, aphasia and/or dysarthria can impede social activities. This clearly emphasizes the serious need of a timely diagnose. Improving physical capacity, treating depression, and anxiety in addition to focusing on aphasia and dysarthria has high potential to contribute to the quality of life of stroke survivors and their social environment [446]. Consequently, systematic evaluation for depression in this patient population should be integrated into daily clinical routine [447].

6.1.3 Psychological burden in caregivers

Psychosocial distress of caregivers should also be considered as crucial and need to be addressed adequately in this context [448]. Culminated stress of caregivers is a common reason for eventual institutionalisation of the stroke survivor. Frequently, this experience leads to additional psychological and physical health compromise for the caring relative [449]. Again, critically assessing of and providing for physical, psychosocial, and educational support requirements of nursing relatives will assist in alleviating the daily burden and prepare for future challenges [450]. Programmes focusing on training in time management and coping strategies as well as respite care provision could be advantageous. This approach might contribute to diminish the burden of caregiving. Additionally, it would certainly also have a beneficial influence on the stroke patient himself [451], [452].

6.1.4 The concept of treatment burden in stroke

"Treatment burden" is a rather novel approach describing self-care procedures that patients with chronic disease must meet to execute management strategies and respond to the demands of health care systems as well as providers [453], [454]. It involves information gathering, taking medications, meeting numerous appointments as well as enacting self-care and financial management to pay for treatments [455].

Individuals rather diverge in their capacity to accommodate and achieve such practices, which may have a considerable impact on patient functioning and well-being [453], [456] and on the above mentioned adherence to scheduled management plans [457], [458]. This coping capability is based on environmental variables such as social support and financial constraints [459]. Additionally, internal factors like health literacy and resilience play a fundamental role [460].

Current research suggests that treatment burden can overpower patients in exceeding their coping threshold thus resulting in ineffective treatment and wasted resources [461], [462]. A recent systematic review of literature revealed that patients with history of stroke indicated four main areas of treatment burden, namely interacting with other individuals, making sense of stroke management and planning care, realizing management strategies, and reflecting on management [454].

Non-adherence to management strategies by patients with chronic disease is a worldwide health problem [457]. This fundamental issue in chronic disease management is well acknowledged by the World Health Organization but not fully grasped yet. It has immense potential to result in negative outcomes for patients in terms of morbidity and dissipated investment for health care systems [463]. As a result, there is growing concern in the concept of treatment burden internationally [453], [456].

It is well described that treatment for, and rehabilitation from stroke can be a prolonged, laborious process, demanding substantial personal input from the affected patient [464].

Gallacher et al. (2013) found that stroke patients spend a significant amount of time and energy seeking out, cognitively handling, and reflecting information about the management of stroke [454], as mentioned before. On a global level, it can be stated that the supply and distribution of this information by health services is presently insufficient. Those findings match with previous research on treatment burden in heart failure patients [456], [465].

A recent Cochrane review on information provision to stroke patients suggested that an amelioration in patient knowledge would raise patient satisfaction and could also lead to a small reduction in depression [466].

Similar to patients with heart failure, shifts from intensive care environments or rehabilitation institutions to self-depended and community-based services can substantially alter the burden of treatment from professionals to patients and their caregivers. In a recent investigation, patients and caregiving relatives judge themselves constantly burdened and described inadequate support from health care services [454].

Understanding restrictions in participation and the role of capacity is fundamental to improve stroke survivorship [446].

6.1.5 Economic burden

Situation worldwide

To facilitate health policy planning, it is compulsory to comprehend projected future prevalence and cost of stroke. This approach enables to determine potential actions that could lead to a reduction of the economic strain.

The long-term direct costs include spending for inpatient stays, outpatient visits, rehabilitation, prescribed medicines, home health care, and nursing home [467]. In the US, direct expenses for non–nursing home stroke care comprises more than 10.7% of the so-called medicare budget, which is a national social insurance program, administered by the US federal government, and more than 1.7% of overall national health expenditures [52].

The total annual direct costs were estimated at $22.8 billion in 2009 for the United States [468] and €26.6 billion in 2010 for the European Union plus Iceland, Norway, and Switzerland [469].

Additionally, there are indirect costs derivable from premature mortality and lost productivity for stroke survivors [470]. Furthermore, costs of informal caregiving usually provided by unpaid family members need to be considered in this matter as well.

Heidenreich et al., (2011) predicted that annual indirect costs will raise in the US from $27 billion in 2010 to $47 billion in 2030 [244]. The attributable one-year cost of post-stroke aphasia was predicted at $1,703 in South Carolina, US [471].

In the US, the direct and indirect cost of stroke in 2010 was $36.5 billion [52]. The mean lifetime costs of ischaemic stroke were estimated at $140,048. This involved inpatient care, rehabilitation as well as follow-up care necessary for enduring disabilities [472]. In the period of 2012 to 2030, total direct medical stroke-related expenses are projected to triple. A range from $71.6 billion to $184.1 billion is expected, with the majority of the projected raise in costs arising from those patients aged 65 to 79 years [11]. Inpatient hospital costs for an acute stroke event can be attributed to 70% of first-year post-stroke costs [472].

It clearly has to be stated that the indirect expenses are greater than all direct costs combined [470].

Situation in Germany

In Central Europe, a similar development has risen in Germany. As the ongoing aging of the German population will still increase in coming decades, the potential raise in stroke costs is fundamental. The combination of an aging population, declining stroke case-fatality rates, and to some extend limited success in reducing the incidence of stroke led to this increase in the prevalence of stroke survivors.

In Germany, cardiovascular diseases accounted for the biggest single item of health expenses with €35 billion per year in 2002. In an international comparison per capita expenditure, Germany ranked in the upper middle group of western industrialized nations [30].

The total cost of illness in Germany was about €223.6 billion in 2002, with cerebrovascular diseases such as strokes accounting for €7.8 billion and ischaemic heart diseases such as cardiac infarction for €7 billion (see figure 6.1).

Based on data from the Erlangen Stroke Registry, hospital care during the first quarter of one year after stroke was the largest component of the costs, accounting for at least 40% [473]. The length of stay in institution care can be described as the main factor influencing the expenses accrued during the acute stage.

The overall cost per first-year survivor of first ischaemic stroke is predicted to be €18,517. Rehabilitation procedures attributed with 37% to this amount. In consecutive years, outpatient care was the major expense factor [474].

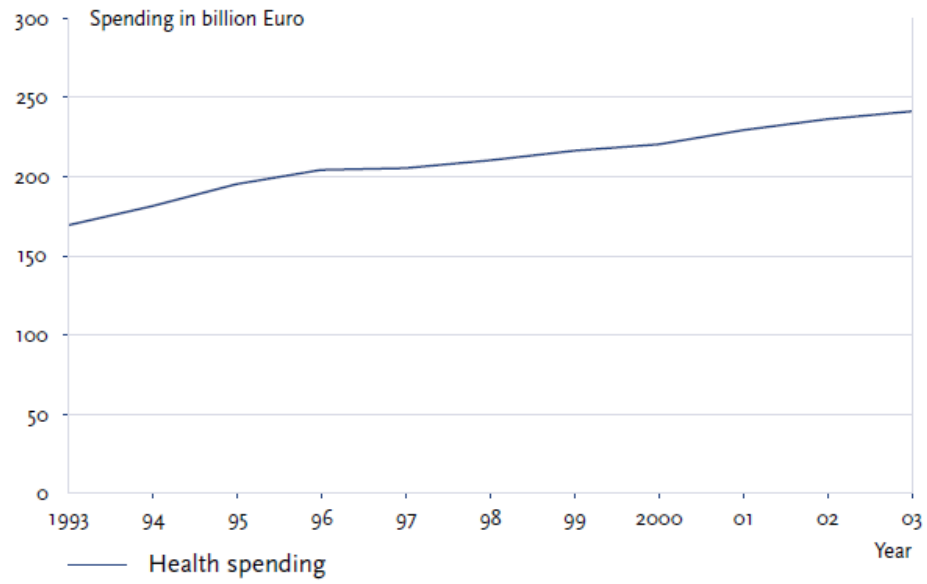

Figure 6.1
Development of health expenditure in Germany [30].

Kolominsky-Rabas et al. (2006) estimated that the overall discounted lifetime costs per case were €43,129. Additionally, higher expenses in men (€45,549) than in women (€41,304) were reported.

National projections for the period of 2006 to 2025 identified 1.5 million new cases of ischaemic stroke in men and 1.9 million in women. Current costs of €51.5 billion for males and €57.1 billion for females were underlined [474]. As the number of stroke patients and the healthcare expenses for strokes in Germany will rise steadily until 2025, stroke prevention and reduction of stroke-related disability should be considered first concerns in health planning policies [475], [474], [476].

6.2 Burden of coronary heart disease

As already mentioned before, the center of attention in this thesis lays on ischaemic stroke. For the sake of completeness, the following paragraph describes the global burden of coronary heart disease, focusing on myocardial infarction.

The burden of CHD is composed of years of life lost from CHD deaths and years of disability lived with mainly three sequelae of disease which are non-fatal. This includes, as mentioned before (see 1.2), non-fatal acute myocardial infarction, angina pectoris,

and ischaemic heart failure.
The Global Burden of Disease 2010 Study analysed projected global and regional estimates of acute myocardial infarction incidence by sex, age, and global region in 1990 and 2010 [477]. This investigation was based on data from a systematic review and nonlinear mixed-effects meta-regression methods. It could be revealed that age-standardized acute myocardial infarction incidence decreased worldwide in the period from 1990 to 2010.
Additionally, the global burden of CHD raised by 29 million DALY in the same timeframe, which is an increase by 29%.
Approximately 32.4% of the growth in global CHD disability-adjusted life-years was derived from aging of the world population, while 22.1% was attributable to population growth. Furthermore, total DALY were attenuated by a 25.3% decrease in per head CHD burden. Moreover, the amount of individuals living with non-fatal CHD elevated more than the number of CHD deaths since 1990, but more than 90% of CHD DALY in 2010 were directly linked with CHD deaths.

In 2006, in-patients costs per discharge for AMI were $14,009. Generally speaking, the estimated expenses, taking together direct and indirect cost of CVD for 2010, were $315.4 billion [52]. By 2030, total direct medical costs of CVD are projected to raise to a level of $918 billion based on methodology described by Heidenreich et al. (2011) [244].

In summary, it can be stated that decreased age-standardized fatal and non-fatal CHD were documented in most regions since 1990. Nevertheless, population increase and general aging resulted overall in a higher global burden of CHD in 2010.

6.3 Research question

As coronary heart disease is known to be the first and stroke the second leading cause of mortality in the industrialized world and future generations need to balance the complex burden described above desperately, this study is more relevant than ever. For further details see figure 1.5 displaying causes of death in high income countries per deceases/100,000 residents.

Bearing all these aspects in mind, the basic objective which drives the present study, is the investigation of risk factor impact such as age, sex, diabetes mellitus, arterial hypertension, atrial fibrillation, lack of movement, LDL/HDL levels, adiposity, alcohol

consumption as well as smoking on the incidence of ischaemic stroke, ischaemic stroke including TIA, and myocardial infarction in a population-based cohort in a rural area of Germany, called Ebersberg.

There is an urgent need to understand how socioeconomic factors like education, family status, occupational level, and living conditions affect the occurrence of stroke and MI on a local level. This would enable an implementation of these findings in future long-term health care management programs focusing on prevention and medical education, adapted to regional demands and on multiple levels in daily life.

7 Methods

The following investigation is based on data derived from the INVADE study, which was launched in 2001. The present trial is a prospective and population-based cohort study in elderly focusing on stroke and myocardial infarction prevention as well as health related education. The observation period ended on 31th May 2008.

7.1 Project aims

The general purpose of the INVADE project is the recording and investigation of epidemiological data in a clearly defined geographical area in Ebersberg, south Bavaria, Germany. This enables the consequent treatment of revealed risk factors based on World Health Organization and American Heart Association recommendations. Furthermore, particular health care requirements shall be revealed based on specific socioeconomic circumstances in the targeted area.

The main objective of this study is the long-term reduction of ischaemic stroke including TIA and MI incidence based on a systematic registration of vascular events, specific treatment of modifiable risk factors, and targeted health education on administrative district level in close cooperation with primary medical care.

7.2 Endpoints

In the present study, the association of ischaemic stroke, ischaemic stroke including TIA, and MI with educational attainment, cohousing, marital status, and occupational level was investigated. Accordingly, the following five endpoints were considered in the present study. The incidence of ischaemic stroke, ischaemic stroke including transient ischaemic attack, and the occurrence of myocardial infarction. The forth endpoint is

marked by participant's death and lastly, the end of the Allgemeine Ortskrankenkasse (AOK) insurance period. All endpoints are summarized in table 7.1.

Table 7.1
INVADE study endpoints

Five study endpoints
1. Incidence of ischaemic stroke
2. Incidence of ischaemic stroke including transient ischaemic attack
3. Incidence of myocardial infarction
4. Death unrelated to ischaemic stroke, TIA, MI
5. Termination of the AOK insurance period

7.3 Responsible persons in research organisation and management

Two clinical branches of the University Hospital Klinikum Rechts der Isar, Technical University Munich were involved conducting the study. PD Dr. D. Sander and Prof. Dr. B. Conrad managed the study centre at the "Neurologische Klinik der Technischen Universität München, Klinikum Rechts der Isar", while Dr. H. Bickel and Prof. H. Förstl were in charge of the study at the „Psychiatrische Klinik der Technischen Universität München".
The local organisational management was administered by Dr. H. Gnahn, supported by Dr. C. Briesenick from the „Qualitätszirkel für Neurologie und Psychiatrie/Psychotherapie im Landkreis Ebersberg".

Immediate patient care and data collection was operated in general practitioners' (GP) practices in the administrative district of Ebersberg, in cooperation with the "AOK Bayern" and the "Stiftung Deutsche Schlaganfallhilfe". The partnership of INVADE with the health insurance company AOK is based on the interest in their insured persons' well-being as well as decreasing the cost for medical care and rehabilitation following vascular events. An overview of those immense expenses is given in chapter 6.1.5 on the burden of disease.

7.4 Aim of the study

As stroke is known to be the second leading cause of mortality in the industrialized world, developing and establishing effective prophylaxes and therapies are of high interest [478]. The global situation as well as the current state in Germany has been discussed in chapter 1.3.

Before the INVADE study was conducted, epidemiological trials have been operated in the Federal Republic of Germany as well. On the one hand, the Erlangen stroke project [32] was originated, on the other hand, there was an epidemiological stroke register in the former German Democratic Republic within the WHO-MONICA-Projects in east Germany [479]. Both trials made valuable contributions to the epidemiological research on stroke in Germany.

Therefore, the aim of the present study is to fill this gap by analyzing the impact of conclusive socioeconomic variables, namely education, family status, occupational level, and living conditions on the incidence of ischaemic stroke, ischaemic stroke including TIA, as well as myocardial infarction in a specific regional area in south Bavaria. As an individual's socioeconomic position in life is closely linked to his or her health condition over the course of life (see chapter 4 and 5 on SEP in general and related to stroke/myocardial infarction), a deeper insight in social inequalities in this specific area could enable the development of concrete procedures to compensate this imbalance. A cooperation between politics, health care providers, and medical support on-site could lead to a further step in optimization of stroke prevention measurements and management policies. As stated in the chapters above, socially deprived citizens represent a higher incidence and greater risk profile of suffering from stroke as well as myocardial infarction, along with greater disability rates [290]. This leads to a "double suffering" on this social level [393].

Additionally, this population at risk is in need of expanded care systems and support during as well as after hospitalization. As a result, forthcoming long-term health care management concepts aiming at medical education for prevention could enable customized answers to regional requirements to address the various and often interconnected layers of continued health and well-being in the addressed population.

7.5 Study protocol

7.5.1 Time frame

The total duration of the INVADE study was set up for eight years. Patient recruitment was conducted in the first two years of the investigation. The baseline phase was carried out from 2001 to 2003.

7.5.2 Design

INVADE is a prospective project on an administrative district level. All potential subjects were identified in the AOK database and then asked via mail to participate in the INVADE trial.

7.6 Study population

7.6.1 Inclusion criteria

All subjects had to be inhabitants of the community of Ebersberg, Germany. Ebersberg consists of 31 municipalities in total. Additional inclusion criteria were the membership in the health insurance company AOK and birth in or before 1946. Lastly, a signed patient information and informed consent had to be present.
A total number of 3,908 participants were included in the present analysis based on the inclusion criteria mentioned above. Table 7.2 displays the study inclusion criteria.

Table 7.2
INVADE inclusion criteria

Four inclusion criteria
1. Residence in Ebersberg
2. Health insurance by AOK
3. Birth $\leq$1946
4. Signature of patient information and informed consent

7.6.2 Ethical approval

The research project was approved by the ethics committee of the University Hospital Klinikum Rechts der Isar, Technical University Munich. An additional submission was made to the ethics committee of the State Medical Council of Bavaria. All clinical investigations were conducted according to the principles stated in the Declaration of Helsinki.

7.6.3 Data privacy protection

The attorney Dr. Baierl was in charge of the data protection. The place of business was located in Ebersberg. The data security concept was coordinated and agreed with the state data protection commissioner in Bavaria.

7.6.4 Informed consent and patient information

In the beginning of the study, an informed consent had to be signed and dated by all participants. Patient information and informed consent were stored in a safe place. Those documents were added to the patient documentation.
The primary or referring physician informed the patient about requirements and intentions of the planned project. The right to refuse the participation at any point of time in the study was underlined. The patient information was handed out in written form. Further questions could be addressed and have been answered thoroughly at all times of the trial. Additionally, every patient had to agree with a storage of his or her medical data and biosamples followed by a data transfer in order to practice data analysis at the corresponding sites.

7.6.5 Project course

A total number of 65 general practitioners of the district of Ebersberg conducted the baseline investigations. This was composed of a standardized questionnaire (see appendix) followed by a physical examination, the evaluation of multiple risk factors as listed below, the patient's medical and disease history, and a 12-lead ECG. Moreover, an overnight

fasting venous blood sample was taken for subsequent analysis carried out by a central laboratory Bieger, Munich, Germany.

Assessment of risk factors

The following risk factors have been evaluated based on questionnaires, physical examinations, and laboratory measurement: arterial hypertension, ankle-brachial index, atrial fibrillation, dyslipoproteinaemia, diabetes mellitus, hyperhomocysteinaemia, body mass index, intima media thickness, cognitive and depressive disorders, current medication, nicotine, and alcohol consumption besides the amount of physical activity. A detailed overview of all these factors and their association with ischaemic stroke and myocardial infarction is provided in chapter 2 and 3.

Going into greater detail, general sociodemographic data was collected by the questionnaire (see appendix), filled in by patient and doctor. Among other variables, the questionnaire assessed marital, educational, and occupational status as well as living conditions at home.
Former episodes of ischaemic stroke and/or TIA and myocardial infarction were recorded additionally. In cases of indictment of depressive or cognitive disorders, a diagnostic clarification was recommended.

Entry examination

Additionally, all subjects received a duplex ultrasonographic examination of the carotid arteries to measure common carotid artery intima-media thickness. This was in accordance with a standardized protocol in eight local practices, internally qualified as centers of excellence. Data captured from these eight experienced investigators were stored on video or digital audiotapes. Subsequently, the data was transferred to the neurovascular laboratory of the Department of Neurology, and digitalized if needed. The measurements of mean common carotid artery IMT (intima media thickness) were performed based on a computer-supported image analysis system, namely Sigmascan-Pro 5.0, SPSS. In this way, the progression of early carotid atherosclerosis could be monitored.

Based on the available risk profile, the GP initiated specific treatment measures in accordance with the catalogue of criteria in the INVADE project. The design of these risk profiles was based on the Framingham risk tables for cardiovascular [480] and cerebrovascular

events, respectively [481]. Detail regarding the population at risk can be seen in chapter 2 and 3.

Follow-up visits

Following the baseline investigation, patients were continuously monitored for major events through linkage of the study database with the three-month visit files from the primary care physicians, the AOK database, and the municipality. If an event was recorded, additional information was retrieved through hospital reports, autopsy records, or death certificates.

After the first period of two years, the complete follow-up investigations for this time period were available for 3,478 participants (98.5%). Intervention measurements were documented on an ongoing basis. Furthermore, the compliance of the subject, the efficiency of the treatment, and a re-evaluation of previous findings were assessed.

At intervals of two, four, and six years after baseline, a comprehensive follow-up examination was scheduled, in which a complete re-assessment of the risk factors, laboratory examinations, and the self-performed questionnaires (see appendix) were performed after the baseline examination. Over the period of eight years, this resulted in four cycles of the basic examination.

Laboratory examinations

Overnight fasting venous blood samples were collected by the according GP. The samples were sent to a central laboratory to evaluate the following parameters: C-reactive protein, creatinine, blood sugar, HbA1c, total cholesterol, lipoprotein(a) and homocysteine, and LDL as well as HDL cholesterol measured in serum. The ankle-brachial index is the ratio of the SBP measured at the ankle to that measured at the brachial artery. It can serve as a prognostic marker for cardiovascular events [482].

7.7 Study variables

7.7.1 Traditional risk factors

According to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), ischaemic stroke (I63) was defined as a neurological deficit that persisted longer than 24 hours.
Stroke was only considered after the confirmation of a neurologist. A TIA was characterized by a neurological deficit that endured less than 24 hours, again assessed by a neurology specialist (ICD-10 I63, G45). Diagnosing by medical professionals can clearly be seen as an advantage of this study [483].
Myocardial infarction was defined as ICD I21, namely as disorder characterized by gross necrosis of the myocardium due to an interruption of blood supply to the area in question [483]. Analysing patient's history, no cases of I22 (subsequent ST elevation and non-ST elevation myocardial infarction) and four cases of I24 (other acute ischemic heart diseases) were present. Consequently, the last two classifications were excluded in the present analysis.
A comprehensive and state-of-the-art definition for ischaemic stroke, TIA, and MI are given in chapter 1.2.

Myocardial infarction and ischaemic stroke were diagnosed according to recent recommendations by the involved GPs, resulting in carefully standardized and verified cases of ischaemic stroke [484], TIA and myocardial infarction [485].

To get a better understanding of the chosen variables in this study, refer to chapter 2 regarding risk factors for stroke and TIA as well as chapter 3 focusing on risk factors for myocardial infarction.

Age and sex

Apart from age and sex, which are well known confounding factors for stroke, TIA [74] and MI [235], a description of the study variables in terms of risk factors are displayed in the following section. The careful selection of those specific variables is based on current research on well-documented modifiable and less well-documented or potentially modifiable risk factors.

Hypertension

Arterial hypertension was defined as blood pressure above 140 and 90 mmHg measured in a standardized fashion and/or the use of any antihypertensive medication. The classification and definition of hypertension in table 7.3 is displayed in the study protocol.

Table 7.3
Thresholds of hypertension

Category	Systole	Diastole
Optimum	<120	<80
Normal	<130	<85
High normal	130-139	85-89
Mild hypertension (grade 1)	140-159	90-99
Moderate hypertension (grade 2)	160-179	100-109
Severe hypertension (grade 3)	$\geq$180	$\geq$110
Isolated systolic hypertension	$\geq$140	< 90

In the results section, it was focused on clinical significant values of SPB $\geq$140 mmHg and DBP $\geq$90 mmHg.

High-density and low-density lipoprotein

Primary dyslipidaemia can be classified in three groups:

Table 7.4
Classification of dyslipidaemia

1. Hypercholesterolaemia (elevated LDL cholesterol)
2. Combined hyperlipidaemia (elevated LDL cholesterol and triglyceride)
3. Isolated hypertriglyceridaemia (elevated triglyceride)

Total HDL and LDL concentrations were measured in mg/dL.

Atrial fibrillation

Atrial fibrillation had to be diagnosed by a GP and documented in the patient's history. An ECG was applied additionally to verify the condition.

Diabetes mellitus

A treatment with anti-diabetic drugs or overnight fasting serum glucose levels $\geq$126 mg/dL defined diabetes mellitus in this study.

Body mass index

The body mass index was calculated as weight in kilograms divided by height in meters squared. A BMI >30.0 kg/m^2 was defined as obese.

Physical activity

At baseline, physical activity was determined by asking participants the number of days per week they performed strenuous activities, like walking, hiking, bicycling, swimming, gardening, or another type of exercise (see appendix).
In this study, the activity performance was divided into two levels, i.e. not active (no activity) versus moderately active (physical exercise less than three times a week) and very active (physical exercise at least three times a week) taken together.
Dichotomization was applied to prevent too small cell formation.

Alcohol consumption

A subject's average alcohol consumption was addressed by the entry questionnaire (see appendix). Intake of no alcohol in contrast to <7 drinks per week up to $\geq$21 drinks per week was chosen. One drink was defined as either one glass of wine (0.2 l) or beer (0.5 l) or one shot of spirit (0.02 l), which is about the same amount of pure alcohol.

Cigarette smoking

In terms of consumption of nicotine, three grades were registered: never having smoked cigarettes, previous or present smoker. For this analysis patients were stratified in two groups, namely current or previous smoking versus no smoking experience, again to gain meaningful data.

7.7.2 Socioeconomic variables

Educational status

Education was classified as low level (primary school qualification: “Volksschulabschluss” or secondary school certificate: “Hauptschulabschluss”) or no school leaving qualification at all versus intermediate/higher education (secondary modern school certificate: “Realschulabschluss“ polytechnic degree: “Fachhochschulabschluss“, A-level: “allgemeine Hochschulreife“, or university degree: “Hochschulabschluss”).

Marital status

Married individuals or those living in cohabitation were classified against subjects who stated to be single, were divorced, or widowed.

Housing conditions

In terms of living conditions at home, a differentiation between individuals living alone and individuals living in a group of two or more people was chosen.

Occupational group

Regarding a subject’s occupation, never having worked in an employment was compared with having pursued a career. Additionally, current employment was investigated as opposed to retirement at baseline.

7.8 Statistical analysis

Multivariate Cox regression was used to calculate hazard ratios and analyse the association between risk factors, socioeconomic variables, and the incidence of ischaemic stroke, TIA, or MI.
All multivariate analysis were adjusted for traditional covariates according to the literature (see chapter 2 for stroke and chapter 3 for myocardial risk factors, respectively). These were age at baseline, sex, hypertension, high-density lipoprotein as well as low-density

lipoprotein, atrial fibrillation, diabetes mellitus, BMI, physical activity, alcohol consumption, and cigarette smoking to give an unbiased estimate for the relation between baseline status and incident events. Calculations were performed with JMP 5.01 software (SPSS Inc.). A p-value of <0.05 was considered to be statistically significant. For ischaemic stroke including TIA, ischaemic stroke, and MI, one model was calculated, respectively.

7.8.1 Time-to-event analysis

In time-to-event analysis or survival analysis, clinical trials usually document the length of time from the beginning of the study to an endpoint defined by a disease or a treatment [486]. Generally, these data are displayed in a Kaplan-Meier curve, from which the median (time at which 50% of cases are resolved) and the mean (average resolution time) can be read [487], [488].

By making comparisons between the number of survivors in each group at multiple points in time, this method becomes effective [486].
The alternative approach would be to exclude patients, who are lost to follow-up but this might lead to considerable bias. The data generated by these patients prior to their exit of the trial is crucial to the validity and the power of the study [486]. Consequently, this study aimed at high completion rates in follow-up.

Additionally, time-to-event analysis is able to include information about subjects that may change over time. Those are called time-dependent covariates. Clinically important differences in the effect of treatment could be concealed if the proportions of survivors or recovered individuals in the treatment group are only compared to that of the control group at a single point in time. For example, this could be the conclusion of the trial [488]. Consequently, survival analysis can be a potentially more powerful and informative method of analysis [486].

7.8.2 Censored data

Survival analysis also provides a method to include patients, who fail to complete the trial or do not reach the study endpoint. This is crucial, as a significant feature of survival times is that the event of interest is very rarely observed in all subjects. Such survival times are called “censored”. It indicates that the period of observation was cut off before the event of interest occurred [489]. Examples for censoring are individuals who do

not experience the event before the study ends, study subjects who are lost to follow-up during the study period, and persons withdrawn from the study because of death, if death is not the event of the interest [490].
Data can be left or right censored. Usually, right censored data is encountered. Additionally, data is left censored if the patient had been on risk for disease for a period of time prior to entering the study. Nevertheless, left censoring is usually manageable, as the starting point is generally defined by a specific event. This could be the entry of the patient in the trial, his or her randomization or the occurrence of a procedure or treatment [491].

7.8.3 Cox proportional hazards model

There are a number of methods available to analyse time-to-event curves [492]. The Cox proportional hazards, log-rank, and Wilcoxon two-sample-test are some examples [490]. Over many years, the Cox proportional hazards model has been the most widely used procedure in medical research in this field of interest [493], due to its applicability to a wide range of clinical studies [494], [495]. The Cox model is a semiparametric regression method for survival data and used to investigate several variables at a time [494]. It provides an estimate of the hazard ratio and its confidence interval [486]. The procedure regresses the survival times, or more specifically the so-called hazard function, on several explanatory variables [496], [497]. The Cox regression is also known as proportional hazards regression analysis [489], [498].

7.8.4 Survival function

The survival function, S(t) describes the probability that a person survives longer than some specified time t. It gives the probability that the random variable T exceeds the specified time t. The survival function is elementary to a survival analysis and is often expressed as a Kaplan-Meier curve as mentioned above [490]. This curve measures the fraction of subjects living for a certain amount of time after an event.

7.8.5 Hazard function

The hazard function is the probability that an individual will experience an event (e.g. death) within a small time interval, given that the individual has survived up to the

beginning of the interval. Consequently, it can be interpreted as the risk of dying at time t. The hazard function, $h(t)$, can be estimated based on the following equation [489].

$$h(t) = \frac{\text{number of individuals expecting an event in interval beginning at } t}{(\text{number of individuals surviving at time } t) \quad * \quad (\text{interval width})}$$

7.8.6 Hazard ratio

The hazard ratio is an equivalent to the odds that an individual in the group with the higher hazard reaches the trial endpoint first [486]. This rate is the probability that if the event in question has not already occurred, it will take place in the next time interval, divided by the length of that interval. As the time interval is made very short, the hazard rate actually shows an instantaneous rate [486].
A fundamental assumption of proportional hazards regression is that the hazard ratio stays constant over time [499]. Therefore, the hazard ratio indicates the relative likelihood of disease resolution in treated versus control subjects at any given point in time in clinical studies which have disease resolution as the endpoint [486].
The hazard ratio deriving from this model serves as a statistical test of treatment efficacy and an estimate of relative risk of events of interest [486].

7.8.7 Regression coefficient

The interpretation of the Cox model includes examining the coefficients for each explanatory variable. A positive regression coefficient for an explanatory variable marks a higher hazard. Consequently, the prognosis is worse. Conversely, a negative regression coefficient involves a better prognosis for patients with higher values of that variable [489].

7.9 Statistical implementations for this study

The three primary goals of survival analysis are first, to estimate and interpret survival and/or hazard functions from the survival data. Second, to analyse survival and/or hazard functions, and lastly, to assess the relationship of explanatory variables to survival time. Survival analysis provides a valuable tool for analysing the time to an event type

of data. In this study, these events are death, end of insurance period, ischaemic stroke ischaemic stroke including TIA, or myocardial infarction (see 7.2). Those endpoints deliver right censored data.

The Cox proportional hazards model is the method of choice in this study as it is both, flexible and powerful.

8 Results

8.1 Population characteristics

After having identified 10,325 potential study subjects in the AOK database, data from a total of 3,908 participants fulfilling all inclusion criteria (see 7.6.1) were analysed in this study. 1,600 (40.9%) men and 2,308 (59.1%) women were included with age ranging from 53.74 to 101.85 years (SD= 7.8). According to the AOK database more than 40% of all inhabitants of the district of Ebersberg aged >55 years were insured by the AOK. Following the official population census at the beginning of the study, the district of Ebersberg was populated by 119,000 inhabitants [500]. The AOK had and still has a market share of >40% in Bavaria [501].

About half of the cohort had lived in the district of Ebersberg for more than 50 years. 3,674 (94.0%) have been residents in this area for $\geq$10 years. 867 (22.3%) had seen their GP less than once quarterly. Additionally, 877 (22.5%) participants had reported an inpatient treatment in the past year (table 8.1).

Table 8.1
Age of study subjects and characteristics of a general practitioner consultation

Characteristics	Men (n=1,600)	Women (n=2,308)	Total (n=3,908)
Age, mean±SD, y	66.7±7.1	68.5±8.1	67.7±7.8
Duration of residency in district, mean±SD, y	44.4±20.0	45.5±20.7	45.0±20.1
GP consultation less than once a quarter	391 (24.5%)	476 (20.7%)	867 (22.3%)
Inpatient treatment in past 12 months	371 (23.2%)	506 (22.0%)	877 (22.5%)

8.1.1 Patients lost to follow-up

Patients, who were lost to follow-up are described in the section below. An overview of in- and exclusion criteria is given under 7.6.1.

3,374 participants were still insured by the AOK until the end of the trial in 2008.

In total 534 cases lost to follow-up were registered. 57 (1.5%) of them were documented due to a termination of the insurance relationship and 477 (12.2%) due to death during the trial period. Among other unspecified reasons, those deaths also include the study endpoints, namely ischaemic stroke including TIA, ischaemic stroke, and MI. The average age at death was 74.41 years (SD= 8.7).

Two (3.7%) individuals of the 57 drop-outs due to termination of the insurance period had an ischaemic stroke including TIA and one (1.9%) experienced an ischaemic stroke. No myocardial infarction was documented.

The category “ischaemic stroke including TIA” was chosen, as both conditions are medically closely related (see 2) and sometimes difficult to distinguish. In order to investigate, if the comparable risk factors for ischaemic stroke and TIA show commensurable outcomes, this classification was applied. In that way, ischaemic stroke alone can be compared to the overlapping category of ischaemic stroke and TIA. Consequently, data lost due to unspecific diagnosing is minimized.

38 (70.4%) subjects who dropped out after to the end of the AOK insurance period had no degree or finished secondary school (“Hauptschule”). Furthermore, 16 (29.6%) finished secondary modern school (“Realschule”) or had a high school graduation (“Abitur”). Additionally, 38 (70.4%) patients were married. Seven (13.0%) individuals were living alone.

8.1.2 Baseline characteristics

The mean systolic blood pressure was 139.4 mmHg (SD= 17.8), while the diastolic blood pressure was reported with 82.2 mmHg (SD= 9.4).
The most common disease documented by the GP was arterial hypertension with 2,242 (57.6%) individuals. 420 (32.5%) of the participants with diagnosed and treated hypertension showed blood pressure in the target range of <140/90 mmHg. At baseline, 1,967 (50.3%)

had a systolic blood pressure ≥140 mmHg and 947 (24.2%) a diastolic blood pressure ≥90 mmHg.

Moreover, in 588 cases (15.0%) high blood pressure was identified at baseline, which was unknown and untreated to this point.
Furthermore, at baseline 1,694 (43.9%) of all patients had dyslipidaemia, 393 (10.1%) participants were initially diagnosed. Additionally, 789 (20.2%) of the patients suffered from diabetes mellitus at baseline. 65 (1.7%) participants were newly diagnosed. 185 (4.7%) subjects suffered from atrial fibrillation at the beginning of the study (table 8.2, figure 8.1).

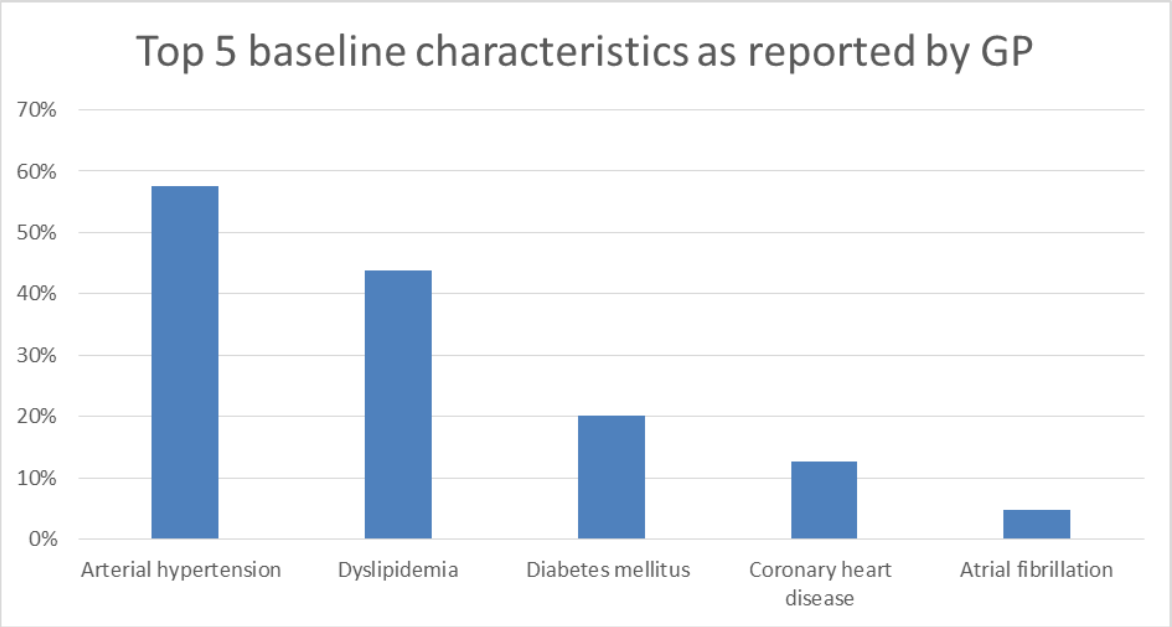

Figure 8.1
Top 5 baseline characteristics as reported by a general practitioner

At baseline, 135 (3.5%) patients suffered from ischaemic stroke (which is 67 (4.2%) men and 68 (3.0%) women), 174 (4.5%) from a TIA (which is 79 (5.0%) men and 95 (4.1%) women) as well as 162 (4.2%) participants from myocardial infarction (which is 115 (7.2%) men and 47 (2.0%) women). For further details please see table 8.2 below.

8.1.3 Laboratory results of cholesterol

The average serum concentration of HDL was 58.0 mg/dL (SD= 16.0) and of LDL 132.5 mg/dL (SD= 34.7). Further details are displayed in table 8.3.

Table 8.2
Baseline characteristics as reported by a general practitioner

Baseline characteristics as reported by GP			
Characteristics	**Men (n=1,600)**	**Women (n=2,308)**	**Total (n=3,908)**
Hypertension	883 (55.4%)	1,359 (59.1%)	2,242 (57.6%)
Systolic blood pressure $\geq$140 mmHg	795 (49.7%)	1,172 (50.8%)	1,967 (50.3%)
Diastolic blood pressure $\geq$90 mmHg	405 (25.3%)	542 (23.5%)	947 (24.2%)
Diabetes mellitus	373 (23.4%)	416 (18.0%)	789 (20.2%)
Dyslipidaemia	691 (43.2%)	1,003 (44.0%)	1,694 (43.9%)
Atrial fibrillation	94 (5.9%)	91 (3.9%)	185 (4.7%)
History of ischaemic stroke	67 (4.2%)	68 (3.0%)	135 (3.5%)
History of TIA	79 (5.0%)	95 (4.1%)	174 (4.5%)
History of myocardial infarction	115 (7.2%)	47 (2.0%)	162 (4.2%)

Table 8.3
Laboratory results of cholesterol

Physical examination and laboratory results			
Characteristics	**Men (n=1,600)**	**Women (n=2,308)**	**Total (n=3,908)**
HDL in mg/dL, mean$\pm$SD	51.8$\pm$13.9	62.4$\pm$15.9	58.0$\pm$16.0
LDL in mg/dL, mean$\pm$SD	128.8$\pm$34.7	135.1$\pm$34.5	132.5$\pm$34.7

8.1.4 Socioeconomic status

Living conditions

In terms of socioeconomic variables, the following picture emerged. 435 subjects (10.9%) had an intermediate or higher education level (“Realschulabschluss“ or “Fachhochschulabschluss“, “allgemeine Hochschulreife” and “Hochschulabschluss”).

To go into detail, 284 (7.3%) individuals finished secondary modern school (“Realschule”, 103 (6.4%) men and 181 (7.8%) women) and 5.6 (1.4%) held a degree from a technical college (“Fachhochschule”, 32 (2.0%) men and 24 (1.0%) women). Furthermore, 66

(1.6%) had passed their A-levels (“Abitur”) and went to university (38 (2.4%) men and 28 (1.2%) women).

Aditionally, 3,473 (89.5%) participants never went to school, only finished primary (“Grundschulabschlus or only secondary school (“Hauptschulabschluss”).

In detail, 186 (4.8%) did not have a school leaving qualification (70 (4.4%) men and 116 (5.0%) women) and 3,287 (84.1%) finished primary or secondary school (1,347 men (84.2%) and 1,940 (84.1%) women).

1,205 (30.8%) subjects described their marital status as widowed, divorced, or single, while 2,701 individuals were married (69.2%). Living alone was indicated by 893 (22.9%) of all participants.

Working conditions

Over their life time, 343 (8.8%) were never working in an employment. It clearly has to be stated that this group consists of four (0.3%) men and 339 (14.7%) women.

3,277 (83.9%) individuals (1,262 (78.9%) men and 2,015 (87.3%) women) indicated that they currently had no active profession, being retired (see table 8.4).

To go into detail regarding former occupation, 343 (8.8%) subjects did not pursue a career in their life or worked as housewives. Four (0.3%) of those never having worked in an employment were males and 339 (14.7%) were females.

Additionally, 1,789 (45.8%) were manual workers, 154 (3.9%) family workers in operating their own businesses, and 81 (2.1%) self-employed farmers.

Furthermore, 1,219 (31.2%) participants were employees, 267 (6.8%) individuals stated that they have been self-employed in trade and services, and 55 (1.4%) subjects worked as civil servants.

Taken together, 2,024 (51.8%) participants were employed in manual-labour occupations, while 1,541 (39.4%) of all subjects belonged to the skilled-labour group.

Table 8.4
Socioeconomic variables

Socioeconomic factors			
Characteristics	**Men (n=1,600)**	**Women (n=2,308)**	**Total (n=3,908)**
Low educational level	1,417 (89.1%)	2,056 (89.8%)	3,473 (89.5%)
Currently married	1,330 (83.2%)	1,371 (59.4%)	2,701 (69.2%)
Living alone	199 (12.4%)	694 (30.2%)	893 (22.9%)
Never working in employment	4 (0.3%)	339 (14.7%)	343 (8.8%)
Currently no active profession	1,262 (78.9%)	2,015 (87.3%)	3,277 (83.9%)

Life style variables

Regarding life style factors, the body mass index was in average 27.7 kg/m^2 (SD= 4.4). 1,007 (25.8%) participants had a BMI >30.0 at the baseline examination and are thus considered as obese according to the WHO standards [502]. 586 (15.0%) stated to be physically inactive. 2,423 (62.0%) individuals drank seven up to 21 drinks per week and were thus considered as current drinkers. 1,345 (34.4%) were current or former smokers (see table 8.5).

Table 8.5
Life style factors

Life style factors			
Characteristics	**Men (n=1,600)**	**Women (n=2,308)**	**Total (n=3,908)**
BMI, mean±SD	27.9±3.8	27.6±4.8	27.7±4.4
Obesity (body mass index >30.0 kg/m^2), kg/m^2	391 (24.4%)	616 (26.7%)	1,007 (25.8%)
No regular physical activity	191 (12.0%)	395 (17.1%)	586 (15.0%)
Current drinker	1,325 (82.9%)	1,098 (47.6%)	2,423 (62.0%)
Current or former smoker	949 (59.4%)	396 (17.2%)	1,345 (34.4%)

8.1.5 Follow-up outcome measures

During the study period, 230 (5.9%) patients suffered from ischaemic stroke including TIA, 161 (4.1%) from ischaemic stroke, and 92 (2.4%) participants from myocardial infarction, as displayed in table 8.6.

Table 8.6
Incidence of ischaemic stroke including TIA, ischaemic stroke, and MI over study period

Incidence of ischaemic stroke, TIA and MI over study period			
Characteristics	**Men (n=1,600)**	**Women (n=2,308)**	**Total (n=3,908)**
Incidence of ischaemic stroke including TIA	96 (6.0%)	134 (5.8%)	230 (5.9%)
Incidence of ischaemic stroke	74 (4.6%)	87 (3.8%)	161 (4.1%)
Incidence of myocardial infarction	61 (3.8%)	31 (1.3%)	92 (2.4%)

Figure 8.2 gives an overview of all pre-defined endpoints it this study. The 477 (12.2%) deaths mentioned above include deceases from ischaemic stroke including TIA, ischaemic stroke, or MI over the study period.

Figure 8.3 compares reported ischaemic stroke, ischaemic stroke including TIA, as well as baseline MI with the development of those diseases in the course of the study.

The following section focuses on the endpoints incidence of ischaemic stroke, ischaemic stroke including TIA, as well as the occurrence of myocardial infarction. The association of generally non-modifiable risk factors such as age and gender and modifiable risk factors like hypertension, LDL, HDL, atrial fibrillation, diabetes mellitus, obesity and body fat distribution, activity level in addition to consumption of alcoholic beverages, and smoking of cigarettes were investigated (see 2 and 3). The category of potentially modifiable risk factors included educational level, living arrangements, marital status, and occupation in a rather rural demographic structure of elderly (see 4 and 5).

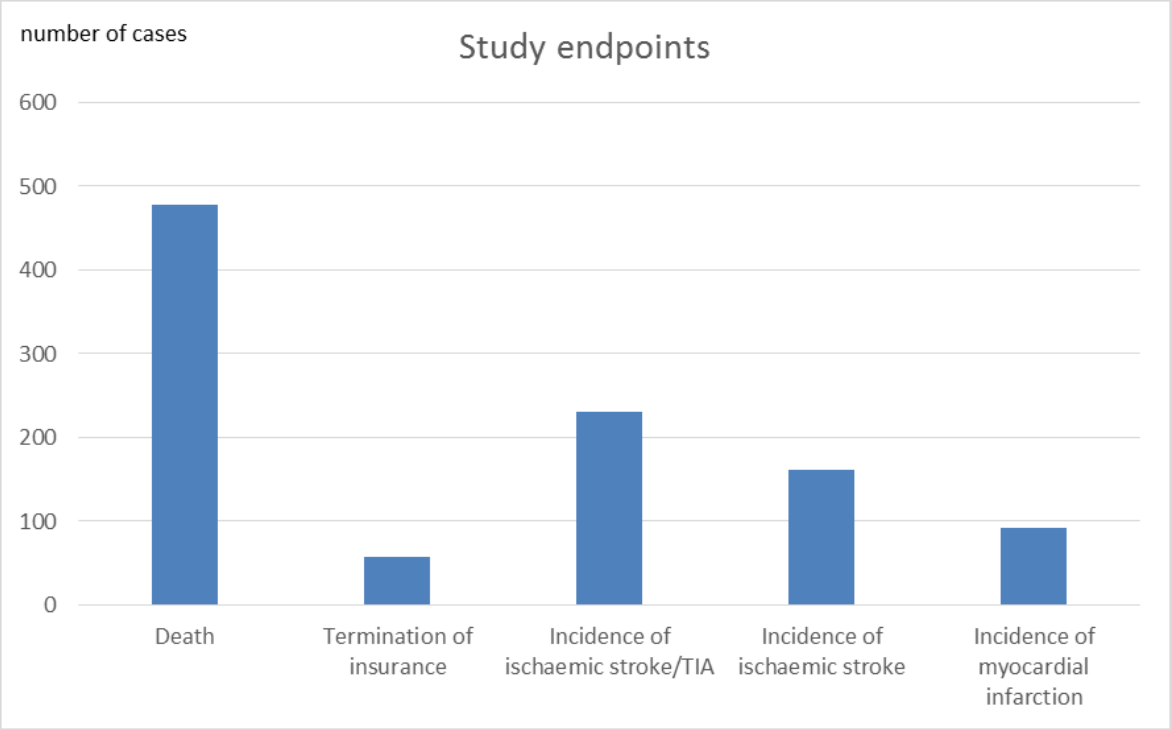

Figure 8.2
Number of cases by study endpoints

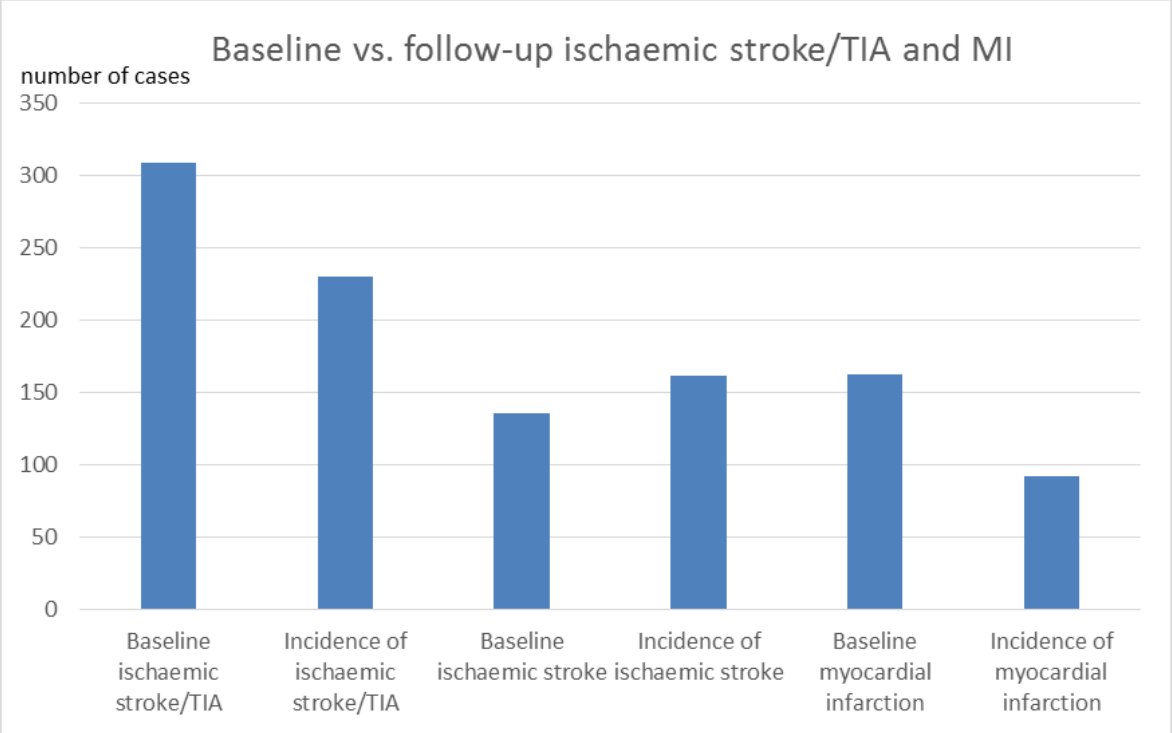

Figure 8.3
Number of cases at baseline compared to follow-up ischaemic stroke including TIA, ischaemic stroke, and MI

8.2 Ischaemic stroke including transient ischaemic attack

8.2.1 Traditional risk factors

Higher age (B= 0.08, SE= 0.01, p= $4.76x10^{-19}$) as well as cigarette smoking (B= 0.35, SE= 0.16, p= 0.03) were associated with an increased hazard to suffer ischaemic stroke including transient ischaemic attack.

Higher physical activity (B= -0.39, SE= 0.16, p= 0.02) had a significant protective effect. The results indicate an increased risk of ischaemic stroke including TIA with atrial fibrillation (B= 0.38, SE= 0.24, p= 0.11), although it did not pass significance level.

Even though considered as risk factors, no association of hypertension (B= 0.17, SE= 0.15, p= 0.27), diabetes mellitus (B= 0.18, SE= 0.16, p= 0.24), low HDL (B= -0.005, SE= 0.005, p= 0.295), high LDL (B= -0.001, SE= 0.002, p= 0.573), alcohol intake (B= -0.09, SE= 0.15, p= 0.55), and BMI (B= 0.001, SE= 0.016, p= 0.981) with ischaemic stroke including TIA was observed (table 8.7).

Table 8.7
Ischaemic stroke including TIA adjusted for traditional risk factors

Association of ischaemic stroke including TIA and traditional risk factors			
Risk factors	**Beta**	**SE**	**p-value**
Age	0.078	0.009	$4.76x10^{-19}$
Sex	-0.087	0.176	0.622
Hypertension	0.169	0.153	0.269
HDL	-0.005	0.005	0.295
LDL	-0.001	0.002	0.573
Atrial fibrillation	0.377	0.235	0.109
Diabetes mellitus	0.182	0.156	0.242
BMI	0.001	0.016	0.981
Physical activity	-0.389	0.159	0.015
Alcohol consumption	-0.090	0.150	0.551
Cigarette smoking	0.353	0.162	0.029

Figure 8.4 shows the survival curve from entry in the study until end of trial, death, drop out due to termination of the insurance period, or ischaemic stroke including TIA. A continuous occurrence of ischaemic stroke events and TIA are displayed.

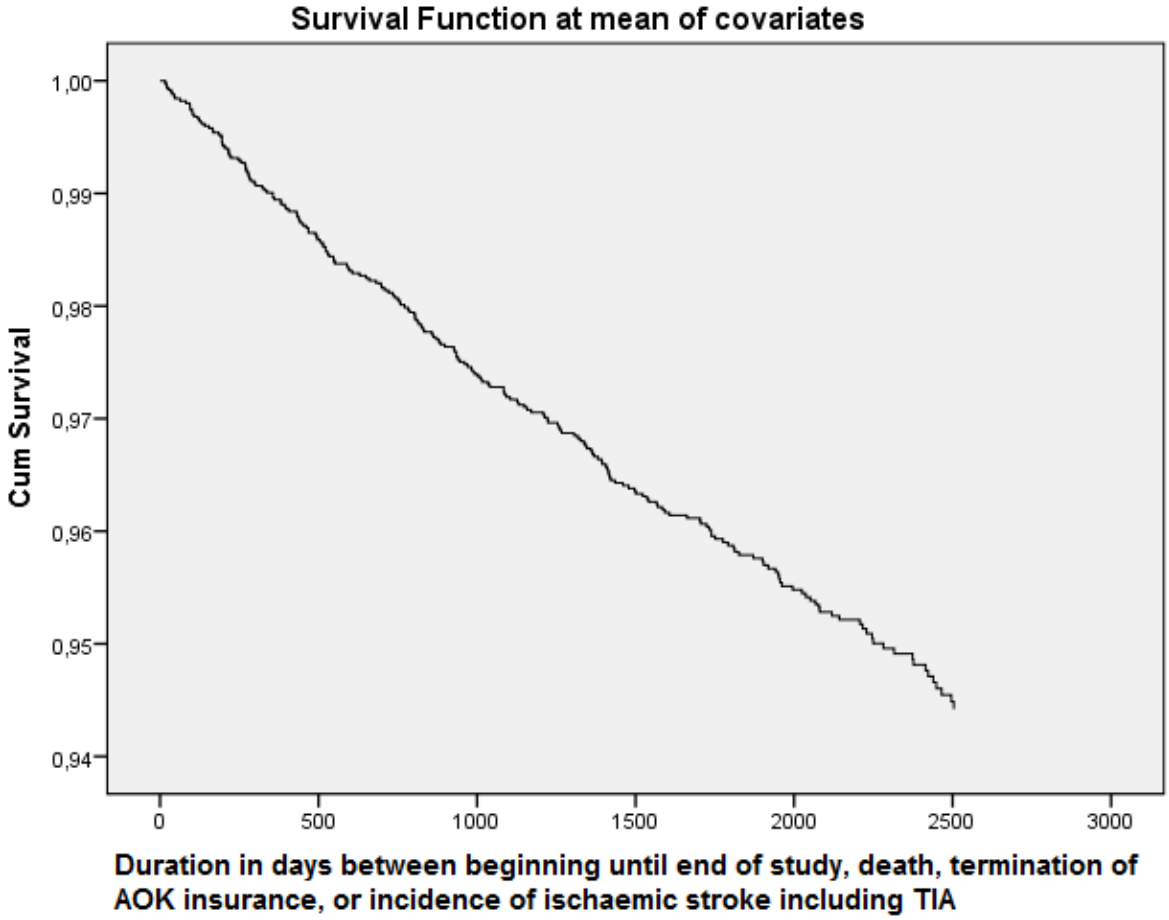

Figure 8.4
Survival curve ischaemic stroke including TIA

8.2.2 Educational status

A higher education status was significantly associated (B= -0.85, SE= 0.42, p= 0.05) with ischaemic stroke including TIA after correction for the confounding factors described above.

8.2.3 Marital status

Being married was not associated with getting an ischaemic stroke including TIA (B= -0.22, SE= 0.20, p=0.27).

8.2.4 Housing conditions

No effect of living arrangements and ischaemic stroke including TIA could be observed (B= 0.24, SE= 0.19, p= 0.21).

8.2.5 Occupation

No association was found between an individual's former or current occupation and the incidence of ischaemic stroke including diagnosed TIA (B= 0.13, SE= 0.24, p= 0.58).

8.3 Ischaemic stroke

8.3.1 Traditional risk factors

Advanced age (B= 0.09, SE= 0.01, p= 1.18×10^{-17}), high LDL (B= 0.005, SE= 0.002, p= 0.041), and the consumption of cigarettes (B= 0.559, SE= 0.193, p= 0.004) significantly increased risk for ischaemic stroke.

Physical activity (B= -0.39, SE= 0.19, p= 0.04) had a significant protective effect.

A slightly increased risk of ischaemic stroke was observed for patients suffering from atrial fibrillation (B= 0.50, SE= 0.27, p= 0.07).

Apart from that, none of the traditional risk factors was associated with ischaemic stroke (see table 8.8).

Figure 8.5 presents the survival curve for ischaemic stroke, indicating a linear incidence over the course of the study.

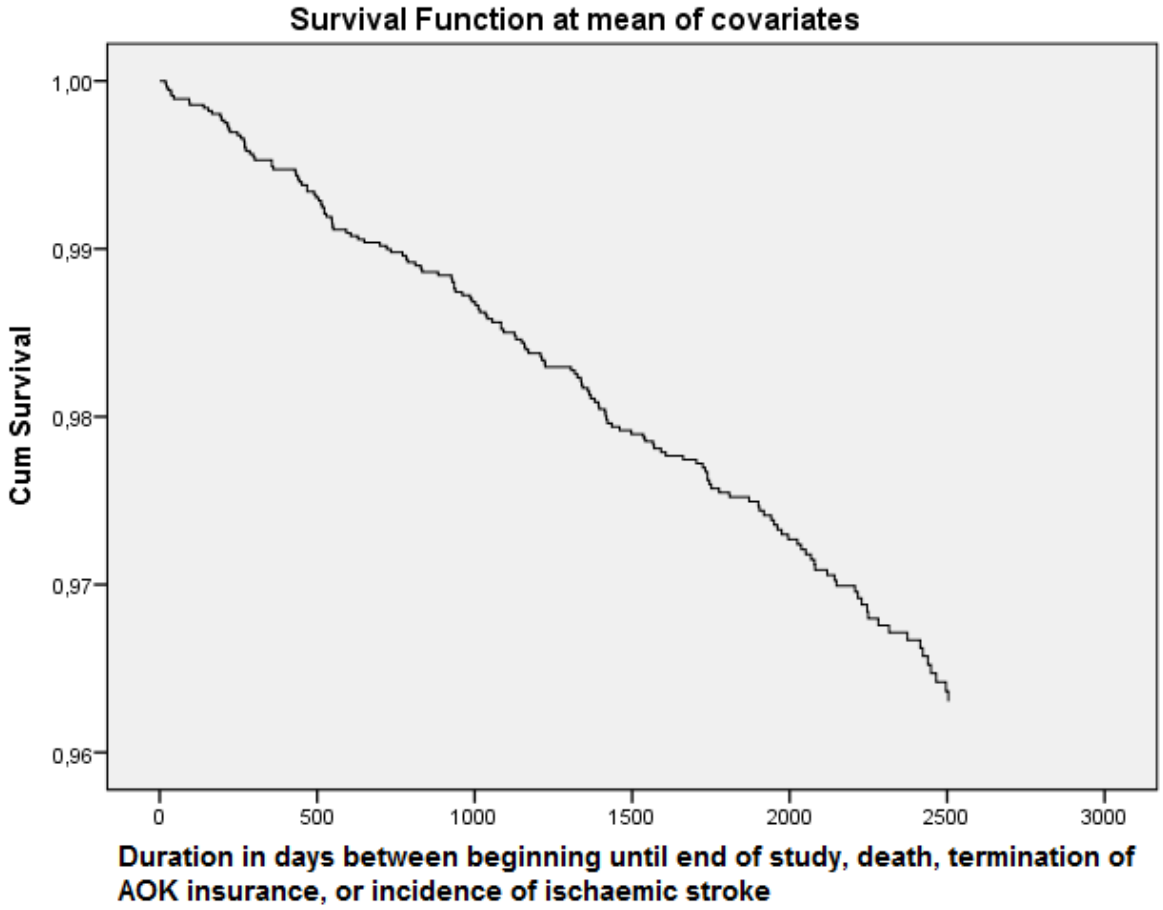

Figure 8.5
Survival curve ischaemic stroke

Table 8.8
Ischaemic stroke adjusted for traditional risk factors

Association of ischaemic stroke and traditional risk factors			
Risk factors	**Beta**	**SE**	**p-value**
Age	0.090	0.011	$1.18x10^{-17}$
Sex	-0.286	0.213	0.179
Hypertension	0.168	0.185	0.363
HDL	-0.003	0.006	0.557
LDL	0.005	0.002	0.041
Atrial fibrillation	0.499	0.270	0.065
Diabetes mellitus	0.285	0.183	0.121
BMI	0.006	0.020	0.777
Physical activity	-0.391	0.189	0.039
Alcohol consumption	-0.180	0.182	0.324
Cigarette smoking	0.559	0.193	0.004

8.3.2 Educational status

For ischaemic stroke, a higher educational status showed a significant influence (B= -1.63, SE= 0.72, p= 0.03).

8.3.3 Marital status

Married life had no effect (B= -0.34, SE= 0.25, p= 0.17) regarding the risk of ischaemic stroke.

8.3.4 Housing conditions

The type of housing was not associated with ischaemic stroke (B= 0.11, SE= 0.23, p= 0.63).

8.3.5 Occupation

Never having worked or no current active profession did not show any association (B= 0.06, SE= 0.28, p= 0.83) with ischaemic stroke.

8.4 Myocardial infarction

8.4.1 Traditional risk factors

Lastly, having had a closer look at the incidence of myocardial infarction, higher age (B= 0.09, SE= 0.01, p= $0.76x10^{-9}$), the incidence of hypertension (B= 0.45, SE= 0.26, p= 0.08), and smoking of cigarettes (B= 0.55, SE= 0.25, p= 0.03) were significant risk factors for MI. Being female (B= -0.946, SE= 0.297, p= 0.001) and high HDL were significantly protective (B= -0.025, SE= 0.009, p= 0.004). All other traditional risk factors did not show any effect (see table 8.9).

Table 8.9
Myocardial infarction adjusted for traditional risk factors

Association of myocardial infarction and traditional risk factors			
Risk factors	**Beta**	**SE**	**p-value**
Age	0.087	0.014	$0.76x10^{-9}$
Sex	-0.946	0.297	0.001
Hypertension	0.446	0.257	0.083
HDL	-0.025	0.009	0.004
LDL	0.002	0.003	0.444
Atrial fibrillation	-0.413	0.470	0.379
Diabetes mellitus	0.126	0.246	0.609
BMI	-0.014	0.029	0.619
Physical activity	0.123	0.300	0.683
Alcohol consumption	-0.189	0.255	0.458
Cigarette smoking	0.551	0.253	0.029

Consequently, figure 8.6 shows the survival curve for myocardial infarction, indicating a continuum in incidence of MI. As the incidence rates are higher for ischaemic stroke including TIA as well as ischaemic stroke separately, the survival curve for MI is flatter.

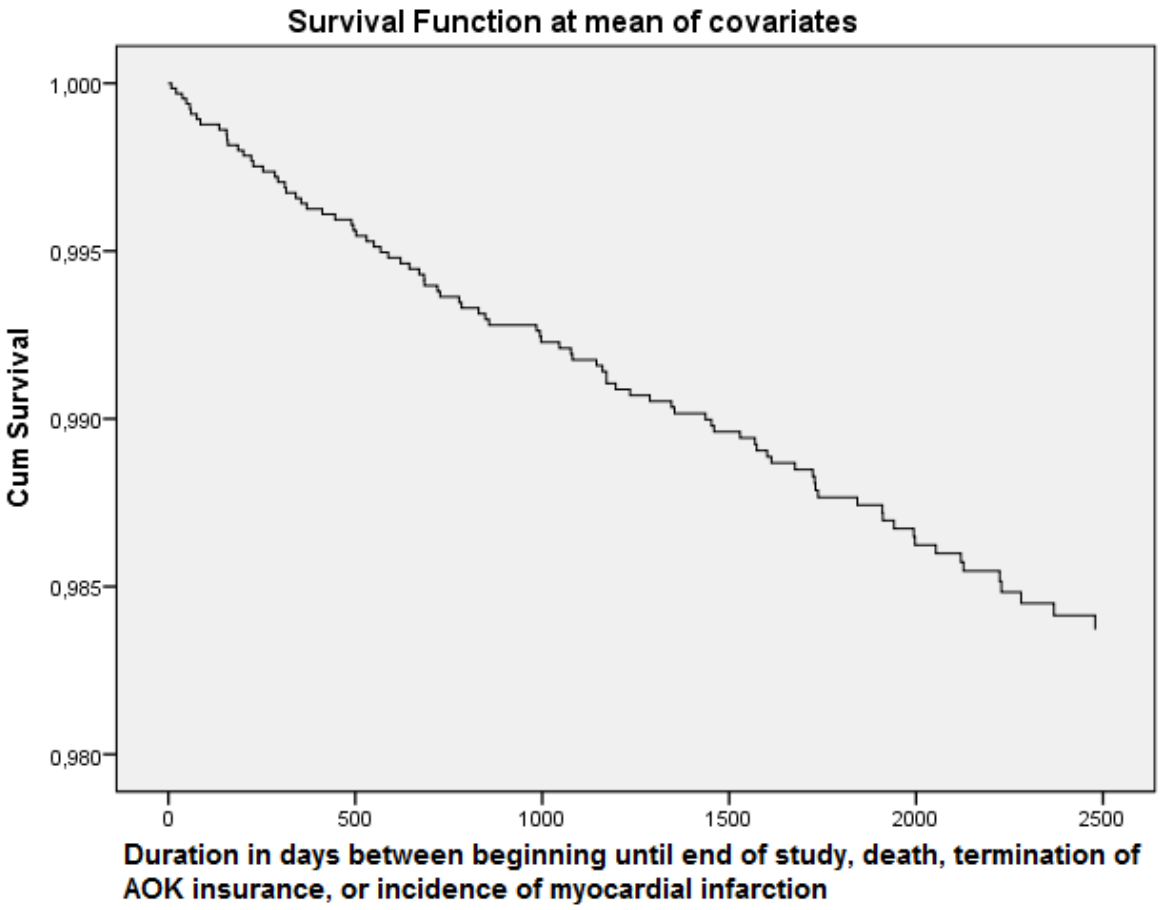

Figure 8.6
Survival curve myocardial infarction

8.4.2 Educational status

Educational level was not associated (B= -12.97, SE= 377.92, p= 0.97) with MI.

8.4.3 Marital status

Marital status had no effect on the incidence of myocardial infarction (B= 0.29, SE= 0.44, p= 0.51).

8.4.4 Housing conditions

Regarding the incidence of myocardial infarction, sharing a home with one or more people showed no association (B= -0.01, SE= 0.40, p= 0.98) with MI.

8.4.5 Occupation

Former or current occupational level had no significant association with suffering from MI (B= -0.43, SE= 0.43, p= 0.32).

9 Discussion

The following section will discuss the influence of previously published risk factors in the INVADE cohort. A detailed overview of current literature on modifiable and non-modifiable risk factors for stroke and MI can be found in chapters 2 and 3.

9.1 Traditional risk factors

9.1.1 Age and sex

1,600 (40.9%) men and 2,308 (59.1%) women were included in this study, showing a greater proportion of female participants.

An investigation on socioeconomic structures and morbidity by German health insurance companies on 21,835 subjects revealed that there are large discrepancies of policy holders by sex [503]. This is based on the fact that women tend to life longer in Germany [423]. In 2008, the AOK insured 53% females, marked in turquois (see figure 9.1). A higher proportion of female AOK policy holders was also documented in the INVADE study. This observation is assumable based on the general gender distribution in Germany, as the investigated age group (mean age 67.7 years) has a higher proportion of women [504].

9.1.2 Hypertension

In the INVADE cohort, arterial hypertension was reported in 2,242 (57.6%) patients.
This confirms the high prevalence of hypertension in Germany compared to most other European and North American countries (see table 2.1). In 2003, the prevalence of hypertension was estimated at 55.3%, matching the status of the baseline period in this study [103].

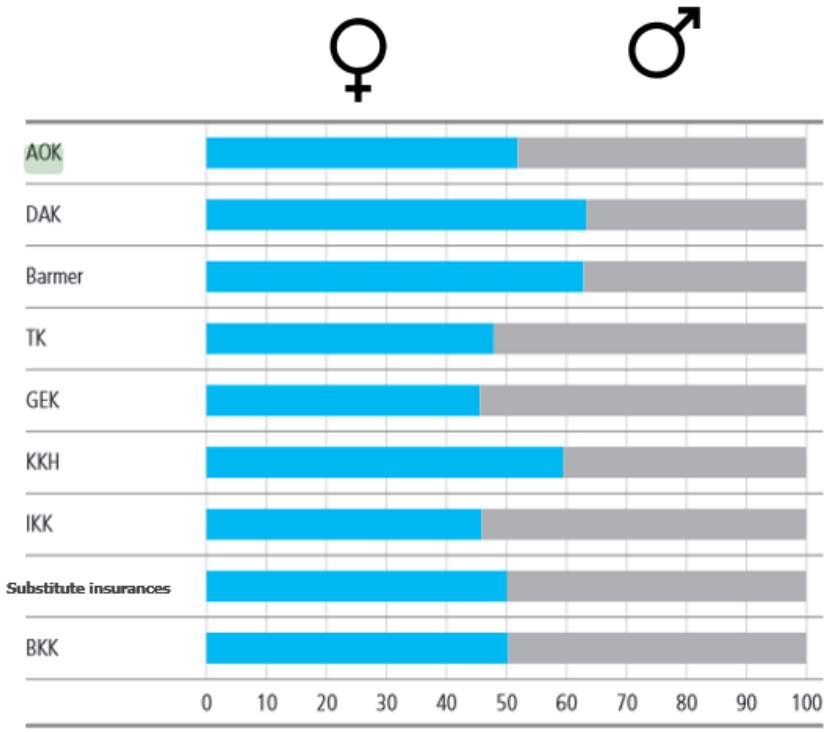

Figure 9.1
Gender distribution by health insurance in Germany [503].

9.1.3 High-density and low-density lipoprotein

Dyslipidaemia was documented in 1,694 (43.9%) participants in the present study. Results from the German Health Update 2009, a recent health interview survey conducted by the Robert-Koch-Institut, confirmed a prevalence of dyslipidaemia of 43.9% in woman. In lower educational groups, a slightly higher prevalence of 47.1% was reported [505]. Thus, the INVADE cohort represents the average on diagnosed dyslipidaemia compared to whole Germany.

9.1.4 Atrial fibrillation

In the INVADE population, atrial fibrillation was reported in 185 (4.7%) of all subjects at baseline.
This is consistent with findings, indicating a prevalence of 4% to 6% of AF in the German population older than 60 years [506].

9.1.5 Diabetes mellitus

789 (20.2%) subjects had diagnosed diabetes mellitus in this study. Results from the German Health Interview and Examination Survey for Adults observed a substantial increase in prevalence of diabetes mellitus with age. While the prevalence was 5% amongst those being 50 years old, it increased to 22% in those aged 70 to 79 years. This was reported for both sexes [507]. These data align with results from the INVADE study.

9.1.6 Body mass index

A mean BMI of 27.7 was documented in the INVADE population, with an average age of 67.7 years, as mentioned above. For males, the mean BMI was 27.9 and for females 27.6.
Compared with data from the German Health Interview and Examination Survey for Adults, a BMI of 28.8 (95% CI [28.4–29.2]) for men and 28.5 (95% CI [28.0–29.0]) for women was published for those aged 60 to 69 years [508].
The reported BMI in the INVADE cohort is consequently outside of the confidence interval, indicating a significant difference from the German average. This might be based on the large proportion of manual workers. 2,024 (51.8%) subjects conducted manual-labour occupations. These professions are associated with increased levels of physical activity leading to decreased body weight.

9.1.7 Physical activity

No regular physical activity was reported in only 586 (15.0%) participants (191 men (12.0%) compared to a slightly higher rate of 395 women (17.1%)) in the present trial.
The German Health Interview and Examination Survey for Adults observed that 15.9% (95% CI [13.5–18.5]) of those aged 60 to 69 years payed little or no attention to physical activity [509]. Thus, the INVADE cohort represents the entire German population in respect to PA.

9.1.8 Alcohol consumption

In the INVADE cohort, 2,423 (62.0%) participants indicated to consume alcohol regularly. 1,325 (82.9%) of those were males and 1,098 (47.6%) females.
Alcohol intake is hard to capture and questionnaires are error-prone. Thus, there is no reliable estimation of alcohol intake in Germany. Data based on the WHO Global status report on alcohol and health 2014 documented the pure alcohol consumption among persons aged 15 years or older in litres per capita per year [510]. For Germany, a total consumption of 11.8 l was published, consisting of 53.6% beer, 27.8% wine, and 18.6% spirits.
Following the statistical yearbook of the German Central Office for Questions Regarding Addiction, 96.4% of the population aged 18 to 64 drink alcohol [511]. Compared to the INVADE cohort, this number seems rather high. It might be based on the different study populations, as a decline in consumption with older aged compared to youth was underlined in the report. Consequently, a decreased level was expected in the present study.

In this context, it clearly has to be reported that men consumed about one third more alcohol than women. This gender distribution was also found in the INVADE study.

9.1.9 Cigarette smoking

1,345 (34.4%) subjects were current or former smokers in this study, these are 949 (59.4%) male and 396 (17.2%) female participants.
According to data from the German Health Interview and Examination Survey for Adults, 29.7% of the population aged 18 to 79 years did smoke in 2013 [512]. This rate is slightly below the one found in the present study. As mentioned before, manual work is commonly linked with higher proportions of smokers, especially in men [201], [333], [513].

9.1.10 Educational status

In the INVADE cohort, 3,473 (89.5%) individuals never went to school, completed primary school (“Grundschulabschluss”) only, or secondary school (“Hauptschulabschluss”) only. This trend can also be confirmed in those insured by the AOK outside of Bavaria. The

AOK holds the highest percentage of individuals with low educational attainment (see figure 9.2) compared to other health care providers. 48% of its customers finished only primary or secondary school [503]. Solely 9% passed the general matriculation standard (A-Level: “allgemeine Hochschulreife”).

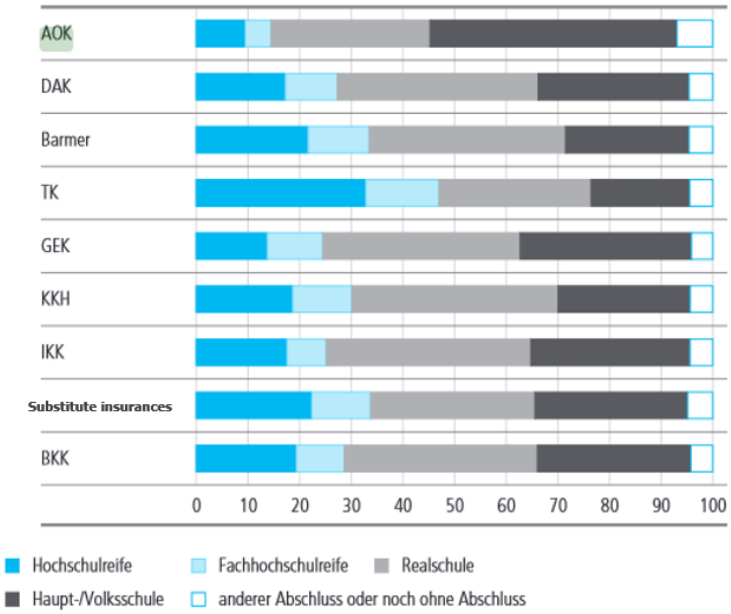

Figure 9.2
Educational level by health insurance in Germany [503];
legend to this overview: “Hochschulreife”: matriculation standard; “Fachhochschulreife”: technical college certificate; “Realschule”: secondary modern school; “Haupt-/Volksschule”: secondary school/ elementary school; “anderer Abschluss oder noch ohne Abschluss”: other degree or not yet graduated.

The higher amount of subjects belonging to lower educational levels might be based on the selected INVADE cohort. It encompasses individuals born in 1946 or before. Consequently, this study involves individuals, who grew up during war or the time after. At the time of World War II and in the post-war generation, education was not one of the first priorities in private and public life. This particularly applied for females [514].

To get a broader picture of how education developed in the administrative district of Upper Bavaria, Bavaria’s population census from 27th May 1970 will give an overview of educational attainment [515] as one of the first official publications after World War II.
This census revealed that 69.5% of all inhabitants finished primary school (“Hauptschulabschluss” or “Volksschulabschluss”) as highest degree (in relation to 77.3% in whole Bavaria). Having a closer look at the gender difference, in upper Bavaria 66.0% males and 72.6% females indicated primary school as their highest school leaving qualification.

In the INVADE cohort, primary or secondary school was finished by 3,287 (84.1%) subjects, 1,347 men (84.2%), and 1,940 (84.1%) women. These numbers are higher as reported in the census because two types of school were taken together in the patients' questionnaires.

For 11.6% secondary modern school ("Realschulabschluss") was the highest qualification (in relation to 9.0% in whole Bavaria). This was reported for 8.8% men and 14.1% woman.
In the present study, 284 (7.3%) participants graduated from secondary modern school, 103 (6.4%) men and 181 (7.8%) women. Those numbers are below the findings documented in the census, indicating a decreased educational level for the administrative district of Ebersberg. This might be explained by a more rural infrastructure and less educational-based interest due to future manual-orientated employments.
In terms of high school graduation ("allgemeine Hochschulreife"), 3.6% in Upper Bavaria (in relation to 2.1% in whole Bavaria) was documented. This level of education was passed by 4.8% of all males and 2.6% of all females.
Finally, a university level degree ("Hochschulabschluss") was obtained by 4.4% of the population of Upper Bavaria (in relation to 3.0% in whole Bavaria). 4.5% of all men and 1.7% of all woman finished college education.
In the INVADE study, 66 (1.6%) participants went to university, 38 (2.4%) men and 28 (1.2%) women. Those numbers are far below the ones registered for Upper Bavaria, confirming the low educational level in the district of Ebersberg for the targeted generation.

The census's calculations were based on 7,788,000 residents of Bavaria having passed the mandatory age to attend school. To conclude, the statements above have to be kept in mind when considering the rather low educational standards in the present cohort, especially observed for woman.

9.1.11 Marital status

69.2% of all participants were married at baseline in the INVADE cohort.
In Germany, a decrease in marriages over the past decades was reported. In 1950, there have been 11.0 marriages/1,000 inhabitants, in total 750,452 marriages. This number declined until 2013 to 4.6 marriages/1,000 inhabitants, in total 373,655 newly wed couples [516]. Figure 9.3 shows the trend in marriages in Germany from 1950 until today [516].

In 2013, Bavaria accounted with 47.5 marriages/10,000 inhabitants, in total 59,623 marriages. This was slightly less than the national average.

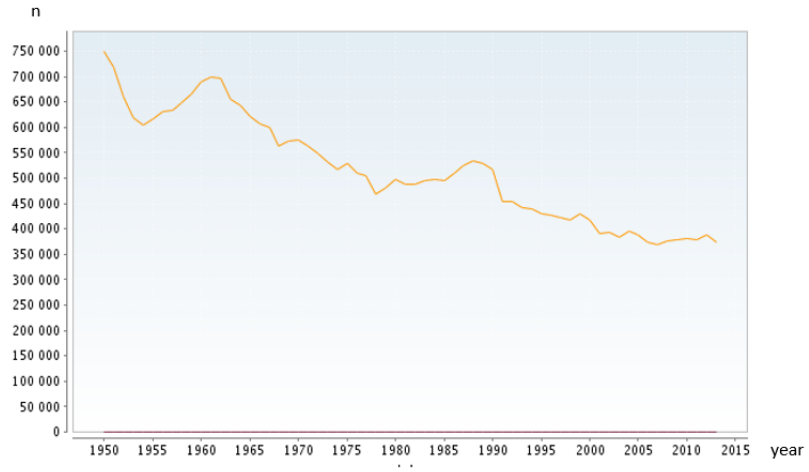

Figure 9.3
Trend in marriages in Germany, 1950 to 2015 [516].

Furthermore, 30.8% of all INVADE study participants stated to be divorced, widowed, or single.

In 1950, 1.9 marriages/1,000 inhabitants got divorced, in total 134,600 divorces. In contrast to this, in 2012, 2.2 marriages/1,000 inhabitants were ended [516]. In 2013, 21.1 divorces/10,000 inhabitants were registered, in total 169,833 divorces. In Bavaria, 19.7 divorces/10,000 inhabitants, in total 24,797 divorces, were below the federal average.

Moreover, in 2000, the year prior to baseline of the INVADE trial, men aged 60 to 69 years had a ratio of widowhood of 5.0%. For woman, this was 20.1%, which can be explained by differences in life expectancy [517].

In 1991, 11.6% of all males and 11.0% of all females aged 65 years and older were single [518].

Taken together, the reported proportions of marriage versus divorce, widowhood, or being single in the general German population are rather similar to those found in the present study.

9.1.12 Housing conditions

At baseline, 893 (22.9%) subjects indicated to live alone in the investigated cohort. In 2003, the end of the baseline period in this study, 21.1% single-person households were

registered in Germany, supporting these findings [519].

9.1.13 Occupation

In Upper Bavaria, the proportion of employees was steadily raising over the last decade [520]. The employment rate of those aged 55 to 65 years was higher in regards to other European countries [521]. In 2012, it was 61.5% for Germany compared with 48.8% in the whole EU. In the post-war generation, as predominant in this cohort, there was a clear distinction in occupational level by gender. Men tended to go to working as single earners. Women stayed at home, taking care of house and children [514]. This was also observed in the INVADE study. As a result, the focus of educational attainment, which attributes to future employment prospects (see 4.3), was on males rather than females. This explains the lower rates in educational level and occupation in women in this cohort, leading to a high number of housewives. On average, the AOK policy holder earned a net household income of €1.500 to €1.750 in 2008 [503]. As already mentioned, data regarding income was not collected in the present study.

9.2 Ischaemic stroke including transient ischaemic attack

In the following, the association of specific established risk factors as well as selected socioeconomic variables with the incidence of ischaemic stroke including TIA will be discussed.

The incidence of ischaemic stroke including TIA was 96 (6.0%) for males and 134 (5.8%) for females, leading to a total of 230 (5.9%) cases in the INVADE population.

9.2.1 Traditional risk factors

In the present investigation, advanced age, cigarette smoking, and atrial fibrillation were associated with an increased hazard to suffer from ischaemic stroke including transient ischaemic attack. Higher amounts of physical exercise had a significant protective effect. The next section will focus on the association of the reported significant risk factors with ischaemic stroke including TIA.

Increased age is a major risk factor for ischaemic stroke including TIA, as described in detail in chapter 2.1.2. At baseline, man had an average age of 66.7 years compared to 68.5 years for woman. In the course of the study, 161 (4.1%) ischaemic strokes were registered. 74 (4.6%) men versus 87 (3.8%) woman suffered from ischaemic stroke. This higher amount of male stroke patients confirms recent publications on higher incidence rates for stroke in males compared to females [522]. For further details on the incidence on stroke see chapter 1.3.
Consistent evidence from literature underlines that stroke risk factors progress over time, leading to an increased risk of ischaemic stroke with advanced age [25], [58], [74] (see chapter 2). This association was also confirmed in the INVADE study.

Moreover, the present trial underlined a significant association of the risk of ischaemic stroke including TIA with nicotine.
Literally every multivariable study on stroke risk factors, e.g. Framingham [20], Cardiovascular Health Study [181], and the Honolulu Heart Study [182], emphasized that smoking leads to an increased risk of stroke. Current smokers have a 50% higher risk of suffering from stroke during their course of life compared to persons who never smoked [186], [187].
Recent data stressed a strong associations between education and smoking for Germany, with higher prevalence rates of smokers in less educated classes [30], as present in this study.
A beneficial impact of PA was also documented in the INVADE cohort.
Furthermore, a wealth of evidence confirmed a significant association of PA and decreased risk of stroke [144], [146], [143]. The attractive leisure opportunities in the area of Ebersberg and frequent ownership of a garden or real estate went along with continuous activity.

Additionally, the present findings indicated an association of arterial fibrillation with an increased risk of ischaemic stroke including TIA, even though the results did not reach significance level.
Recent guidelines identified a relation of AF to a four- to five-fold increased risk of ischaemic stroke [74], which can also be assumed to highly contribute to the incidence of TIA.

Despite the fact that hypertension, diabetes mellitus, increased level of LDL, BMI, and alcohol consumption (see table 8.7) are considered as crucial risk factors for ischaemic stroke including TIA, no association could be found here. In the following, those results will be discussed.

Regarding hypertension, another study in the INVADE population analysed the reduction of long-term care dependence based eight year primary care prevention for stroke and dementia [523]. In this trial, the use of antihypertensive medications rose from 57.4% at baseline to 70.6% at follow-up. Additionally, the intake of statins increased from 16.1% to 25.9% and anticoagulants combined with antiplatelet drugs from 31.0% to 43.5%. Patient recognition of stroke risk factors, including BP, had improved continuously. Higher awareness might lead to a better adherence to recommended health behaviours and an increased motivation of life-style changes [524]. This modified attitude could have a huge impact on other listed risk factors, diminishing the negative influence of hypertension.
The same underlying principles might be assumed for a modified adaption by diagnosed diabetes mellitus as well as increased level of LDL. All these variables can be attributed to well-documented and modifiable risk factors [74]. Pathways mediating associations not significant for hypertension could also be connected to diabetes mellitus, because diabetes is perceptibly linked to hypertension [56].
As hypertension, diabetes mellitus as well as increased levels of LDL were documented at baseline, an appropriate therapy was initiated by the attending GP. As a result, the absence of a relationship might also indicate that the applied treatments worked, confirming the value of the INVADE study. The addressed cohort highly benefits from participating in the trial through closely and ongoing monitoring of their medical health and well-being. To further investigate this progress, follow-up treatments would have to be analysed.

Furthermore, the classification of consumption of no alcohol in contrast <7 drinks up to $\geq$21 drinks per week was applied. For ischaemic stroke including TIA, a J-shaped relationship with alcohol intake has been repeatedly reported [203], [202]. Compared to international standards, Germany ranks as one of the countries with the highest alcohol consumption for years [30]. Based on data of the German Central Office for Questions Regarding Addiction, 96.4% individuals in the age of 18 to 64 consume alcohol [511], as mentioned above. In the INVADE cohort, the majority of participants were not excessive but rather occasional drinkers. Thus, no significant effect was reported.

In terms of BMI, the absence of an association of BMI with ischaemic stroke including TIA was documented in the INVADE cohort. A generally high level of physical activity and increased proportions of manual working groups leading to a decreased body weight, might explain this finding. There is an ongoing discussion about the accuracy of the index. In a recent cross-sectional study, BMI misclassified 25% men and 48% women as not obese, underestimating obesity prevalence, especially in women [525]. The prevalence of falsely measured BMIs, increased misclassifications in females with advancing

age, and the reliability of gender-specific revised BMI cut-offs clearly have to be kept in mind. Consequently, a biased BMI can be assumed in the present trial.

In addition to BMI, measurement of abdominal body fat predicting stroke risk seem more efficient [176], [177]. Finally, the effect of BMI on stroke risk is to some extend driven by the influence of adiposity on other stroke risk factors [56], which were accounted for individually.

9.2.2 Educational status

Beside the risk factor analysis, the focus in the present study was on specific socioeconomic variables and their association with ischaemic stroke including TIA.
In the INVADE cohort, a higher educational status was significantly protective against ischaemic stroke including TIA after adjusting for the risk factors discussed above.
This is in agreement with numerous studies confirming an association of low educational attainment and ischaemic stroke [335], [203], [327], [363]. Generally, this effect can be attributed to specific health related behaviour, general life style, and the knowledge of stroke-related connections. A higher prevalence of well-established risk factor for stroke, such as increased smoking, higher prevalence of hypertension, and more frequent consumption of alcohol, are more common among groups with low SES and lower educational attainment [201], [333].
In the INVADE study however, a significantly increased risk for ischaemic stroke after correcting for these risk factors was documented. This is a clear strength of the present study. These findings indicate that low educational level is independently associated with an increased risk of ischaemic stroke.
A detailed overview of risk factors for stroke and the particular influence of lower SEP on stroke is given in chapters 4 and 5.
As a higher education level is also associated with an increased awareness of warning signs for stroke and a timely admission to hospital [367], health education is particularly crucial in areas with lower educational attainment, as in the present study. Health information programs might have an immense impact on stroke outcome and therefore quality of life in survivors.

9.2.3 Marital status

Measuring social isolation is a multiplex effort involving both structural, such as marital status and living arrangements, and functional aspects, like emotional and perceived support, of social relationships [526]. The next section will focus on the association of marital status with ischaemic stroke including TIA.

The implementation of contraceptives, student revolts in the so called "'68 generation", and women's liberation at home as well as on the labor market led to significant changes of the importance of marriage and its effect on health in Germany [424].
This is also applicable for Upper Bavaria, a region which is still strongly influenced by catholic faith. As the meaning of marriage diverges across countries and even varies within Germany, a generalization of the impact of marriage on stroke might be problematic.
In this context, no significant association between marital status and ischaemic stroke including TIA was found in the administrative district of Ebersberg in an elderly population.
A variety of studies from different regions questioned the protective effect of married life on risk for stroke.
For instance, the US Health and Retirement Study included participants born in 1947 or before [382], comparable with the cohort in the present trial. The association of being unmarried with stroke diminished after controlling for financial property. Unfortunately, values on income were not collected in the present study.
Moreover, another US community-based study found that patient characteristics of never married individuals seemed to resemble those of married persons [527]. This was found particularly for older people, who represent the target group in the INVADE study as well.
In this line, it was reported that single women older than 75 years did not differ from married or divorced women in their risk profile for stroke [424]. These findings suggest an attenuated meaning of marriage in later life. As mentioned above, this was also reported in the present cohort.

9.2.4 Housing conditions

The following section will discuss an additional aspect of life spent together with another person, namely cohousing.

To our knowledge, this is the first study investigating the effect of cohousing and the incidence of stroke including TIA. Most trials so far focused on related aspects, such

as referral time to the hospital, adherence to medical regimes, and outcome post-stroke regarding cohabitation (see chapter 5.2.5). No direct impact on the incidence of ischaemic stroke including TIA were determined. In this study, no significant association between living together with another individual and ischaemic stroke including TIA could be observed. In rural structures, as present in the INVADE study, an increased social support in the neighborhood by societies and clubs can be assumed. Those helping networks might compensate for the absence of a housemate by some extend. This daily social bonding could ameliorate the effects of living alone. Close neighborhood communities and proximity to family members could be decisive for a timely admission to the hospital and the ongoing stroke rehabilitation process.
Future research is needed to delve deeper into the multilayered interrelationship among living alone, social isolation, access to acute stroke care [384], and the incidence of ischaemic stroke including TIA.

9.2.5 Occupation

Former profession or current occupation did not show any association with ischaemic stroke including TIA. Occupation was highly correlated with age and sex in the present population, as people only work up to a certain age. Currently, the retirement age for Germany is 67 years.

In the INVADE cohort, 629 (16.1% regarding the whole study population) individuals (337 (53.6%) males and 292 (46.4%) females regarding working people) were employed at baseline. Age ranged from 53.74 to 82.90 years (SD= 3.97), with a mean age of 59.90 years for persons, who were still working at baseline. 14 (2.2%) out of these 629 participants in the working group suffered from ischaemic stroke including TIA during the trial phase.
In contrast to this, there were 3,277 (83.9% regarding the whole study population) participants (1,262 males (38.5%) and 2,015 females (61.5%) regarding retired people) not working at baseline. Age ranged from 53.95 to 101.85 years, with a mean age of 69.23 years in persons still working. On average, this group of retired persons is ten years older than the working subjects. Furthermore, it consist of two thirds of woman. The dominating proportion of females, both, in the retried group and those never having been employed, go back to historical reasons, as already stated above [514]. In the investigated cohort, woman working as housewives, raising children, and doing the household were prevalent. This proportion was consequently expected.

216 (6.6%) participants of the non-working subjects, composed of 3,277 individuals, suffered from ischaemic stroke including TIA during the trial phase. These higher rates in incidence of stroke in pensioners are supposedly mainly driven by advanced age and the resulting impact on risk factors for ischaemic stroke including TIA as discussed in chapter 2.

In general, occupational classification schemes can be rather diverse and pose a challenge to extract specific effects of individual indicators (see chapter 4).
In the Survey on Health and Ageing in Europe, 11,462 participants aged 50 to 64 years were investigated [528]. It could be revealed that stroke was strongly associated with early retirement and other types of non-participation in the labour force. This involved being a housewife or not having paid employment.
As in this study, no association of being housewife/unemployment with ischaemic stroke including TIA could be observed, the number of ischaemic stroke and TIA events might have been too small to get significant results.
Today, retirees are more than ever able to make the most of their free time after employment due to a comparable economical wealth, general improvements in the health care system, and broad life style modifications. A social rethinking process applies for the investigated cohort. An example for this would be the former omnipresence of smoking in politics, cinema, and daily life [232] in addition to increased consumption of traditional meals containing larger amounts of fat [505].
The termination of daily obligation, both, for men at work and for woman at home, might lead to a benefit and enjoyment of retirement. The observed generation still receives a comparatively secure pension. Living in the district of Ebersberg, Upper Bavaria, a Germany-wide economical strong area, facilitates deserved sunset years.

9.3 Ischaemic stroke

The following section contextualises the findings for ischaemic stroke separately.

Traditional risk factors and socioeconomic variables

In this cohort, the incidence of ischaemic stroke was 74 (4.6%) for males and 87 (3.8%) for females, leading to a total of 161 (4.1%) cases in the observed population.
The same pattern and trends as described above for ischaemic stroke including transient

ischaemic attack were reported for ischaemic stroke considered separately. This underlines the described distinct similarities (see 2) between ischaemic stroke and TIA [43], confirming the medically close connection. By considering both, ischaemic stroke including TIA and ischaemic stroke as individual groups, the strong association of the two diseases was confirmed.
Similar tends were also found regarding the selected socioeconomic variables. Again, there was a significant association of lower educational status with the incidence of ischaemic stroke.

9.4 Myocardial infarction

Furthermore, the next section will discuss the observations made for myocardial infarction.

In this study, the incidence of myocardial infarction was 61 (3.8%) for males and 31 (1.3%) for females, resulting in a total of 92 (2.4%) cases in the INVADE population.

9.4.1 Traditional risk factors

Having had a closer look at the incidence of MI, higher age, the incidence of hypertension, and nicotine consume were significantly associated with an increased risk of myocardial infarction while high levels of HDL were significantly protective against MI. The risk to suffer from MI was found to be significantly lower for women.
In agreement with numerous other studies [101], [235], [468], [226], [5], age and hypertension were also major risk factors for MI in the present study.
In general, smoking rates declined over the past decades, especially in old age [324], [30]. Nevertheless, the high prevalence of current smokers, particularly in males, induced an increased risk of myocardial infarction in this cohort.
Even though considered as traditional risk factors, no association of higher concentration of LDL, was found in this study. Furthermore, diagnosed diabetes mellitus, increased alcohol consumption, higher BMI, and physical inactivity did also not show any association.

In contrast to several other studies [247], [5], [246] we could not observed an increased risk of MI in diabetes patients. However, due to the design of the INVADE study, all cases of diabetes were treated instantly after diagnosis, as described above. Again, no

relation might be based on the effective treatment applied in the cohort, closely medically monitoring its patients.

This might also be applicable for LDL concentrations, as no association was found between LDL level and incidence of MI in the present cohort. A large number of trials reported treatments targeting lower LDL in dyslipidaemic patients were highly efficient in preventing MI [249], [235], [226]. At baseline, 1,694 (43.9%) of all participants had dyslipidaemia, 393 (10.1%) subjects were initially diagnosed. The immediate initiation of an appropriate therapy might have helped to control the disease, weakening the association with the risk of MI.
As mentioned earlier, the strength of the association between alcohol consumption and risk of MI decreases with advanced age [529]. Thus, this might have weakened a potential relation.

Additionally, the measure of BMI could lead to misclassifications of overweight and obesity [530]. On the one hand, some people are overweight according to BMI but nevertheless live healthy and move a lot and on the other hand, others are not overweight based on BMI but do not move regularly. As a result, the latter group has for instance a high proportion of body fat, which is unhealthier than actual overweight. This potentially hidden effect could also be present in this cohort, including individuals with higher BMI but good general fitness.
In terms of physical activity, the actual level of physical exercise might have easily been underestimated, as a large number of individuals live in and/or possess larger estates in and around Ebersberg. Employees in jobs with a high proportion of physical activity, such as craftsman or farmers, might not do any regular sport after work, but are moving a lot all day long.

9.4.2 Educational status

In the present study, no significant association of MI and educational level could be observed. A number of trials reported no significant or only a weak association of lower educational attainment and mortality after myocardial infarction [531], [532]. In opposition to this, other researchers observed a significant inverse association of low educational level and MI mortality [436].
The majority of investigations analysed mortality rates rather than incidence, which was investigated in the INVADE cohort. Kirchberger et al. (2014) emphasized that additional studies on the association between education and long-term mortality after first AMI in

Germany are required. The present study however underlines the importance of further studies on MI incidence in association with educational attainment as well.
In this context, it can be argued that individuals with different educational levels diverge in unobservable ways. This might involve different preferences regarding long term investment in their future [294].
Instead of assuming that good health is induced by education, underlying hidden variables could cause both, good health and better education. In the present study, this is corrected for risk factors like high BMI, raised BP, and high lipid concentration. It might be that the lack of an association between MI and education is not due to a better general health of those, who have a higher educational attainment.
Furthermore, education might spring into action through improving health related knowledge, enabling the choice of healthier lifestyles, which decreases mortality risk. Again, education leads to advantageous employment situations with higher salary, improving living conditions throughout adulthood.

9.4.3 Marital status

In the INVADE cohort, marital status had no protective effect on the incidence of myocardial infarction.
There are some studies, which have reported commensurable findings. After controlling for socioeconomic and lifestyle factors, women, who were married or living with a partner, had a similar risk of developing CHD in comparison with women, who were not married or living with a partner [533].
Additionally, after adjusting for potential risk factors, a protective effect of marriage on incidence of MI could not be documented among men [427].
On the other hand, other investigations reported a protective effect of marital status on incidence of MI [425], [314]. Populations of studies that found this effect were comparatively younger.
Consequently, it is not fully understood, if an association between marriage and AMI is independent of other psychosocial factors including social support and living alone [425]. In this line, a Swedish study investigated the impact on psychosocial factors for prognosis after myocardial infarction. It could be revealed that marital status, marital strain, and dissatisfaction with family life were not significantly associated with mortality after first infarction having controlled for social support [534].
A decreased protective effect of marriage with advanced age compared to younger age

groups was observed [428], [314]. This might also apply for the present study. The beneficial effects attributed to marriage, such as dietary patters, physical activation, and adherence to heath care variables, could already be incorporated into daily life in the elderly INVADE population, becoming independent of the mediation by the social support of spouses.
This aspect of accumulation of positive effects of marriage over long periods of time was specifically reported for Germany [424]. The wealth of experience older people obtained during the course of their lives might lead to a prolongation of it.

9.4.4 Housing conditions

The impact of cohousing on MI is controversial. The majority of studies was focusing on mortality after MI rather than on incidence of MI. Further research is needed to fill this gap. While some studies found a positive association between living alone and mortality after MI [535], other trials did not reveal any impact [536].
After multivariable adjustment for patients' demographic, medical history, clinical treatment, and baseline health status, subjects living alone had a comparable risk of mortality and readmission to hospital (HR, 0.99, 95% CI [0.76-1.28]) compared to individuals in cohousing [425].
In the present study, no association between cohousing and the risk of AMI could be found. As already discussed before (see 9.2.4), a potential negative impact of living alone might be mediated through intensified interpersonal relationships in this specific cohort. Social network measures collect the number of different domains in which an individual cultivates social contacts. These were strong predictors of mortality risk, but weak to predict incident disease [537]. It might also be true in the present study. Marital status alone does not always incorporate a protective effect against the incidence of MI. The true impact of living together correlates with the outcome of the disease, which was not measured in this study.

9.4.5 Occupation

In the INVADE cohort, no association was found regarding former or current occupation and MI. As stated above (see 9.2.5), 629 (16.1%) subjects (337 (53.6%) of those males and 292 (46.4%) females) were in employment at baseline. Eight (1.3%) participants of the working group, composed of 629 subjects, suffered from myocardial infarction over

the course of the trial.
Opposed to this, 3,277 (83.9%) individuals (1,262 of those males (38.5%) and 2,015 females (61.5%) regarding retired people) had no active profession at baseline.
84 (2.6%) out of these 3,277 participants of the non-working subjects suffered from MI during the trial phase. These higher rates in incidence of myocardial infarction in retired persons were assumedly mediated by advanced age and the resulting effects on risk factors of MI, as discussed in chapter 3.

Even if occupational class is largely considered as an exceedingly comprehensive indicator of an individual's socioeconomic status [287], substantial differences within occupational classes might not have been registered in this study. Collecting additional information, such as income or ownership structures, might be helpful in future studies. However, in Germany, especially in rural areas as applicable for the investigated cohort, disclosure of wealth is considered as taboo. Therefore, it is questionable if information about the individual financial situation can be reliably collected. Particularly, if this information had to be handed over to the GP, a widely honored but exceedingly public figure within the community.
Educational attainment might reflect gradual alterations in factors like health behaviour and access to health information, influencing mortality differentials over a long period of time. Contrarily, trends in occupational diversity may mirror modifications in variables, such as the physical and psychosocial ranges of work [538].
As a result, the informative value and the validity of the education level as applied measurement regarding occupation was emphasized.

To conclude this section, not all studies confirmed an association of socioeconomic position and MI [539], [540], [541]. Other investigations reported an inverse association of low SES with increased risk of MI [415], [414].
In this context, it clearly has to be mentioned that a direct comparison of the reported findings might be challenging as these studies differ significantly regarding country of origin, follow-up time, and indicators used for measuring SES [436]. As a result, the impact of socioeconomic variables on the incidence of MI is an ongoing debate to which INVADE contributes in the present study.

9.5 Strengths and limitations

In the following, strength and limitations of the INVADE study will be considered.

9.5.1 Strengths

Approximately half of the study population had lived in the district of Ebersberg for more than 50 years. 94.0% of all participants have been residents in this area for more than ten years. This leads to a stable group of study subjects without considerable confounding due to moves or frequent changes of GP, as it can be expected in larger cities in the same area, such as Munich, Upper Bavaria, Germany.
80.5% of all subjects have seen their GP more than once quarterly. This ensured a timely and ongoing monitoring of changes in the patient's health status. Furthermore, it enables an individually tailored treatment approach, which is highly beneficial for the included patients. Examples for this connection were given above. Germany-wide, the AOK ranks on first place in terms of number of doctor appointments compared with other health insurance companies, reporting five consultations on average in the last 12 month. This number clearly confirms the observations made in the INVADE trial.
In this line, the long and rather complete follow-up of all patients initially included in the study is a fundamental strength of the present investigation.

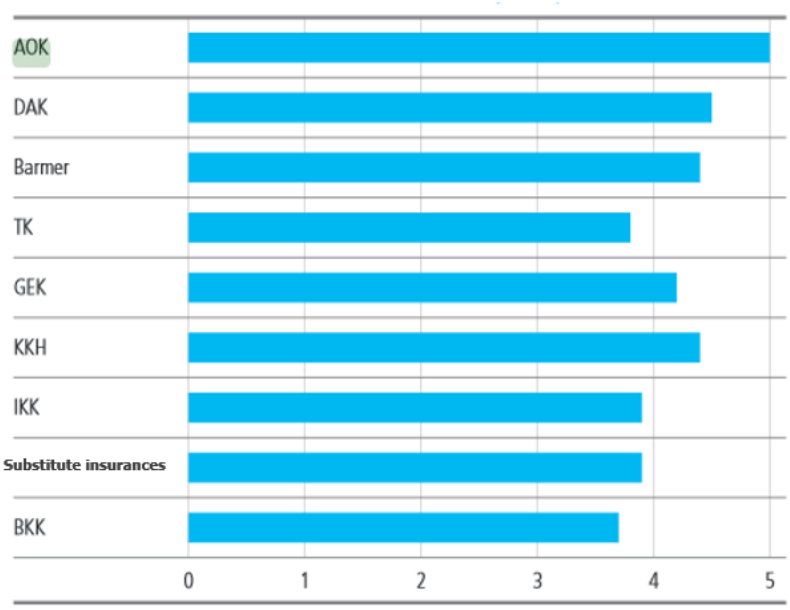

Figure 9.4
Number of doctor's consultations per year by health insurance in Germany [503].

Most importantly, a large number of reviewed studies showed the essentiality of adjusting for relevant risk factors for stroke and MI. The majority of trials reported a significant crude association between SES and mortality of MI, which generally weakens significantly

after controlling for confounders such as diabetes or smoking [541]. In contrast to this, the present study adjusted for numerous traditional risk factors based on current literature review for both, ischaemic stroke including TIA (see chapter 2) and MI (see chapter 3).

9.5.2 Limitations

All potential subjects were identified in the AOK database and then asked via mail to participate in the INVADE trial. This can be considered as a study limitation as subjects were selected based on only one insurances company. More than 40% of all inhabitants of the district of Ebersberg older than 55 years were insured by the AOK. The AOK has a market share of more than 40% in Bavaria [501] and covers about one third of the German population.
Generally, different insurance companies tend to represent special patient clienteles [503]. With 51%, the AOK shows the highest percentage of policyholders in lower social classes. Only 2% can be attributed to the upper class (see figure 9.5). In this context, it clearly has to be underlined that the present cohort in the administrative district of Ebersberg is a very selective sample based on rural structures. In addition to this, there is a disproportionately high number of individuals, who have only attended secondary school in the observed age group. Consequently, this might not always allow a direct comparison with current findings published within the Anglo-American area. Educational attainment might act as an intervening variable in this case.

Furthermore, to be able to further decode potential interconnections of incidence of ischaemic stroke, TIA, and MI, psychosocial measures, including social isolation, social assistance, or psychosocial loneliness, were not directly included in the present analysis. Associations might exist in the present cohort, but could not be revealed.
Additionally, previous publications investigating the INVADE population have focused on dementia [542], [543], [544], aspects of long-term care dependence [523], chronic kidney disease [545], [546] as well as atherosclerosis [547], [548]. Consequently, not only the endpoints differ substantially from those selected in the present study, but also variables diverged substantially. Beside the traditional risk factors of which some of the selected variables have also been addressed in prior studies [478], [549], the inclusion of socioeconomic variables is so far a new and singular approach. The collected data during baseline and follow-up examinations were not primarily designed for the research issue addressed here. If focused from the start, more sensitive and concise approaches

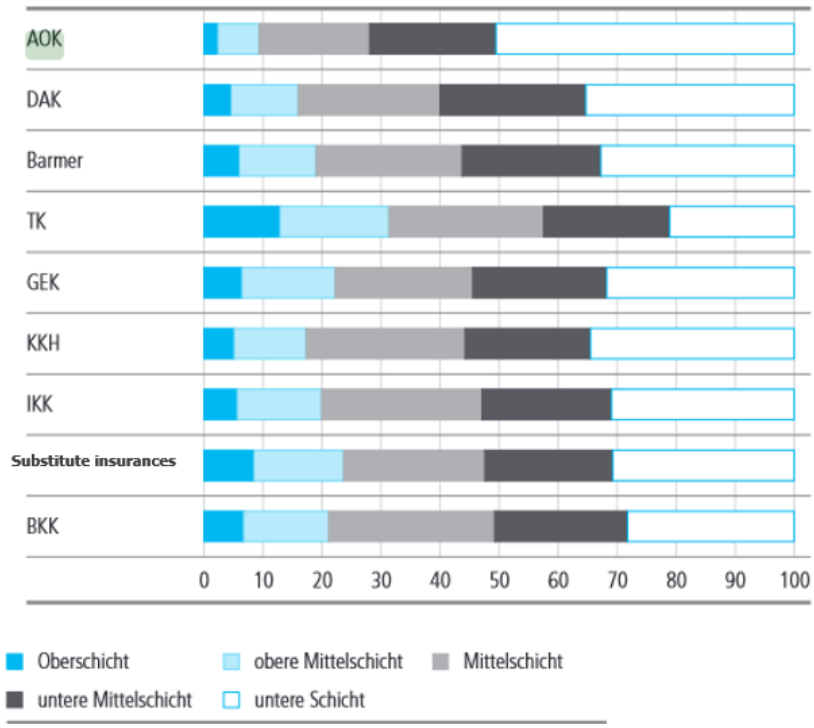

Figure 9.5
Socioeconomic position by health insurance in Germany [503];
legend to this overview: “Oberschicht”: upper class; “obere Mittelschicht”: upper middle class, “Mittelschicht”: middle class; “untere Mittelschicht”: lower middle class; “untere Schicht”: lower class.

might have been included in the methods and design of the questionnaires.
Moreover, a long-term investigation on mortality after ischaemic stroke, TIA, and MI would have been highly interesting. Most of the reviewed trials took stroke or MI mortality as study endpoint. As the INVADE trial is still actively running, a follow-up study to compare alterations in the influence of the discussed socioeconomic variables with the status stated here, might be highly interesting.

9.6 Implementations

9.6.1 Value of health care education for health economics

Regarding the described raising prevalence of stroke and DALYs lost due to stroke and MI (see chapter 1.3), health resources worldwide are already overburdened [8].
As a result, health-care providers should focus on the provision of stroke and MI chronic care, involving the prevention of secondary cases [550]. In this course, the integration of community rehabilitation, including self-managed rehabilitation procedures are recommended.
Stroke and MI share a large number risk factors. At the same time, socioeconomic differences in stroke mortality remained relatively stable, while disparities in CHD mortality widened over time in most European countries [324]. Educational disparities in stroke mortality remained of comparable magnitude, while increasing in ischemic heart disease mortality.
Even though research on older age groups in developed countries with old age structures is increasing [551], it persist to be rather sporadic compared to the number of trials conducted in younger or middle aged subjects [552], [553].
In the population of elderly, recommended stroke therapies are often underused. In addition to this, several studies underlined that subjects with a poor education were more likely to discontinue medication after MI. The effect of advanced age on medication therapy cessation was more pronounced in women than men [554].

Those aspects relating compliance and age clearly have to be considered when designing health care campaigns. More efficient strategies are required to appropriately educate the general as well as high-risk population regarding stroke [11] and MI in terms of warning signs and an immediate response enabling a timely hospitalisation. In order to increase awareness of warnings signs and symptoms regarding stroke, the INVADE network actively contributed to a recent information event in Ebersberg [555]. The main

aim of this campaign was to call the emergency ambulance immediately, as every single minutes of delay in hospitalization may result in significantly wore prognosis. More initiatives like this should be launched to ensure public attention.

Health care education can be based on a variety of different efficient approaches. Policies should include improved access to heathy, affordable, and labelled foods within the community. More frequent physical education in schools and also at worksites, increased access to recreational spaces, higher taxes on tobacco and alcohol, promotion of public funding for heart disease, stroke intervention programs, and CVD preventive benefits in health insurances should be addressed.

To deliver this crucial message, mass media has a huge impact on distributing information about prevention of CVD. As the source of information varies according to patient characteristics [556], health education programs should be adapted accordingly. For instance, a recent study suggested a “stroke riskometer app”, individually indicating the absolute risk of suffering from stroke in the upcoming years [557].

To summarize, well directed health care education in lower socioeconomic classes can contribute to decreased incidence rates in stroke and MI, lowering overall costs in the German health care system [505]. Direct and indirect effects based on those strategies might not be seen immediately, but future generations will feel their impact.

9.6.2 Perspectives

The Global Burden of Diseases, Injuries, and Risk Factors Study revealed a substantial geographical difference in stroke burden by regions and country income level. This is presumably attributed to the diversity in the national income per person [8]. Within highly industrialized countries, like Germany, good health services and strategies for stroke prevention and care are the most likely elucidations for the decrease in stroke and MI incidence, mortality, and DALYs lost. Development and monitoring of the effectiveness of preventive programs focusing on risk factors for stroke and myocardial infarction, such as control of blood pressure, smoking cessation, effective preventive strategies [8], and optimisation of acute stroke and chest pain units, could fulfil a most effective contribution. These approaches should be culturally acceptable, economical, and aimed at both, high-risk individuals and the general population.
Research plays an essential role in lowering the burden of stroke [11], [558] and MI by improving quality standards in medical care, disseminating interdisciplinary knowledge,

and providing data on comparative effectiveness. In all sectors and on all levels of health care, including not only governmental committees, but also health care providers, patient groups, and non-governmental agencies, combined effort should be directed on the decrease of projected incidence rates for stroke and MI (see chapter 1.3).

In January 2009, the existing German risk structure compensation scheme between sickness funds from 1994, called “Risikostrukturausgleich” (RSA), has been extended in order to involve morbidity-oriented factors as well [559]. This led to the term “morbi-RSA”, aiming at preventing risk selection, improving the medical care for patients with chronic diseases, and equalizing starting positions for competition between sickness funds. The morbi-RSA implicated a fundamental reorganization of finance flows which is highly controversial. Diagnostics are profitable for the health insurance companies, creating economic costs. In the present study, educational attainment was reported as an independent and significant risk factor for ischaemic stroke and TIA. This variable is currently not included in the morbi-RSA, indicating a disadvantage for the AOK. In the future, a potential involvement of educational level might lead to intense socio-political discussions.

There is an urgent need for ongoing well-designed, easy to compare, community-based stroke epidemiology and surveillance trials. Implementation of preventive strategies have proven highly effective at community level [557]. A deepened health care education focusing on the revealed discrepancies in the INVADE cohort might lower incidence rates and the burden of disease in the administrative district of Ebersberg.
Furthermore, the generated results from future research will ameliorate our knowledge of stroke as well as MI determinants and burden worldwide. Moreover, an in-dept understanding of assumed causes of discrepancies and alterations in trends in disease burden will be enabled by this approach. Delving deeper into the question why lower educational level was significantly and independently associated with the incidence of ischaemic stroke and TIA in this study, but not with MI, would be exceedingly enlightening. As stroke including TIA are diseases directly affecting the brain, a closer connection between knowledge and brain compared to diseases aiming at the heart could be assumed. Qureshi et al. (2003) reported that the effect of educational attainment on myocardial infarction was more prominent in persons aged 50 years or less [328]. This finding might lead to the conclusion that the adverse consequences of low educational level are more likely to manifest in younger individuals. In older age groups, as in the present study, traditional risk factors might have a higher impact than educational attainment in determining an individual’s risk for MI, as opposed to stroke and the closely linked TIA.

To conclude, the third Report on Poverty and Wealth in Germany clearly states that prevention and participation services should aim at diminishing the effects of illness and disability to achieve the longest re(integration) in life [423]. According to the coalition agreement of November 2005, prevention and health promotion are to be highly promoted in order to increase life expectancy and quality of life in Germany.

The present study attributed to this goal with a further step on a long way ahead.

10 References

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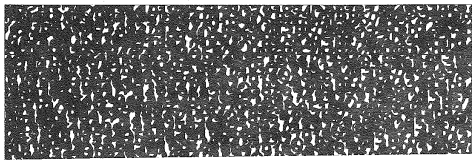
A Appendix

INVADE **PATIENTENFRAGEBOGEN (AUFNAHME)**



Geschlecht
☒ männlich
☐ weiblich

Praxis (Stempel)
Gemeinschaftspraxis
Dr. med. Eckart Giensch
Dr. med. Michael Hora
Arzt für Allgemeinmedizin / H-Arzt der BG
Dr.-Hariaub-Ring 3 - Tel. 0 61 21 / 9 34 00 - Fax 93 40 40
85570 Markt Schwaben
64/84 307

Wir möchten darauf hinweisen, dass die Beantwortung der Fragen freiwillig ist. Ihre Angaben werden streng vertraulich und anonym – entsprechend den Grundsätzen des Datenschutzes – behandelt. Bitten Sie Ihren Hausarzt oder die Arzthelferin um Hilfe, wenn eine Frage unverständlich ist. Lassen Sie möglichst keine Frage aus. Die AOK Nr. wird von Ihrem Arzt oder der Arzthelferin eingetragen.

ALLGEMEINE ANGABEN

01 Nationalität
☒ deutsch
☐ andere, bitte angeben welche

02 Familienstand
☒ verheiratet ☐ geschieden
☐ verwitwet ☐ ledig

03 Wohnform
☐ allein lebend
☒ Zwei-Personen-Haushalt
☐ Mehr-Personen-Haushalt
☐ Senioren-/Pflegeheim

04 Seit wann wohnen Sie schon im Landkreis Ebersberg?
1955 bitte das Jahr angeben

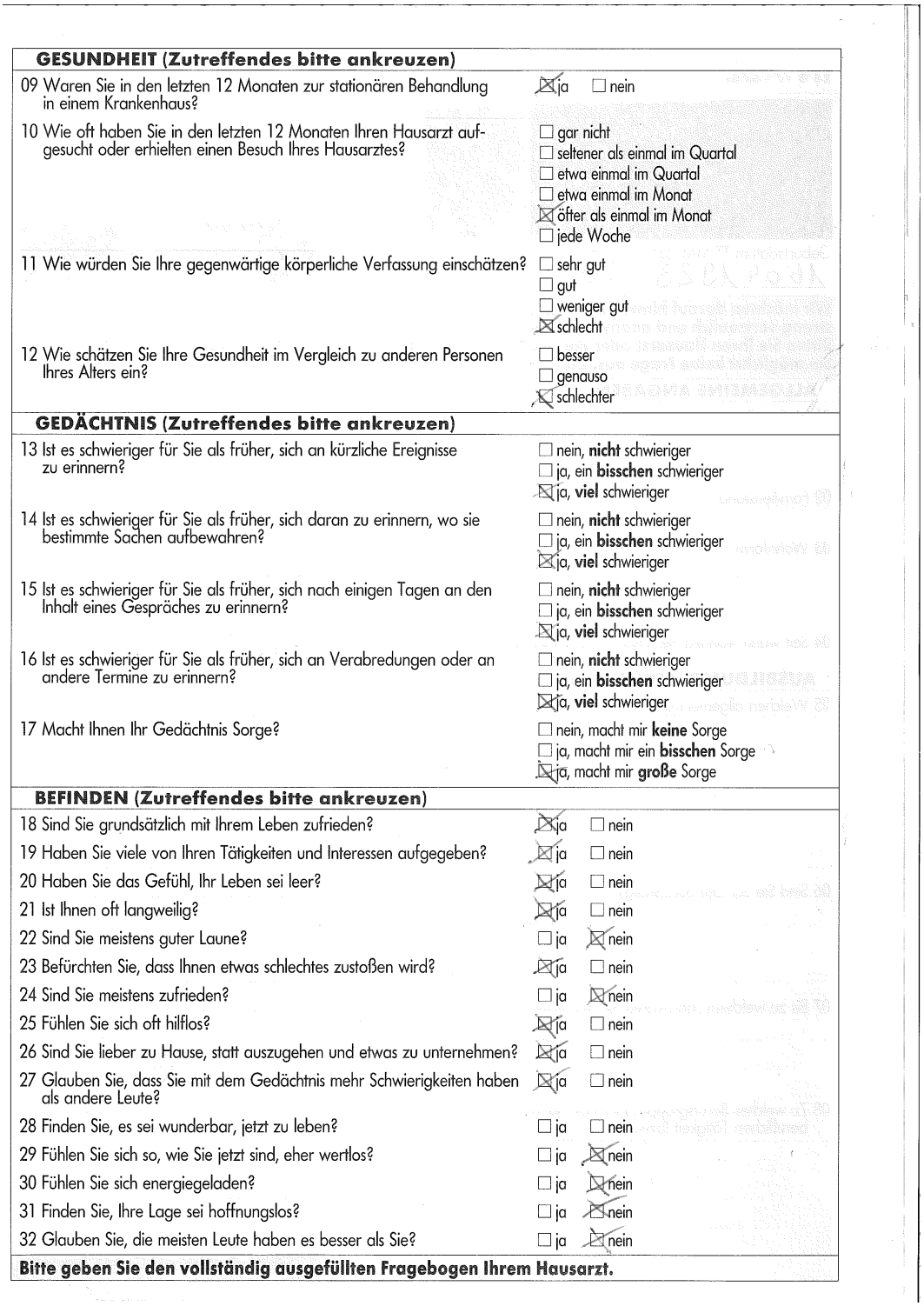
AUSBILDUNG, BERUF (Zutreffendes bitte ankreuzen)

05 Welchen allgemeinbildenden Schulabschluss haben Sie?
☐ Schule **ohne Abschluss** beendet
☒ **Volks-/Hauptschulabschluss**
☐ **Mittlere Reife, Real**schulabschluss
☐ **Fachhochschulreife** (Abschluss einer Fachoberschule)
☐ **Abitur**, Hochschulreife
☐ **anderer** Schulabschluss, und zwar

06 Sind Sie zur Zeit berufstätig?
☐ ja, mit einer **Ganztags**beschäftigung
☐ ja, mit einer **Teilzeit**beschäftigung
☐ nein, **arbeitslos**
☐ nein, **Hausfrau/Hausmann**
☒ nein, **Renter/Rentnerin**

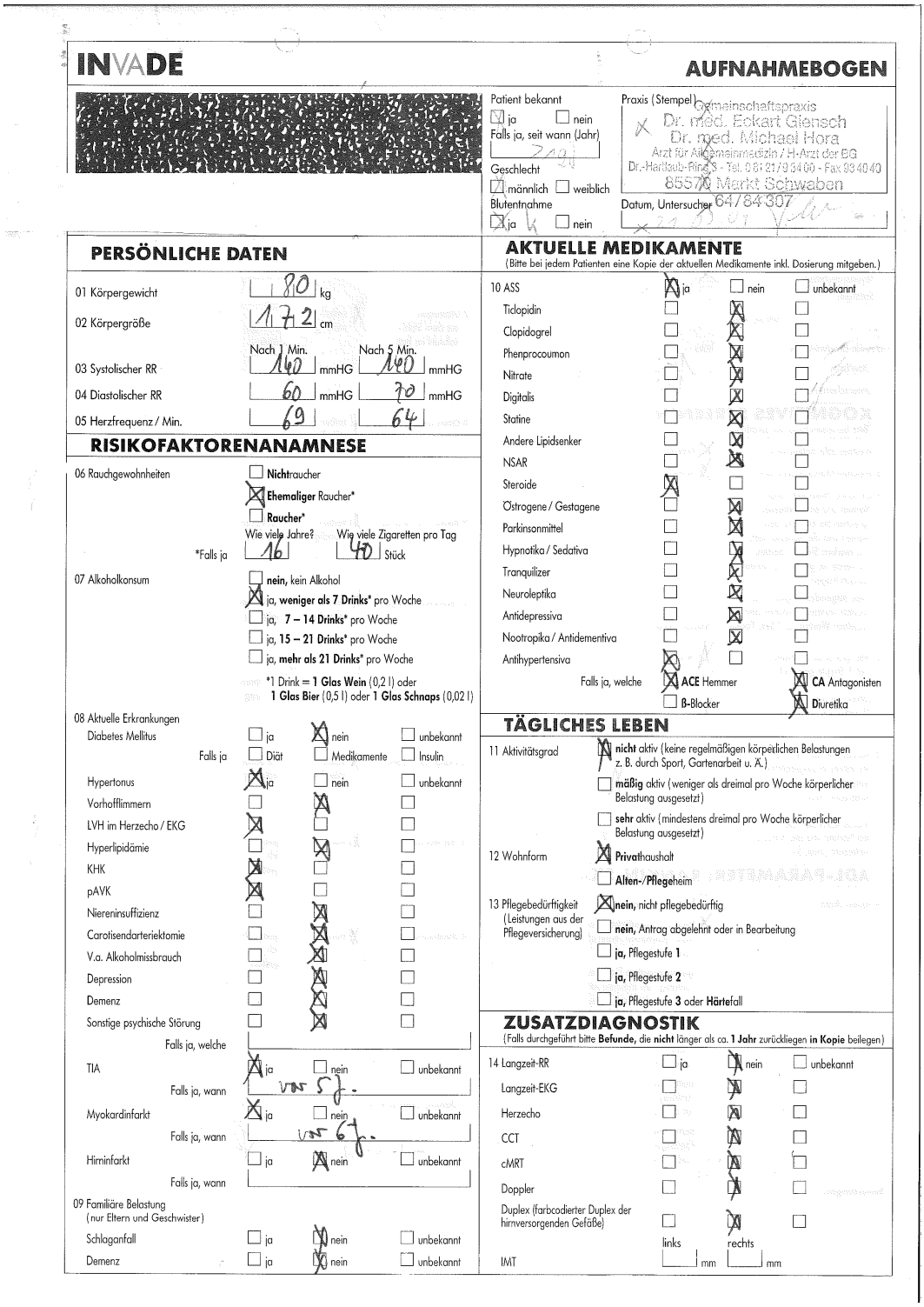
07 Bis zu welchem Jahr waren Sie hauptberuflich erwerbstätig?
☐ war **nie** hauptberuflich erwerbstätig
☐ **bin noch** hauptberuflich erwerbstätig
☒ **war** hauptberuflich erwerbstätig
bis zum Jahr 1986

08 Zu welcher Berufsgruppe gehörten Sie bei Ihrer letzten hauptberuflichen Tätigkeit (bzw. derzeit, wenn Sie noch berufstätig sind)?
☐ keinen Beruf ausgeübt, Hausfrau
☐ mithelfende(r) Familienangehörige(r) im eigenen Betrieb
☒ Arbeiter, Arbeiterin
☐ Angestellter, Angestellte
☐ Beamter, Beamtin
☐ selbstständige(r) Landwirt(in)
☐ Selbstständige(r) in Handel, Gewerbe, Dienstleistung



GESUNDHEIT (Zutreffendes bitte ankreuzen)	
09 Waren Sie in den letzten 12 Monaten zur stationären Behandlung in einem Krankenhaus?	☒ ja ☐ nein
10 Wie oft haben Sie in den letzten 12 Monaten Ihren Hausarzt aufgesucht oder erhielten einen Besuch Ihres Hausarztes?	☐ gar nicht ☐ seltener als einmal im Quartal ☐ etwa einmal im Quartal ☐ etwa einmal im Monat ☒ öfter als einmal im Monat ☐ jede Woche
11 Wie würden Sie Ihre gegenwärtige körperliche Verfassung einschätzen?	☐ sehr gut ☐ gut ☐ weniger gut ☒ schlecht
12 Wie schätzen Sie Ihre Gesundheit im Vergleich zu anderen Personen Ihres Alters ein?	☐ besser ☐ genauso ☒ schlechter
GEDÄCHTNIS (Zutreffendes bitte ankreuzen)	
13 Ist es schwieriger für Sie als früher, sich an kürzliche Ereignisse zu erinnern?	☐ nein, **nicht** schwieriger ☐ ja, ein **bisschen** schwieriger ☒ ja, **viel** schwieriger
14 Ist es schwieriger für Sie als früher, sich daran zu erinnern, wo sie bestimmte Sachen aufbewahren?	☐ nein, **nicht** schwieriger ☐ ja, ein **bisschen** schwieriger ☒ ja, **viel** schwieriger
15 Ist es schwieriger für Sie als früher, sich nach einigen Tagen an den Inhalt eines Gespräches zu erinnern?	☐ nein, **nicht** schwieriger ☐ ja, ein **bisschen** schwieriger ☒ ja, **viel** schwieriger
16 Ist es schwieriger für Sie als früher, sich an Verabredungen oder an andere Termine zu erinnern?	☐ nein, **nicht** schwieriger ☐ ja, ein **bisschen** schwieriger ☒ ja, **viel** schwieriger
17 Macht Ihnen Ihr Gedächtnis Sorge?	☐ nein, macht mir **keine** Sorge ☐ ja, macht mir ein **bisschen** Sorge ☒ ja, macht mir **große** Sorge
BEFINDEN (Zutreffendes bitte ankreuzen)	
18 Sind Sie grundsätzlich mit Ihrem Leben zufrieden?	☒ ja ☐ nein
19 Haben Sie viele von Ihren Tätigkeiten und Interessen aufgegeben?	☒ ja ☐ nein
20 Haben Sie das Gefühl, Ihr Leben sei leer?	☒ ja ☐ nein
21 Ist Ihnen oft langweilig?	☒ ja ☐ nein
22 Sind Sie meistens guter Laune?	☐ ja ☒ nein
23 Befürchten Sie, dass Ihnen etwas schlechtes zustoßen wird?	☒ ja ☐ nein
24 Sind Sie meistens zufrieden?	☐ ja ☒ nein
25 Fühlen Sie sich oft hilflos?	☒ ja ☐ nein
26 Sind Sie lieber zu Hause, statt auszugehen und etwas zu unternehmen?	☒ ja ☐ nein
27 Glauben Sie, dass Sie mit dem Gedächtnis mehr Schwierigkeiten haben als andere Leute?	☒ ja ☐ nein
28 Finden Sie, es sei wunderbar, jetzt zu leben?	☐ ja ☐ nein
29 Fühlen Sie sich so, wie Sie jetzt sind, eher wertlos?	☐ ja ☒ nein
30 Fühlen Sie sich energiegeladen?	☐ ja ☒ nein
31 Finden Sie, Ihre Lage sei hoffnungslos?	☐ ja ☒ nein
32 Glauben Sie, die meisten Leute haben es besser als Sie?	☐ ja ☒ nein
Bitte geben Sie den vollständig ausgefüllten Fragebogen Ihrem Hausarzt.	

Figure A.1
INVADE questionnaire admission examination for patient.



INVADE

AUFNAHMEBOGEN

[redacted]

Patient bekannt: [X] ja [ ] nein
Falls ja, seit wann (Jahr): 2004
Geschlecht: [X] männlich [ ] weiblich
Blutentnahme: [X] ja [ ] nein

Praxis (Stempel):
Gemeinschaftspraxis
Dr. med. Eckart Glensch
Dr. med. Michael Hora
Arzt für Allgemeinmedizin / H-Arzt der BG
Dr.-Hartlaub-Ring 3 · Tel. 0 83 21 / 9 34 00 · Fax 93 40 40
85570 Markt Schwaben

Datum, Untersucher: 21.03.07 64784307

PERSÖNLICHE DATEN

01 Körpergewicht	80 kg	
02 Körpergröße	172 cm	
	Nach 1 Min.	Nach 5 Min.
03 Systolischer RR	160 mmHG	140 mmHG
04 Diastolischer RR	60 mmHG	70 mmHG
05 Herzfrequenz / Min.	69	64

RISIKOFAKTORENANAMNESE

06 Rauchgewohnheiten
- [ ] **Nicht**raucher
- [X] **Ehemaliger** Raucher*
- [ ] **Raucher***

*Falls ja: Wie viele Jahre? 16 | Wie viele Zigaretten pro Tag? 40 Stück

07 Alkoholkonsum
- [ ] **nein,** kein Alkohol
- [X] ja, **weniger als 7 Drinks*** pro Woche
- [ ] ja, **7 – 14 Drinks*** pro Woche
- [ ] ja, **15 – 21 Drinks*** pro Woche
- [ ] ja, **mehr als 21 Drinks*** pro Woche

*1 Drink = **1 Glas Wein** (0,2 l) oder **1 Glas Bier** (0,5 l) oder **1 Glas Schnaps** (0,02 l)

08 Aktuelle Erkrankungen

Diabetes Mellitus	[ ] ja	[X] nein	[ ] unbekannt	
Falls ja	[ ] Diät	[ ] Medikamente	[ ] Insulin	
Hypertonus	[X] ja	[ ] nein	[ ] unbekannt	
Vorhofflimmern	[ ]	[X]	[ ]	
LVH im Herzecho / EKG	[X]	[ ]	[ ]	
Hyperlipidämie	[ ]	[X]	[ ]	
KHK	[X]	[ ]	[ ]	
pAVK	[X]	[ ]	[ ]	
Niereninsuffizienz	[ ]	[X]	[ ]	
Carotisendarteriektomie	[ ]	[X]	[ ]	
V.a. Alkoholmissbrauch	[ ]	[X]	[ ]	
Depression	[ ]	[X]	[ ]	
Demenz	[ ]	[X]	[ ]	
Sonstige psychische Störung	[ ]	[X]	[ ]	
Falls ja, welche				
TIA	[X] ja	[ ] nein	[ ] unbekannt	
Falls ja, wann	vor 5 J.			
Myokardinfarkt	[X] ja	[ ] nein	[ ] unbekannt	
Falls ja, wann	vor 6 J.			
Hirninfarkt	[ ] ja	[X] nein	[ ] unbekannt	
Falls ja, wann				

09 Familiäre Belastung (nur Eltern und Geschwister)

Schlaganfall	[ ] ja	[X] nein	[ ] unbekannt
Demenz	[ ] ja	[X] nein	[ ] unbekannt

AKTUELLE MEDIKAMENTE

(Bitte bei jedem Patienten eine Kopie der aktuellen Medikamente inkl. Dosierung mitgeben.)

	ja	nein	unbekannt
10 ASS	[X]	[ ]	[ ]
Ticlopidin	[ ]	[X]	[ ]
Clopidogrel	[ ]	[X]	[ ]
Phenprocoumon	[ ]	[X]	[ ]
Nitrate	[ ]	[X]	[ ]
Digitalis	[ ]	[X]	[ ]
Statine	[ ]	[X]	[ ]
Andere Lipidsenker	[ ]	[X]	[ ]
NSAR	[ ]	[X]	[ ]
Steroide	[X]	[ ]	[ ]
Östrogene / Gestagene	[ ]	[X]	[ ]
Parkinsonmittel	[ ]	[X]	[ ]
Hypnotika / Sedativa	[ ]	[X]	[ ]
Tranquilizer	[ ]	[X]	[ ]
Neuroleptika	[ ]	[X]	[ ]
Antidepressiva	[ ]	[X]	[ ]
Nootropika / Antidementiva	[ ]	[X]	[ ]
Antihypertensiva	[X]	[ ]	[ ]

Falls ja, welche: [X] **ACE** Hemmer; [ ] **β**-Blocker; [X] **CA** Antagonisten; [X] **D**iuretika

TÄGLICHES LEBEN

11 Aktivitätsgrad
- [X] **nicht** aktiv (keine regelmäßigen körperlichen Belastungen z. B. durch Sport, Gartenarbeit u. Ä.)
- [ ] **mäßig** aktiv (weniger als dreimal pro Woche körperlicher Belastung ausgesetzt)
- [ ] **sehr** aktiv (mindestens dreimal pro Woche körperlicher Belastung ausgesetzt)

12 Wohnform
- [X] **Privat**haushalt
- [ ] **Alten-/Pflege**heim

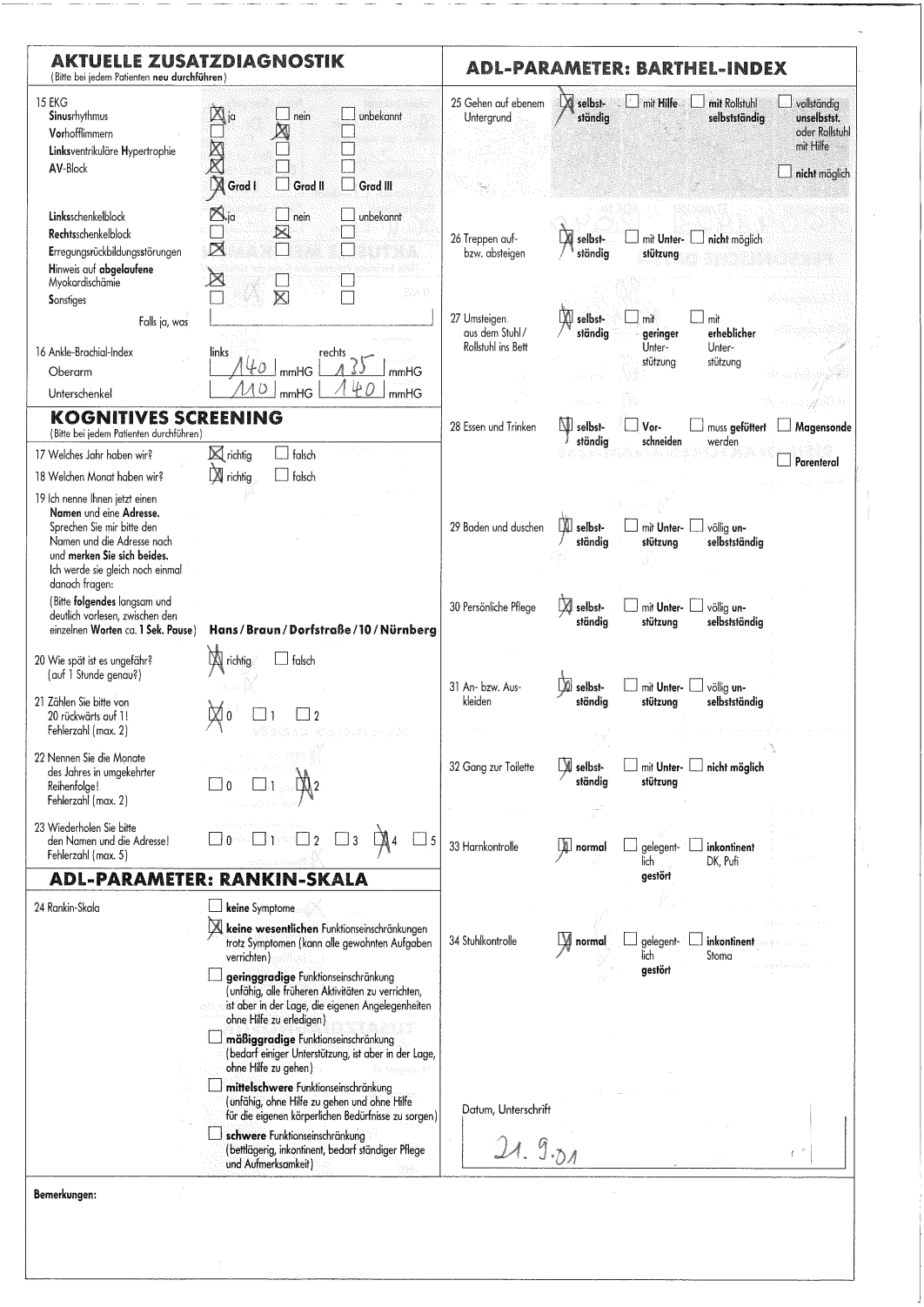
13 Pflegebedürftigkeit (Leistungen aus der Pflegeversicherung)
- [X] **nein,** nicht pflegebedürftig
- [ ] **nein,** Antrag abgelehnt oder in Bearbeitung
- [ ] **ja,** Pflegestufe **1**
- [ ] **ja,** Pflegestufe **2**
- [ ] **ja,** Pflegestufe **3** oder **Härte**fall

ZUSATZDIAGNOSTIK

(Falls durchgeführt bitte **Befunde,** die **nicht** länger als ca. **1 Jahr** zurückliegen **in Kopie** beilegen)

	ja	nein	unbekannt
14 Langzeit-RR	[ ]	[X]	[ ]
Langzeit-EKG	[ ]	[X]	[ ]
Herzecho	[ ]	[X]	[ ]
CCT	[ ]	[X]	[ ]
cMRT	[ ]	[X]	[ ]
Doppler	[ ]	[X]	[ ]
Duplex (farbcodierter Duplex der hirnversorgenden Gefäße)	[ ]	[X]	[ ]

	links	rechts
IMT	mm	mm



AKTUELLE ZUSATZDIAGNOSTIK
(Bitte bei jedem Patienten **neu durchführen**)

15 EKG
- **Sinus**rhythmus: [X] ja [ ] nein [ ] unbekannt
- **Vor**hofflimmern: [ ] [X] [ ]
- **Links**ventrikuläre **H**ypertrophie: [X] [ ] [ ]
- **AV**-Block: [X] [ ] [ ]
  - [X] **Grad I** [ ] **Grad II** [ ] **Grad III**
- **Links**schenkelblock: [X] ja [ ] nein [ ] unbekannt
- **Rechts**schenkelblock: [ ] [X] [ ]
- **E**rregungsrückbildungsstörungen: [X] [ ] [ ]
- **H**inweis auf **abgelaufene** Myokardischämie: [X] [ ] [ ]
- **S**onstiges: [ ] [X] [ ]

Falls ja, was: [ ]

16 Ankle-Brachial-Index

	links	rechts
Oberarm	140 mmHG	135 mmHG
Unterschenkel	110 mmHG	140 mmHG

KOGNITIVES SCREENING
(Bitte bei jedem Patienten durchführen)

17 Welches Jahr haben wir? [X] richtig [ ] falsch

18 Welchen Monat haben wir? [X] richtig [ ] falsch

19 Ich nenne Ihnen jetzt einen **Namen** und eine **Adresse.** Sprechen Sie mir bitte den Namen und die Adresse nach und **merken Sie sich beides.** Ich werde sie gleich noch einmal danach fragen:
(Bitte **folgendes** langsam und deutlich vorlesen, zwischen den einzelnen **Worten** ca. **1 Sek. Pause**) **Hans / Braun / Dorfstraße / 10 / Nürnberg**

20 Wie spät ist es ungefähr? (auf 1 Stunde genau?) [X] richtig [ ] falsch

21 Zählen Sie bitte von 20 rückwärts auf 1! Fehlerzahl (max. 2) [X] 0 [ ] 1 [ ] 2

22 Nennen Sie die Monate des Jahres in umgekehrter Reihenfolge! Fehlerzahl (max. 2) [ ] 0 [ ] 1 [X] 2

23 Wiederholen Sie bitte den Namen und die Adresse! Fehlerzahl (max. 5) [ ] 0 [ ] 1 [ ] 2 [ ] 3 [X] 4 [ ] 5

ADL-PARAMETER: RANKIN-SKALA

24 Rankin-Skala
- [ ] **keine** Symptome
- [X] **keine wesentlichen** Funktionseinschränkungen trotz Symptomen (kann alle gewohnten Aufgaben verrichten)
- [ ] **geringgradige** Funktionseinschränkung (unfähig, alle früheren Aktivitäten zu verrichten, ist aber in der Lage, die eigenen Angelegenheiten ohne Hilfe zu erledigen)
- [ ] **mäßiggradige** Funktionseinschränkung (bedarf einiger Unterstützung, ist aber in der Lage, ohne Hilfe zu gehen)
- [ ] **mittelschwere** Funktionseinschränkung (unfähig, ohne Hilfe zu gehen und ohne Hilfe für die eigenen körperlichen Bedürfnisse zu sorgen)
- [ ] **schwere** Funktionseinschränkung (bettlägerig, inkontinent, bedarf ständiger Pflege und Aufmerksamkeit)

ADL-PARAMETER: BARTHEL-INDEX

25 Gehen auf ebenem Untergrund: [X] **selbst-ständig** [ ] mit **Hilfe** [ ] **mit** Rollstuhl **selbstständig** [ ] vollständig **unselbstst.** oder Rollstuhl mit Hilfe [ ] **nicht** möglich

26 Treppen auf- bzw. absteigen: [X] **selbst-ständig** [ ] mit **Unter-stützung** [ ] **nicht** möglich

27 Umsteigen aus dem Stuhl / Rollstuhl ins Bett: [X] **selbst-ständig** [ ] mit **geringer** Unter-stützung [ ] mit **erheblicher** Unter-stützung

28 Essen und Trinken: [X] **selbst-ständig** [ ] **Vor-schneiden** [ ] muss **gefüttert** werden [ ] **Magensonde** [ ] **Parenteral**

29 Baden und duschen: [X] **selbst-ständig** [ ] mit **Unter-stützung** [ ] völlig **un-selbstständig**

30 Persönliche Pflege: [X] **selbst-ständig** [ ] mit **Unter-stützung** [ ] völlig **un-selbstständig**

31 An- bzw. Aus-kleiden: [X] **selbst-ständig** [ ] mit **Unter-stützung** [ ] völlig **un-selbstständig**

32 Gang zur Toilette: [X] **selbst-ständig** [ ] mit **Unter-stützung** [ ] **nicht möglich**

33 Harnkontrolle: [X] **normal** [ ] gelegent-lich **gestört** [ ] **inkontinent** DK, Pufi

34 Stuhlkontrolle: [X] **normal** [ ] gelegent-lich **gestört** [ ] **inkontinent** Stoma

Datum, Unterschrift: 21.9.01

Bemerkungen:

Figure A.2
INVADE questionnaire admission examination for general practitioner.

IN DE **PATIENTENFRAGEBOGEN (2. VERLAUFSUNTERSUCHUNG)**

[redacted]

Praxis (Stempel)
Dr. med. Timm Gallitz
Internist
Heinrich-Marschner-Str. 70 · 85599 Baldham
Telefon 0 81 06 / 58 15
64/19 464

[redacted]

Wir möchten darauf hinweisen, dass die Beantwortung der Fragen freiwillig ist. Ihre Angaben werden streng vertraulich und anonym – entsprechend den Grundsätzen des Datenschutzes – behandelt. Bitten Sie Ihren Hausarzt oder die Arzthelferin um Hilfe, wenn eine Frage unverständlich ist. Lassen Sie möglichst keine Frage aus. Die AOK Nr. wird von Ihrem Arzt oder der Arzthelferin eingetragen.

ALLGEMEINE ANGABEN

01 Familienstand
- ☒ verheiratet
- ☐ geschieden
- ☐ verwitwet
- ☐ ledig

02 Wohnform
- ☐ allein lebend
- ☒ Zwei-Personen-Haushalt
- ☐ Mehr-Personen-Haushalt
- ☐ Senioren-/Pflegeheim

AUSBILDUNG, BERUF (Zutreffendes bitte ankreuzen)

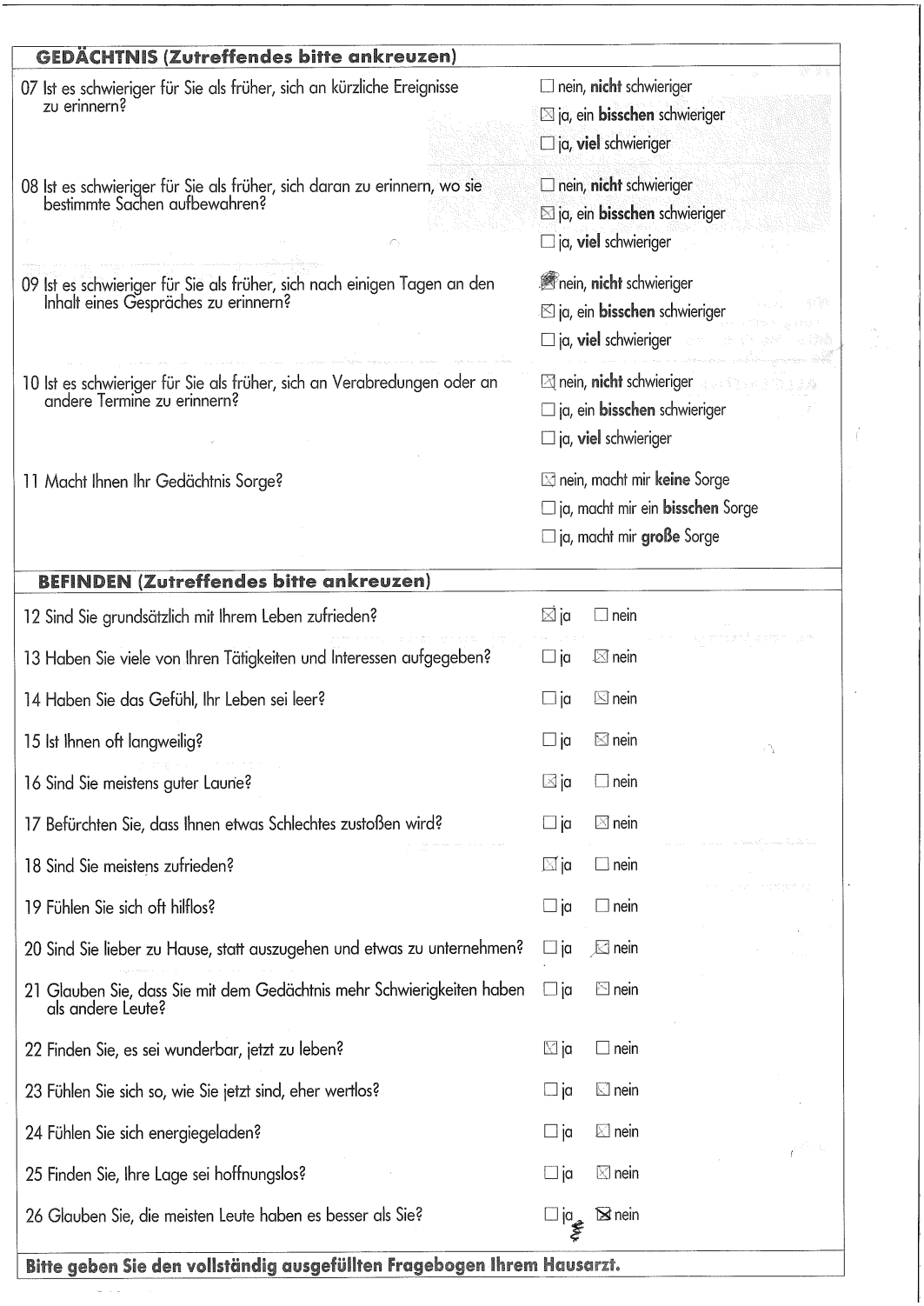
03 Sind Sie zurzeit berufstätig?
- ☐ ja, mit einer **Ganztags**beschäftigung
- ☐ ja, mit einer **Teilzeit**beschäftigung
- ☐ nein, **arbeitslos**
- ☐ nein, **Hausfrau/Hausmann**
- ☒ nein, **Renter/Rentnerin**

GESUNDHEIT (Zutreffendes bitte ankreuzen)

04 Waren Sie in den letzten 12 Monaten zur stationären Behandlung in einem Krankenhaus?
- ☐ ja
- ☒ nein

05 Wie oft haben Sie in den letzten 12 Monaten Ihren Hausarzt aufgesucht oder erhielten einen Besuch Ihres Hausarztes?
- ☐ gar nicht
- ☐ seltener als einmal im Quartal
- ☒ etwa einmal im Quartal
- ☐ etwa einmal im Monat
- ☐ öfter als einmal im Monat
- ☐ jede Woche

06 Wie würden Sie Ihre gegenwärtige körperliche Verfassung einschätzen?
- ☐ sehr gut
- ☒ gut
- ☐ weniger gut
- ☐ schlecht



GEDÄCHTNIS (Zutreffendes bitte ankreuzen)

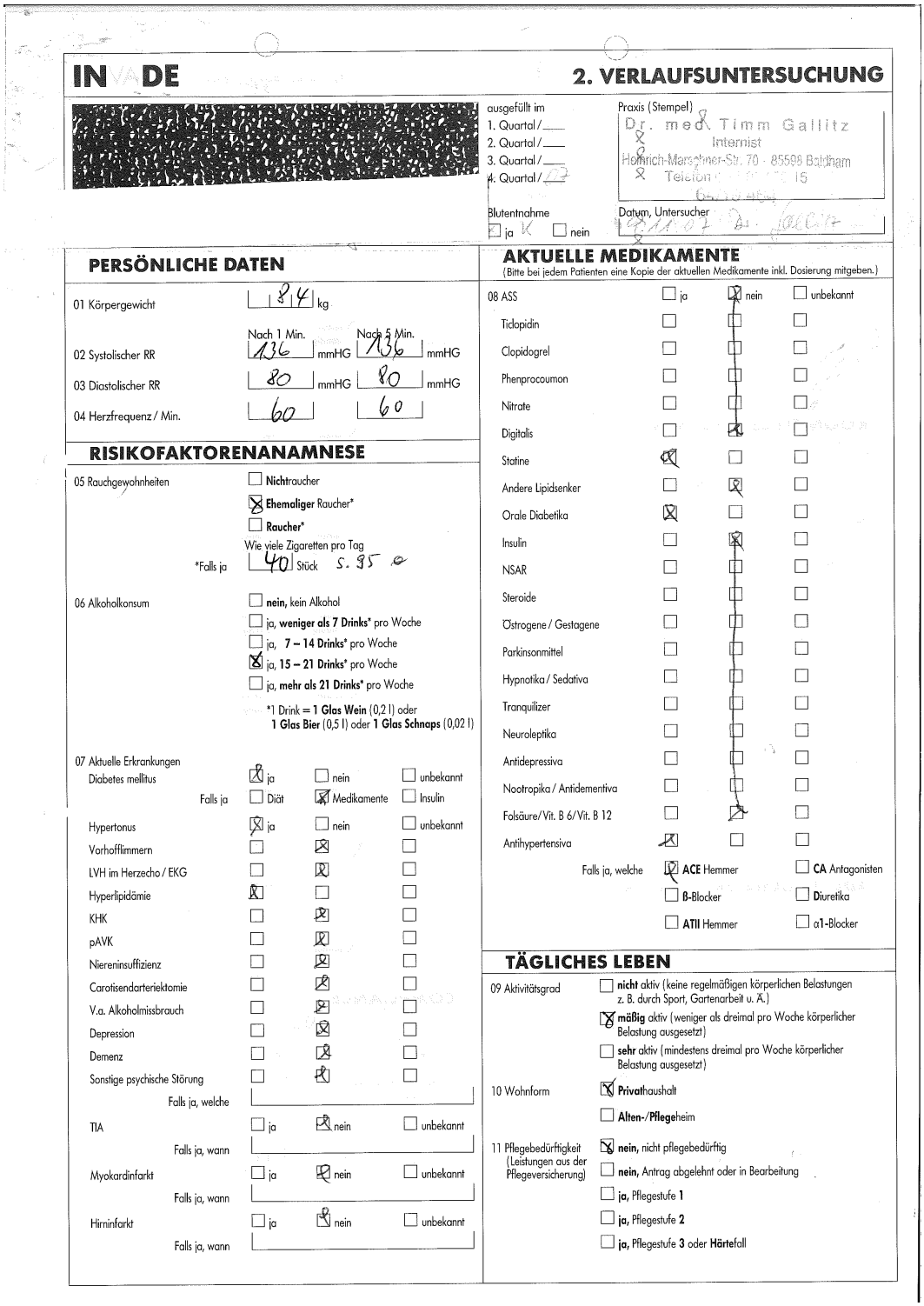
07 Ist es schwieriger für Sie als früher, sich an kürzliche Ereignisse zu erinnern?	☐ nein, **nicht** schwieriger ☒ ja, ein **bisschen** schwieriger ☐ ja, **viel** schwieriger
08 Ist es schwieriger für Sie als früher, sich daran zu erinnern, wo sie bestimmte Sachen aufbewahren?	☐ nein, **nicht** schwieriger ☒ ja, ein **bisschen** schwieriger ☐ ja, **viel** schwieriger
09 Ist es schwieriger für Sie als früher, sich nach einigen Tagen an den Inhalt eines Gespräches zu erinnern?	☒ nein, **nicht** schwieriger ☒ ja, ein **bisschen** schwieriger ☐ ja, **viel** schwieriger
10 Ist es schwieriger für Sie als früher, sich an Verabredungen oder an andere Termine zu erinnern?	☒ nein, **nicht** schwieriger ☐ ja, ein **bisschen** schwieriger ☐ ja, **viel** schwieriger
11 Macht Ihnen Ihr Gedächtnis Sorge?	☒ nein, macht mir **keine** Sorge ☐ ja, macht mir ein **bisschen** Sorge ☐ ja, macht mir **große** Sorge

BEFINDEN (Zutreffendes bitte ankreuzen)

12 Sind Sie grundsätzlich mit Ihrem Leben zufrieden?	☒ ja ☐ nein
13 Haben Sie viele von Ihren Tätigkeiten und Interessen aufgegeben?	☐ ja ☒ nein
14 Haben Sie das Gefühl, Ihr Leben sei leer?	☐ ja ☒ nein
15 Ist Ihnen oft langweilig?	☐ ja ☒ nein
16 Sind Sie meistens guter Laune?	☒ ja ☐ nein
17 Befürchten Sie, dass Ihnen etwas Schlechtes zustoßen wird?	☐ ja ☒ nein
18 Sind Sie meistens zufrieden?	☒ ja ☐ nein
19 Fühlen Sie sich oft hilflos?	☐ ja ☐ nein
20 Sind Sie lieber zu Hause, statt auszugehen und etwas zu unternehmen?	☐ ja ☒ nein
21 Glauben Sie, dass Sie mit dem Gedächtnis mehr Schwierigkeiten haben als andere Leute?	☐ ja ☒ nein
22 Finden Sie, es sei wunderbar, jetzt zu leben?	☒ ja ☐ nein
23 Fühlen Sie sich so, wie Sie jetzt sind, eher wertlos?	☐ ja ☒ nein
24 Fühlen Sie sich energiegeladen?	☐ ja ☒ nein
25 Finden Sie, Ihre Lage sei hoffnungslos?	☐ ja ☒ nein
26 Glauben Sie, die meisten Leute haben es besser als Sie?	☐ ja ☒ nein

Bitte geben Sie den vollständig ausgefüllten Fragebogen Ihrem Hausarzt.

Figure A.3
INVADE questionnaire follow-up examination for patient.



IN[illegible]DE

2. VERLAUFSUNTERSUCHUNG

[redacted]

ausgefüllt im
1. Quartal /____
2. Quartal /____
3. Quartal /____
4. Quartal /22

Praxis (Stempel)
Dr. med. Timm Gallitz
Internist
Heinrich-Marschner-Str. 70 - 85598 Baldham
Telefon [illegible]15

Blutentnahme
☒ ja ☐ nein

Datum, Untersucher
[illegible]

PERSÖNLICHE DATEN

		Nach 1 Min.	Nach 5 Min.
01 Körpergewicht	84 kg		
02 Systolischer RR		136 mmHG	136 mmHG
03 Diastolischer RR		80 mmHG	80 mmHG
04 Herzfrequenz / Min.		60	60

RISIKOFAKTORENANAMNESE

05 Rauchgewohnheiten
- ☐ **Nicht**raucher
- ☒ **Ehemaliger** Raucher*
- ☐ **Raucher***

Wie viele Zigaretten pro Tag
*Falls ja 40 Stück 5.95 ☺

06 Alkoholkonsum
- ☐ **nein,** kein Alkohol
- ☐ ja, **weniger als 7 Drinks*** pro Woche
- ☐ ja, **7 – 14 Drinks*** pro Woche
- ☒ ja, **15 – 21 Drinks*** pro Woche
- ☐ ja, **mehr als 21 Drinks*** pro Woche

*1 Drink = **1 Glas Wein** (0,2 l) oder **1 Glas Bier** (0,5 l) oder **1 Glas Schnaps** (0,02 l)

07 Aktuelle Erkrankungen

Diabetes mellitus	☒ ja	☐ nein	☐ unbekannt
Falls ja	☐ Diät	☒ Medikamente	☐ Insulin
Hypertonus	☒ ja	☐ nein	☐ unbekannt
Vorhofflimmern	☐	☒	☐
LVH im Herzecho / EKG	☐	☒	☐
Hyperlipidämie	☒	☐	☐
KHK	☐	☒	☐
pAVK	☐	☒	☐
Niereninsuffizienz	☐	☒	☐
Carotisendarteriektomie	☐	☒	☐
V.a. Alkoholmissbrauch	☐	☒	☐
Depression	☐	☒	☐
Demenz	☐	☒	☐
Sonstige psychische Störung	☐	☒	☐
Falls ja, welche			
TIA	☐ ja	☒ nein	☐ unbekannt
Falls ja, wann			
Myokardinfarkt	☐ ja	☒ nein	☐ unbekannt
Falls ja, wann			
Hirninfarkt	☐ ja	☒ nein	☐ unbekannt
Falls ja, wann			

AKTUELLE MEDIKAMENTE

(Bitte bei jedem Patienten eine Kopie der aktuellen Medikamente inkl. Dosierung mitgeben.)

08	ja	nein	unbekannt
ASS	☐	☒	☐
Ticlopidin	☐	☐	☐
Clopidogrel	☐	☐	☐
Phenprocoumon	☐	☐	☐
Nitrate	☐	☐	☐
Digitalis	☐	☒	☐
Statine	☒	☐	☐
Andere Lipidsenker	☐	☒	☐
Orale Diabetika	☒	☐	☐
Insulin	☐	☒	☐
NSAR	☐	☐	☐
Steroide	☐	☐	☐
Östrogene / Gestagene	☐	☐	☐
Parkinsonmittel	☐	☐	☐
Hypnotika / Sedativa	☐	☐	☐
Tranquilizer	☐	☐	☐
Neuroleptika	☐	☐	☐
Antidepressiva	☐	☐	☐
Nootropika / Antidementiva	☐	☐	☐
Folsäure/Vit. B 6/Vit. B 12	☐	☒	☐
Antihypertensiva	☒	☐	☐

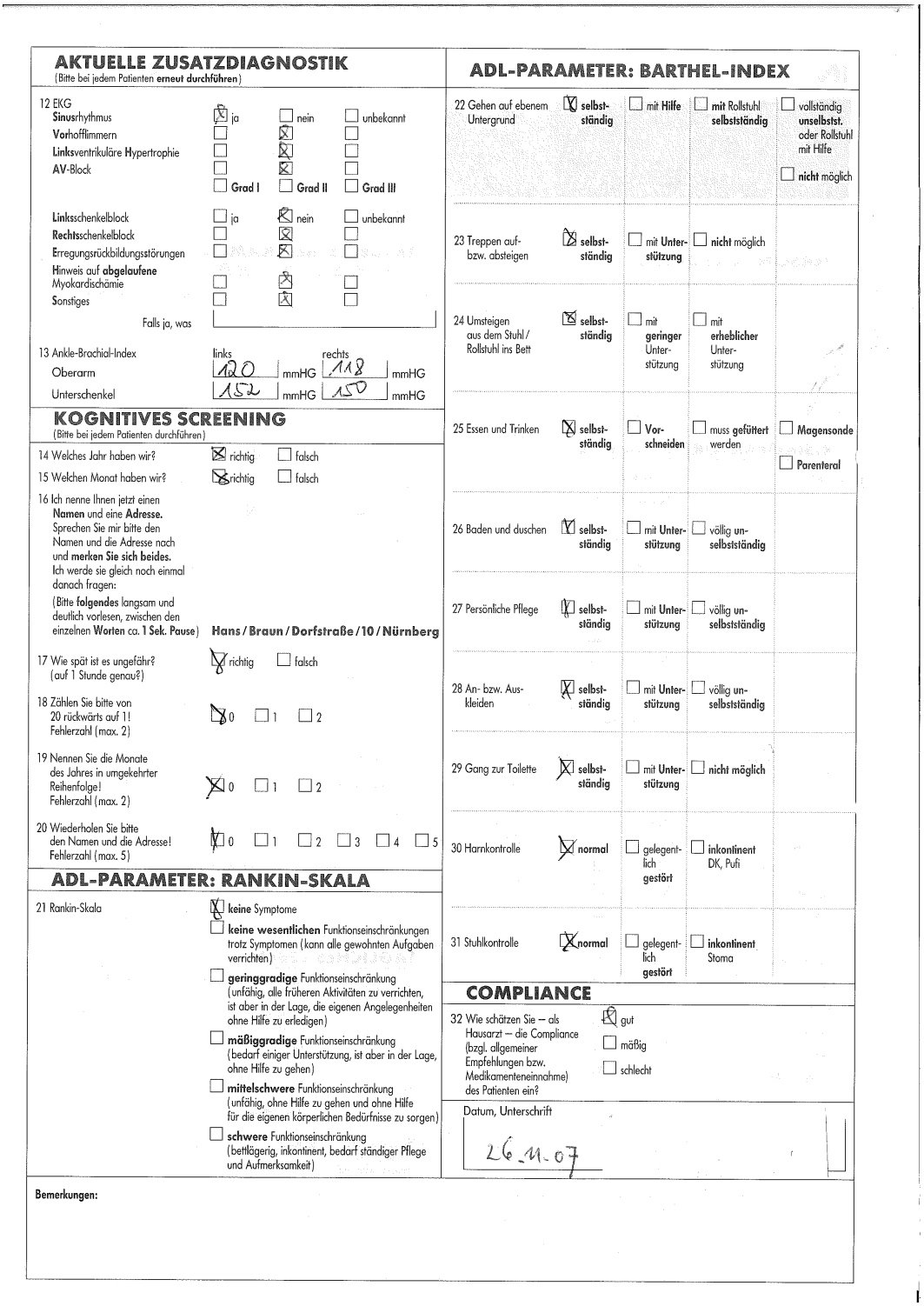
Falls ja, welche
- ☒ **ACE** Hemmer
- ☐ **CA** Antagonisten
- ☐ **B**-Blocker
- ☐ **D**iuretika
- ☐ **ATII** Hemmer
- ☐ **α1**-Blocker

TÄGLICHES LEBEN

09 Aktivitätsgrad
- ☐ **nicht** aktiv (keine regelmäßigen körperlichen Belastungen z. B. durch Sport, Gartenarbeit u. Ä.)
- ☒ **mäßig** aktiv (weniger als dreimal pro Woche körperlicher Belastung ausgesetzt)
- ☐ **sehr** aktiv (mindestens dreimal pro Woche körperlicher Belastung ausgesetzt)

10 Wohnform
- ☒ **Privat**haushalt
- ☐ **Alten-/Pflege**heim

11 Pflegebedürftigkeit (Leistungen aus der Pflegeversicherung)
- ☒ **nein,** nicht pflegebedürftig
- ☐ **nein,** Antrag abgelehnt oder in Bearbeitung
- ☐ **ja,** Pflegestufe **1**
- ☐ **ja,** Pflegestufe **2**
- ☐ **ja,** Pflegestufe **3** oder **Härte**fall



AKTUELLE ZUSATZDIAGNOSTIK
(Bitte bei jedem Patienten **erneut durchführen**)

12 EKG

	ja	nein	unbekannt
Sinusrhythmus	☒	☐	☐
Vorhofflimmern	☐	☒	☐
Linksventrikuläre Hypertrophie	☐	☒	☐
AV-Block	☐	☒	☐
	☐ **Grad I**	☐ **Grad II**	☐ **Grad III**
Linksschenkelblock	☐	☒	☐
Rechtsschenkelblock	☐	☒	☐
Erregungsrückbildungsstörungen	☐	☒	☐
Hinweis auf abgelaufene Myokardischämie	☐	☒	☐
Sonstiges	☐	☒	☐

Falls ja, was

13 Ankle-Brachial-Index

	links	rechts
Oberarm	120 mmHG	118 mmHG
Unterschenkel	152 mmHG	150 mmHG

KOGNITIVES SCREENING
(Bitte bei jedem Patienten durchführen)

14 Welches Jahr haben wir? ☒ richtig ☐ falsch

15 Welchen Monat haben wir? ☒ richtig ☐ falsch

16 Ich nenne Ihnen jetzt einen **Namen** und eine **Adresse.** Sprechen Sie mir bitte den Namen und die Adresse nach und **merken Sie sich beides.** Ich werde sie gleich noch einmal danach fragen:
(Bitte **folgendes** langsam und deutlich vorlesen, zwischen den einzelnen **Worten** ca. **1 Sek. Pause**) **Hans / Braun / Dorfstraße / 10 / Nürnberg**

17 Wie spät ist es ungefähr? (auf 1 Stunde genau?) ☒ richtig ☐ falsch

18 Zählen Sie bitte von 20 rückwärts auf 1! Fehlerzahl (max. 2) ☒ 0 ☐ 1 ☐ 2

19 Nennen Sie die Monate des Jahres in umgekehrter Reihenfolge! Fehlerzahl (max. 2) ☒ 0 ☐ 1 ☐ 2

20 Wiederholen Sie bitte den Namen und die Adresse! Fehlerzahl (max. 5) ☒ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

ADL-PARAMETER: RANKIN-SKALA

21 Rankin-Skala

- ☒ **keine** Symptome
- ☐ **keine wesentlichen** Funktionseinschränkungen trotz Symptomen (kann alle gewohnten Aufgaben verrichten)
- ☐ **geringgradige** Funktionseinschränkung (unfähig, alle früheren Aktivitäten zu verrichten, ist aber in der Lage, die eigenen Angelegenheiten ohne Hilfe zu erledigen)
- ☐ **mäßiggradige** Funktionseinschränkung (bedarf einiger Unterstützung, ist aber in der Lage, ohne Hilfe zu gehen)
- ☐ **mittelschwere** Funktionseinschränkung (unfähig, ohne Hilfe zu gehen und ohne Hilfe für die eigenen körperlichen Bedürfnisse zu sorgen)
- ☐ **schwere** Funktionseinschränkung (bettlägerig, inkontinent, bedarf ständiger Pflege und Aufmerksamkeit)

ADL-PARAMETER: BARTHEL-INDEX

22 Gehen auf ebenem Untergrund	☒ **selbst-ständig**	☐ mit **Hilfe**	☐ **mit** Rollstuhl **selbstständig**	☐ vollständig **unselbstst.** oder Rollstuhl mit Hilfe ☐ **nicht** möglich
23 Treppen auf- bzw. absteigen	☒ **selbst-ständig**	☐ mit **Unter-stützung**	☐ **nicht** möglich	
24 Umsteigen aus dem Stuhl / Rollstuhl ins Bett	☒ **selbst-ständig**	☐ mit **geringer** Unter-stützung	☐ mit **erheblicher** Unter-stützung	
25 Essen und Trinken	☒ **selbst-ständig**	☐ **Vor-schneiden**	☐ muss **gefüttert** werden	☐ **Magensonde** ☐ **Parenteral**
26 Baden und duschen	☒ **selbst-ständig**	☐ mit **Unter-stützung**	☐ völlig **un-selbstständig**	
27 Persönliche Pflege	☒ **selbst-ständig**	☐ mit **Unter-stützung**	☐ völlig **un-selbstständig**	
28 An- bzw. Aus-kleiden	☒ **selbst-ständig**	☐ mit **Unter-stützung**	☐ völlig **un-selbstständig**	
29 Gang zur Toilette	☒ **selbst-ständig**	☐ mit **Unter-stützung**	☐ **nicht möglich**	
30 Harnkontrolle	☒ **normal**	☐ gelegent-lich **gestört**	☐ **inkontinent** DK, Pufi	
31 Stuhlkontrolle	☒ **normal**	☐ gelegent-lich **gestört**	☐ **inkontinent** Stoma	

COMPLIANCE

32 Wie schätzen Sie – als Hausarzt – die Compliance (bzgl. allgemeiner Empfehlungen bzw. Medikamenteneinnahme) des Patienten ein? ☒ gut ☐ mäßig ☐ schlecht

Datum, Unterschrift

26.11.07

Bemerkungen:

Figure A.4
INVADE questionnaire follow-up examination for general practitioner.