The Mediterranean Diet and its Components and the Risk of Heart Failure in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study – A Top-Down Approach

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“The head is round so that thought can change its direction”

Francis Picabia (1824-1912)

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Abbreviations

ACC/AHA	American College of Cardiology / American Heart Association
ACE	Angiotensin Converting Enzyme
aMED	Alternate Mediterranean diet score
ARIC	Atherosclerosis Risk in Communities Study
BMI	Body mass index
CHD	Coronary heart disease
CHS	Cardiovascular Health Study
CI	Confidence interval
CSM	Cohort of Swedish Men
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DASH	Dietary Approaches to Stop Hypertension
DHA	Docosahexaenoic acid
ECG	Electrocardiography
EPA	Eicosapentaenoic acid
EPIC	European Prospective Investigation into Cancer and Nutrition
ESC	European Society of Cardiology
FFQ	Food frequency questionnaire
FUP	Follow-up time
HF	Heart failure
HF-PEF	Heart failure with preserved ejection fraction

HF-REF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD-10	International Classification of Disease, tenth version
IQR	Interquartile range
JACC	Japan Collaborative Cohort
KI	Konfidenzintervall
LVSD	Left ventricular systolic dysfunction
MUFA	Monounsaturated fatty acid
n.s.	not significant
n3FA	omega-3 fatty acids
NHANES	National Health and Nutrition Examination Survey
NYHA	New York Heart Association
PAR	Population attributable risk
PHS	Physicians' Health Study
p_{nonlin}	p value for nonlinearity
PREDIMED	PREvención con DIeta MEDiterránea
p_{trend}	p value for linear trend
PUFA	Polyunsaturated fatty acids
RR	Relative risk
RS	Rotterdam Study
SD	Standard deviation
SFA	Saturated fatty acid
SMC	Swedish Mammography Cohort
tMED	traditional Mediterranean diet score / traditioneller Mediterrane Ernährungs-Score
WHI	Women’s Health Initiative

ABSTRACT

Background and Aims

Heart failure is a complex syndrome with growing burden to public health. In spite of improved therapeutic opportunities, heart failure is still the third leading cause of death in Germany and linked to high hospitalization rates, treatment costs and impaired quality of life.

Cardio-protective effects of the Mediterranean diet have been well documented: inverse associations have been reported between adherence to the diet and several cardiovascular outcomes. The Mediterranean diet is characterised by a high intake of fruits and vegetables, cereals, fish and legumes. On the other side, the proportion of saturated fats is usually low due to a frequent use of olive oil in salads and dishes and low consumption of meat. Another typical component of the diet is the moderate consumption of alcohol, mainly in form of wine, during meals. The use of scores to assess adherence to the Mediterranean diet and the building of scores is widely used in observational studies.

Despite its great potential in heart failure prevention, the Mediterranean diet has yet not been investigated in relation to heart failure development in prospective studies based on the general population.

Therefore, the aim of the present thesis was to examine the association between the Mediterranean dietary pattern and the risk of heart failure. By analyzing different levels of nutrition (i.e. dietary pattern, food groups, nutrients), components should be identified that influenced most strongly the overall effect of this dietary pattern and could provide more insights into possible underlying mechanisms.

Methods

The study was carried out in 9,225 men and 14,783 women of the *European Prospective Investigation into Cancer and Nutrition* (EPIC)-Potsdam study who were free of coronary heart disease at baseline. To assess the adherence to the Mediterranean diet, the revised traditional Mediterranean diet score (tMED) was generated using Greek median intakes as cut-points. By means of a *top-down* approach the diet-disease association was investigated systematically, starting with the examination of the relationship between tMED categories and the risk of heart failure up to selected relevant components of the score (food groups) to the most representative nutrients of these components. Cox proportional hazards regression analysis was performed to calculate hazard ratios (HRs) and 95% confidence intervals (95%CIs) of heart failure according to the adherence to the Mediterranean-style diet. Three methods were used to assess the relevance of the score

components: 1. Calculation of HRs of heart failure for continuous intakes of the food groups covered by tMED components using restricted cubic spline Cox regression analyses, 2. computing HRs of heart failure according to tMED components on a dichotomous scale (receiving one point versus zero point), and 3. calculating the relative changes in the HRs per two units increase of tMED before and after exclusion of each of the score components. Relevant components were then disaggregated into its constituents (i.e.: food subgroups, and main representative macro-and micronutrients), and the relationship with the risk of developing heart failure was further investigated on these lower levels of nutrition.

Results

After a mean follow-up period of 8.2 years, 209 heart failure cases occurred. Adherence to the Mediterranean diet was generally low (mean score points: 3.5). An inverse relationship between the adherence to the Mediterranean diet and the risk of heart failure was observed. After multivariable adjustment, individuals who received five or more score points had a 37% decreased risk compared to participants who were assigned a score of zero to two points. However, this association narrowly missed the significance level (p_{trend}=0.06).

Further analysis revealed that not every tMED component contributed to the heart failure risk reduction of the overall score. Three components were identified as being the most influencing factors for the overall inverse association, namely high fatty fish intake, moderate alcohol consumption, and low consumption of meat and meat products, especially processed meat. High meat consumption was associated with a 2.5-fold increased risk of heart failure relative to low consumption after adjustment for age, sex, education, physical activity, smoking, and intakes of the remaining score components. In contrast, moderate alcohol consumption was associated with a 33% (95% CI: 11%-49%) lower risk of heart failure compared to low or high intakes. Intake of canned fish (mainly comprising fatty fish) was also inversely associated with heart failure risk (HR (95% CI) for the highest versus the lowest quintile of intake: 0.59 (0.36-0.96).

Analyses on nutrient level indicated that in particular fat quality might explain these findings: cholesterol and especially saturated fat intakes were positively associated with heart failure risk, whereas the intake of marine omega-3 fatty acids was inversely associated.

Conclusion

The results of the present thesis indicate that the adherence to a Mediterranean-style dietary pattern may reduce the risk of developing heart failure. Of the nine components that were used in the tMED, only three played a major role for heart failure risk. These were: low intakes of meat and meat products, moderate consumption of alcohol and a high intake of fish. Saturated fat and cholesterol seem most likely to be responsible for the risk-increasing effect of meat consumption, while the containing omega-3 fatty acids might explain the protective effect of fatty fish intake.

The results indicate that even a moderate change of dietary habits might have strong impact on heart health, when primarily the three identified factors are involved. Responsible and moderate alcohol consumption (in particular of wine), increasing the intake of fatty fish and lowering consumption of meat products in the diet are, furthermore, messages easy to communicate by public health policies. However, the consumption of alcohol should not be recommended to abstainers only for the suspected health benefits.

Furthermore, the use of a score to assess the Mediterranean diet in this non-Mediterranean population was a challenging task, as types of foods (especially the fat sources), preparation, and the amount of consumption differ to a great extend from those in Mediterranean countries. It was demonstrated that there is a persistent need to improve application of these scores in non-Mediterranean countries. One suggestion to increase the validity of a Mediterranean diet score might be to modify certain components. This could be achieved e.g. by a replacement of the fat-ratio component with intakes of saturated fatty acids. A second modification might be the weighting of score components according to the importance to the effect on health outcomes.

Further studies are warranted to replicate and validate the findings observed in this thesis.

ZUSAMMENFASSUNG

Hintergrund und Ziele

Herzinsuffizienz ist ein komplexes Syndrom das eine zunehmende Belastung für die öffentliche Gesundheit darstellt. Ungeachtet der verbesserten therapeutischen Möglichkeiten ist Herzinsuffizienz weiterhin die dritthäufigste Todesursache in Deutschland und mit einer hohen Krankenhausaufenthaltsrate, teuren Behandlungskosten und einer starken Beeinträchtigung der Lebensqualität verbunden.

Kardio-protektive Effekte der mediterranen Ernährung wurden bereits vielfach beschrieben: von inversen Assoziationen zwischen der Einhaltung dieser Ernährung und diversen kardiovaskulären Ereignissen wurden berichtet. Die Mediterrane Kost zeichnet sich durch eine hohe Aufnahme von Obst und Gemüse, Getreide, Fisch und Hülsenfrüchte aus. Auf der anderen Seite ist der Anteil der gesättigten Fette in der Regel gering aufgrund der häufigen Verwendung von Olivenöl in Salaten und anderen Gerichten und des geringen Verzehrs von Fleisch. Ein weiterer typischer Bestandteil der Ernährung ist der moderate Konsum von Alkohol, hauptsächlich in Form von Wein, während der Mahlzeiten. Zur Bewertung der Einhaltung eines mediterranen Ernährungsmusters ist die Verwendung von Scores in Beobachtungsstudien weit verbreitet.

Trotz des großen Potenzials für die Herzinsuffizienz-Prävention wurde die Mediterrane Ernährung noch nicht in prospektiven, auf der Allgemeinbevölkerung basierenden, Studien bezüglich ihre Assoziation zur Herzinsuffizienz-Entwicklung untersucht.

Das Ziel der vorliegenden Studie war es daher, den Zusammenhang zwischen dem Mediterranen Ernährungsmuster und dem Risiko von Herzinsuffizienz zu erforschen. Durch die Analyse verschiedener Ebenen der Ernährung (d.h. Ernährungsmuster, Lebensmittelgruppen und Nährstoffe) sollten Komponenten identifiziert werden, die den Gesamteffekt dieses Ernährungsmusters am stärksten beeinflussen und mehr Einblicke in mögliche zugrundeliegende Mechanismen liefern.

Methoden

Die Studie wurde mit 9.225 Männern und 14.783 Frauen der *European Prospective Investigation into Cancer and Nutrition* (EPIC)-Potsdam-Studie durchgeführt, bei denen zu Studienbeginn keine koronare Herzkrankheit vorlag. Um das Einhalten der Mediterranen Ernährung zu beurteilen, wurde der erweiterte traditionelle Mediterrane Ernährungs-Score (tMED) unter Verwendung griechischer Grenzwerte (mediane Aufnahmemenge) erzeugt. Durch einen *Top-down*-Ansatz wurde die Ernährungs-Erkrankungs-Beziehung systematisch untersucht, beginnend mit der Analyse der Assoziation zwischen tMED-Kategorien und dem Risiko von Herzinsuffizienz, über ausgewählte relevante Komponenten des Scores (Lebensmittelgruppen) bis hin zu den repräsentativsten Nährstoffe dieser Komponenten. Eine Cox-Regressionsanalyse wurde durchgeführt, um Hazard Ratios (HRs) und 95% Konfidenzintervalle (95% KI) für Herzinsuffizienz zu berechnen. Drei Methoden wurden angewendet, um die Relevanz der Score-Komponenten zu beurteilen: 1. Die Berechnung der HRs der Herzinsuffizienz für kontinuierliche Aufnahmen der Lebensmittelgruppen jeder Komponente durch „*Restricted cubic spline*“ Cox-Regressionen, 2. mittels Errechnen der HRs von Herzinsuffizienz nach tMED-Komponenten auf dichotomer Skalierung (Erreichen eines Punktes im Vergleich zu keinem) und 3. Durch die Berechnung der relativen Veränderung der HRs pro zwei tMED-Einheiten vor und nach Ausschluss jeder Score-Komponente. Die so ausgewählten Komponenten wurden dann in ihre Bestandteile zerlegt (d.h. Lebensmittelgruppen und repräsentative Makro- und Mikronährstoffe) und die Risiko-Beziehung zur Herzinsuffizienz wurde weiter auf diesen tieferen Ebenen der Ernährung untersucht.

Ergebnisse

Nach einer mittleren Nachbeobachtungszeit von 8,2 Jahren traten 209 Fälle von Herzinsuffizienz auf. Im Allgemeinen war die Einhaltung des Mediterranen Ernährungsmusters eher gering (durchschnittlicher Score: 3,5 Punkte). Eine inverse Beziehung zwischen den erreichten Punkten im tMED und dem Risiko einer Herzinsuffizienz wurde beobachtet. Nach multivariabler Adjustierung wiesen Personen, die fünf oder mehr Punkte erhalten hatten, ein um 37% geringeres Herzinsuffizienz-Risiko auf als Teilnehmer denen null bis zwei Punkte vergeben wurden. Doch diese Assoziation verfehlte knapp das Signifikanzniveau (p_{trend} = 0,06).

Eine weitere Analyse ergab, dass nicht jede der tMED-Komponenten zu der Herzinsuffizienz-Risikoreduktion des Scores beigetragen hat. Drei Komponenten wurden als die wichtigsten Einflussfaktoren für die insgesamt inverse Assoziation identifiziert, nämlich eine hohe Aufnahme von Fettfisch, moderater Alkoholkonsum, sowie ein geringer Konsum von Fleisch und Fleischprodukten, insbesondere verarbeitetem Fleisch. Nach

Adjustierung für Alter, Geschlecht, Bildung, körperlicher Aktivität, Rauchverhalten und der Aufnahme der übrigen Score-Komponenten war ein hoher Fleischkonsum verglichen zu geringem Konsum mit einem 2,5-fach erhöhten Risiko für Herzinsuffizienz verbunden. Im Gegensatz dazu wurde moderater Alkoholkonsum mit einem um 33% (95% KI: 49% - 11%) niedrigeren Risiko für Herzinsuffizienz in Verbindung gebracht im Vergleich zu niedrigem oder hohem Konsum. Der Verzehr von Fischkonserven (hauptsächlich aus fettem Fisch bestehend) stand ebenfalls in einem inversen Zusammenhang mit dem Herzinsuffizienz-Risiko (HR (95% KI) für das höchste gegenüber dem niedrigsten Quintil der Aufnahme: 0,59 (0,36-0,96)).

Die Untersuchungen auf Nährstoff-Ebene deuteten darauf hin, dass besonders die Fettqualität diese Ergebnisse erklären könnte: die Aufnahmen von Cholesterin und vor allem gesättigten Fettsäuren zeigten eine positive Assoziation zum Herzinsuffizienzrisiko, während marine Omega-3-Fettsäuren invers mit dem Herzinsuffizienzrisiko assoziiert waren.

Schlussfolgerungen

Die Ergebnisse der vorliegenden Analyse zeigen, dass die Einhaltung eines Mediterranen Ernährungsmusters das Risiko der Entwicklung einer Herzinsuffizienz reduzieren kann. Von den neun Komponenten, die in dem tMED verwendet wurden, spielten nur drei eine wichtige Rolle für das Herzinsuffizienz-Risiko. Diese waren: eine geringe Aufnahme von Fleisch und Fleischprodukten, mäßiger Alkoholkonsum und eine hoher Verzehr von Fisch. Gesättigte Fettsäuren und Cholesterin scheinen höchstwahrscheinlich für die risiko-steigernde Wirkung von Fleischkonsum verantwortlich zu sein, während die enthaltenden Omega-3-Fettsäuren die Schutzwirkung durch Fischkonsum erklären könnten.

Die Ergebnisse weisen darauf hin, dass bereits eine moderate Änderung der Ernährungs-gewohnheiten einen starken Einfluss auf die Gesundheit des Herzens haben könnte, wenn in erster Linie die drei identifizierten Faktoren beteiligt sind. Ein verantwortungsvoller und moderater Alkoholkonsum, eine hohe Aufnahme von fettem Fisch und ein geringer Verzehr von Fleischprodukten in der Ernährung sind darüber hinaus einfach von der öffentlichen Gesundheitspolitik zu kommunizierende Botschaften. Jedoch sollte davon abgesehen werden Abstinenzlern den Konsum von Alkohol nur wegen des vermuteten gesundheitlichen Nutzens zu empfehlen.

Des Weiteren war die Verwendung eines Scores zur Beurteilung der Mediterranen Ernährung in dieser nicht-Mediterranen Bevölkerung eine anspruchsvolle Aufgabe, da sich Lebensmittelsorten (vor allem die Fettquellen), die Zubereitung sowie die Verzehrsmengen stark von denen in Mittelmeerländern unterscheiden. Dennoch wurde

Die vorliegende Arbeit demonstrierte die immer noch bestehende Notwendigkeit die Anwendbarkeit dieser Scores in Nicht-Mittelmeerländern zu verbessern. Ein Vorschlag zur Steigerung der Validität ist die Veränderung bestimmter Komponenten. Dies könnte beispielsweise durch den Austausch der Fettverhältnis-Komponente mit der Aufnahme von gesättigten Fettsäuren erreicht werden. Eine zweite Modifikation könnte die Gewichtung der Score-Komponenten nach ihrer Bedeutung für die gesundheitlichen Folgen darstellen.

Weitere Studien sind erforderlich, um die in dieser Arbeit beobachteten Ergebnisse und Schlussfolgerungen zu validieren und zu bekräftigen.

1. INTRODUCTION

1.1 Scope and Structure of the Thesis

There is growing evidence that nutrition might be a critical factor in the prognosis and treatment of heart failure (HF). Compared to other cardiovascular diseases (CVD), examinations about the influence of nutritional intakes and the risk of HF are still scarce and often based on limited data. An investigation of nutrition and its impact on HF, which is based on latest data, can contribute important insights to prevention and health promotion.

In advance, some research work has taken place to search for an *a priori* dietary pattern that might be associated to HF risk. For this purpose, the existing literature has been scrutinized for investigations that examined the association between diet (on different nutritional levels) and HF risk. The Mediterranean diet was identified as a dietary pattern with great preventive potential, as it is part of several guidelines and recommendations for primary and secondary prevention of CVD endpoints. Further literature review revealed several Mediterranean diet scores to assess this type of diet in observational studies. Despite its great potential in HF prevention, the Mediterranean diet and its association to HF risk has not yet been studied in a population of apparently healthy adults.

Thus, the present doctoral thesis deals with the primary research question whether the adherence to a Mediterranean-style diet, and/or the intakes of individual components of this diet, are associated with the risk of developing HF. This work was carried out at the German Institute of Human Nutrition in the Department of Epidemiology, Research Group of Cardiovascular Epidemiology. Data from the *European Prospective Investigation into Cancer and Nutrition* (EPIC)-Potsdam – a prospective cohort study in Eastern Germany - were used to answer the research question. It was hypothesized that greater adherence to the diet is inversely associated to the risk of HF and that the contribution of dietary elements to the overall effect might differ assuming higher importance of particularly high fish intake.

The present thesis is structured as follows: In the current Chapter 1, an introduction in the disease HF and nutrition as an exposure is following. In the latter part, a special focus lies on the Mediterranean diet regarding its characteristics, the estimation of adherence and its potential for heart health. After that, the applied methods and materials are described in Chapter 2, followed by the presentation of results according to the three levels of nutrition (Chapter 3). The thesis concludes with a detailed discussion in Chapter 4.

1.2 Heart Failure

In the following chapter the disease HF is introduced starting with commonly used definitions and classifications, a short overview about epidemiologic and pathophysiologic characteristics up to a brief summary of current diagnostic and treatment opportunities.

1.2.1 Definition and Classification

HF is "(…) an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate to commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures)." (McMurray 2012, p. 808)[1] This makes HF a complex clinical syndrome that combines various symptoms and signs (Table 1) and may occur in different entities.

Table 1: Symptoms and Signs Typical of Heart Failure (ESC Guidelines 2012, p 811)[1]

SYMPTOMS	SIGNS
Typical	**More specific**
Breathlessness	Elevated jugular venous pressure
Orthopnea	Hepatojugular reflux
Paroxysmal nocturnal dyspnea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover after exercise	Cardiac murmur
Ankle swelling	
Less typical	**Less specific**
Nocturnal cough	Peripheral edema (ankle, sacral, scrotal)
Wheezing	Pulmonary crepitations
Weight gain (>2 kg/week)	Reduced air entry and dullness to percussion at lung bases (pleural effusion)
Weight loss (in advanced heart failure)	Tachycardia
Bloated feeling	Irregular pulse
Loss of appetite	Tachypnea (>16 breaths/min)
Confusion (especially in the elderly)	Hepatomegaly
Depression	Ascites
Palpitations	Tissue wasting (cachexia)
Syncope	

Abbreviation: ESC, European Society of Cardiology

Several attempts have been made to define HF satisfactory. Since 1995 the European Society of Cardiology (ESC) publishes *Guidelines for the diagnosis and treatment of heart failure* approximately every four years to provide an overview of symptoms, signs and diagnostic procedures of HF to practitioners. According to the ESC Guidelines from 2005[2] two criteria should be fulfilled to define HF:

1. presence of typical HF symptoms and
2. objective evidence of cardiac dysfunction

There are some other common - more medically focused - criteria[3] and in the meanwhile the ESC criteria have been extended.[1] However, to conform to the relevant time frame of the investigation and the specific study population of the present work, only the above mentioned definition is considered relevant.

Furthermore, HF can be distinguished by function (diastolic versus systolic), location (left versus right), and disease progression (chronic versus acute). The most commonly used HF terminologies are summarized as follows.

Definition of Heart Failure by Functional Cardiovascular Abnormalities

Systolic and diastolic HF are commonly used terms to distinguish the disease by its functional condition. In systolic HF (also referred to HF with reduced ejection fraction (HF-REF)) a left-ventricular systolic dysfunction (LVSD) is present - an impairment of the heart to pump adequate amounts of blood through the circulation during systole.[4] LVSD is indicated by an ejection fraction of <35-40%. In contrast, diastolic HF is characterized by maintained LVS function and therefore generally termed as HF with preserved ejection fraction (henceforth HF-PEF).[5] In this case, a normal end-diastolic volume of the left ventricle can be achieved only at the expense of an increased filling pressure. Diastolic and systolic dysfunctions are not necessarily mutually exclusive; therefore the classification by ejection fraction might be more appropriate.[4] It is assumed that approximately half of all HF patients suffer from diastolic HF.[4]

Definition of Heart Failure by Severity

In contrast to acute HF, which requires emergency hospital treatment and is usually caused by pulmonary edema with life-threatening breathlessness, HF is generally a chronic condition commonly indicated by shortness of breath and fatigue on exertion.[5] For chronic HF different stages of severity are described that are most commonly measured using the New York Heart Association (NYHA) scale (Table 2).[1, 4]

Table 2: NYHA Classification of Heart Failure Severity (Source: ESC-Guidelines 2012, p 810)[1]

NYHA Class	Description
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitation
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue and palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue and palpitations
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased

Abbreviations: ESC, European Society of Cardiology; NYHA, New York Heart Association

According to NYHA, HF is separated into four classes starting with asymptomatic conditions up to HF with symptoms even at rest.

Another classification by stages of disease progression is given by the American College of Cardiology / American Heart Association (ACC / AHA).[6] It also includes stages prior to the onset of HF and therefore aims at primary prevention measures (Appendix I). However, this classification is not used in the present work and, therefore, not explained further.

Differentiation of HF by its location is not recommended and thus also not be considered in the present work.[4]

1.2.2 Epidemiology and Pathophysiology

Occurrence of Heart Failure

The overall prevalence of HF is 1-2% in Western societies but it increases considerably with age reaching about 10% in the age of 70-80 years.[1, 5] In Germany, about 1.8 million people are affected with approximately 300,000 new cases annually. Data about the occurrence of HF are scarce. In the USA, lifetime risk of developing HF is estimated at 20% and is similar in men and women above 40 years.[7]

Nevertheless, little is known about the temporal course of prevalence and incidence rates, except from some investigations that indicate a stagnation of incidence while prevalence is rising.[8, 9] This development may be attributed to improved therapeutic opportunities and survival probabilities. Nevertheless, hospitalization is still frequent and cost-intensive,[10, 11] e.g. the disease-specific mean costs of patients with atrial fibrillation are 3,274 ± 5,134 Euro, of which a large proportion is attributed to HF therapy.[12]

In spite of increasing therapeutic opportunities (pharmacological and non-pharmacological), the prognosis of HF remains poor. Patients still have shorter life expectancies (5-years survival after HF diagnosis: ~50%) with death mainly due to cardiovascular causes, especially sudden cardiac death (~43% of deaths) and progressive HF (~32% of deaths).[3, 5] In Germany, HF is subsequent to chronic ischemic heart disease and acute myocardial infarction the most common cause of death, with nearly 50,000 deaths per years.[13] Since high mortality is still a major problem in HF patients various survival scores have been generated to assess individual risk and need for treatment: e.g. the Heart Failure Survival Score[14], or scores introduced by Bouvy et al. [15], Lee et al. [16], Kearney et al. [17], and Levy et al..[18]

Risk Factors for Heart Failure

Risk factors for HF include coronary heart disease (CHD, meaning myocardial infarction and angina pectoris), hypertension, cardiomyopathies, arrhythmias, pericardial and valve disease, intoxication (e.g. by alcohol abuse) and infection.[1, 5, 19] In Western populations CHD is the predominant cause of HF, about one third of patients developing HF within seven to eight years after myocardial infarction.[5] More than 60% of HF cases are attributed to prevalent CHD in the USA (population attributable risk (PAR): 61.6%, relative risk and 95% confidence interval (RR (95%CI)): 8.1 (6.95-9.46).[20] Therefore, risk factors for cardiovascular diseases are similarly relevant for HF development. Results from the U.S. National Health and Nutrition Examination Survey (NHANES) showed that smoking (PAR: 17.1%, RR: 1.59 (1.39-1.83), hypertension (PAR: 10.1%, RR: 1.40 (1.24-1.59), overweight (PAR: 8.0%, RR: 1.30 (1.12-1.52), diabetes (PAR: 3.1%, RR: 1.85 (1.51-2.28), low education (PAR: 8.9%, RR: 1.22 (1.04-1.42) and low physical activity (PAR: 9.2%, RR: 1.23 (1.09-1.38) all are associated with higher risk of HF.[20] However, results from the Framingham Heart Study suggest a greater impact of hypertension, rather than of myocardial infarction, due to a higher prevalence, especially in women (PAR of hypertension: 39% for men and 59% for women; PAR of myocardial infarction: 34% for men, 13% for women). A possible explanation might be the older study population of the Framingham Heart Study compared to NHANES. However, it is generally difficult to determine the impact of individual risk factors in the development of HF, since most of them coexist.

Despite the growing evidence about the role of diet in the context of HF development, data are still inconclusive. An overview of the scientific evidence on this topic is presented in Chapter 1.3.2.

Disease Development, Progression and Compensatory Mechanisms

The development of HF can take many pathways. The most common one in developed countries is via CHD. If the heart suffers a myocardial infarction, parts of the muscle may be irreparably damaged resulting in decreased pumping capacity. The impaired heart function is compensated by increased heart rate and blood pressure to preserve cardiac output. Chronically, these mechanisms promote further dysfunction and failure. Release of cytokines and growth factors activates fibrosis and hypertrophy as well as apoptosis and necrosis. A vicious circle ensues. [4, 21]

HF due to hypertension frequently leads to LV hypertrophy which preserves contractile function and is therefore often the underlying cause of HF-PEF, but progressed LV hypertrophy also results in systolic dysfunction.[4] Yet, maintenance of contractile function necessitates an increase in pulmonary venous pressure, which results in pulmonary edema along with typical HF symptoms such as breathlessness.

Valve diseases may be a primary and a secondary (consequence of other factors, e.g. prior myocardial infarction) cause of HF. Often it is triggered by chronic inflammation followed by calcification of the valve. Generally, HF due to valve disease progresses slowly and may be asymptomatic in early stages. Furthermore, valve diseases are rare and the impact on HF development is not considered very high (PAR: 2.2%, RR: 1.46 (1.17-1.82)).[20]

Another pathway is possible via cardiomyopathies due to, or along with, arrhythmia. Atrial fibrillation might be the most important arrhythmia in this context that induces reduced cardiac output when untreated. However, it is difficult to disentangle whether arrhythmias are the cause or the consequence of HF. Conversely, dilated cardiomyopathies may also be induced by alcohol abuse (>90g/d).[4]

1.2.3 Diagnosis and Treatment

Apparently, symptoms and signs of HF (Table 1) are often non-specific and to discriminate HF and other disorders (e.g. lung diseases) purely on the basis of symptoms is rather impossible. Therefore, the diagnosis of HF often requires a combination of several tests. Certain diagnostic procedures are available to identify HF signs. Some of these procedures are presented as follows. Furthermore, a brief overview of HF treatment is given.

General Diagnostic Procedures in Heart Failure

Echocardiogram is a non-invasive method for cardiac imaging and considered as gold standard in HF diagnosis, since it is applicable for the evaluation of both systolic and diastolic dysfunction.

Another useful diagnostic device is the electrocardiography (ECG) provides detailed information on underlying prevalent CHD and any type of arrhythmia, which may be related to HF.

Chest x-ray can additionally be applied to detect edema in HF as well as ventricular hypertrophy and cardiomegaly. However, it is most commonly used to identify alternative explanations for the patients' symptoms and signs and, therefore, to exclude HF.[22]

Lastly, cardiac catheterization is a valuable measure to gain information about filling pressure, vascular resistance and cardiac output. However, the use in clinical practice is limited due to its invasive nature. Generally, it is applied more frequently prior to cardiac transplantation than in routine diagnosis of HF.[1, 22]

The diagnosis of HF is generally classified according to the disease classification of the World Health Organization, the International Classification of Disease, tenth version (ICD-10). Based on this, it is distinguished between congestive HF (I50.0), left ventricular failure (I50.1), and unspecified HF (I50.9).[23]

Treatment of Heart Failure

The pharmacological treatment of HF aims essentially at relieving symptoms and improving quality of life. Typically this includes the prevention of tachycardia, the normalization of blood pressure and treatment of congestion, edema and LV hypertrophy. The main agents of pharmacological therapy in HF are, thus, antihypertensive drugs (e.g. angiotensin converting enzyme (ACE) inhibitors or beta blockers) and diuretics (e.g. loop diuretics and thiazides).

Beside the pharmacological therapy, devices may help where drugs fail, especially in case of arrhythmias. By implantation of cardioverter-defibrillators the risk of sudden death is strongly declined. Other surgical procedures include bypasses, valve surgeries and in end-stage HF heart transplantation, to name a few. Invasive therapies are often a consequence of CHD, resistant disease symptoms and severity and always rely on individual case decisions.[1, 21, 22, 24]

1.3 Exposure Nutrition

The following chapter provides a brief introduction to nutrition and gives an overview of the current scientific knowledge about the impact of nutrition on the risk of HF. Special emphasis is given to the Mediterranean diet, which is presented in Chapter 1.3.3.

1.3.1 From Single Nutrients to Food Pattern Analysis

In the field of nutritional epidemiology, it is generally distinguished between three levels of dietary exposures: the level of nutrients, food groups and dietary patterns. Further subgroups can be defined, as depicted in Figure 1.

While analyses based on single nutrients or food groups are easy to implement and communicate, this approach carries several limitations. Nutrients reflect only a small part of the diet and interactive or synergistic effects between nutrients or food groups are often not adequately taken into account. Single components might highly correlate or interact with each other. With the development of dietary patterns the entire diet is considered and the problem of multicollinearity is taken into account. Nowadays, different methods to generate food patterns are implemented, e.g. factor analysis, cluster analysis or scores/indices. While factor- and cluster analyses are *a posteriori* methods based on the data observed, the use of scores is usually an *a priori* approach and based upon dietary recommendations.[25]

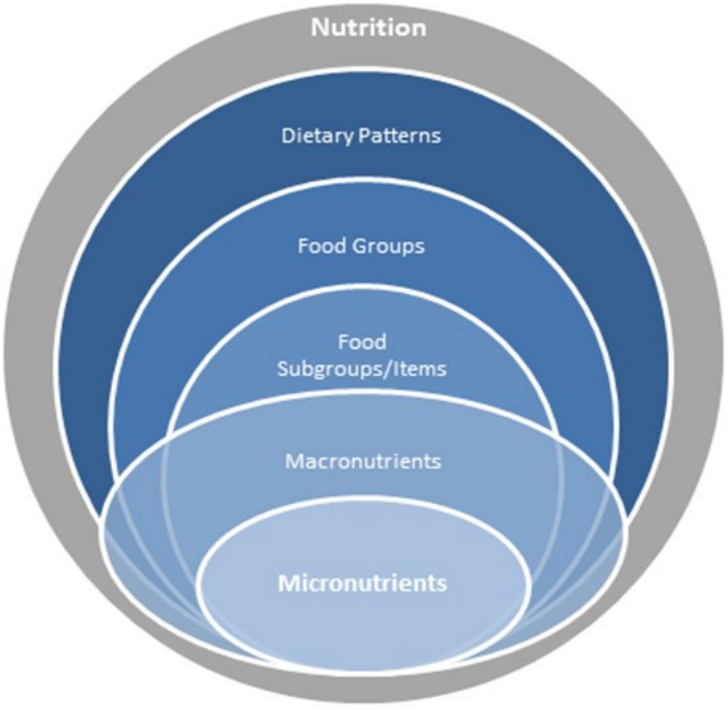

Figure 1: Schematic Illustration of the Different Levels of Nutrition

As demonstrated in Figure 1, dietary patterns are covering a large proportion of the entire diet. They consist of food groups that comprise one or more food items. The level of food items is the level at which diet is normally assessed in observational studies, often by means of food frequency questionnaires (FFQs).

Contrary to micronutrients (like vitamins and minerals), macronutrients are usually defined as nutrients that supply energy: fat, protein, carbohydrates and alcohol.[26] In the present work, fiber (subgroup of carbohydrates) and cholesterol (subgroup of lipids) are counted as macronutrients (see Appendix II). Although nutrients are embedded in food groups and items, they cross to a certain extent all dimensions of nutrition as outlined in Figure 1.

1.3.2 The Scientific Evidence on Nutrition and Heart Failure

In the last decades, clinical studies have shown that diet plays an important role in the treatment and prognosis of HF. In this context, investigations were initially performed at the level of nutrients investigating malnutrition and resulting nutrient deficiencies. The family of B vitamins, but also vitamin D, iron, selenium, and zinc have been examined in this context.[27] [28] [29] Also the harmful effect of salt and sodium intake and the influence of sodium restriction were investigated in relation to CVD risk and HF development and prognosis.[30-32] However, despite the numerous studies showing successful improvements in the prognosis of HF, so far no clear conclusions can be drawn about the role of these nutrients.

Few prospective studies exist that investigated the dietary impact on HF incidence at the level of nutrients. These were furthermore contradictory and focussed mainly on intakes of fatty acids, especially marine omega-3-fatty acids (n3FAs). In Table 3, prospective cohort studies on nutrients (fatty acids, vitamins and minerals) and the risk of HF are summarized.

Within the last decade, first prospective studies appeared investigating the level of food groups, especially fish consumption. Besides the eight studies listed in Table 4, three meta-analyses were published recently.[33-35] Djousse et al.[35] and Li et al.[34] observed an inverse association between fish intake and HF, while Hou et al.[33] found no association between fish and HF incidence but an increased HF risk with consumption of fried fish.

There is some support of a beneficial effect of whole grain intake[22, 23] on HF development. However, most other food groups were investigated by only few studies with controversial results. In this context, red meat, eggs and dairy products seemed more likely to be associated with an increased risk of HF.[36, 37] These and further examined foods are summarized in Table 5.

Table 3: Summary of Prospective, Population-based Cohort Studies on Nutrients and Heart Failure Risk

First author, year	Study, Country	Population					Exposure	Result
		Number	Cases	Sex	Age [range]	FUP§ [years]	Dietary intake of…	
Fatty acids								
Levitan et al., 2012[38]	SMC, Sweden	36,234	651	w	48-83	~9	α-linolenic/ linoleic acid	no association to HF risk
Lemaitre et al., 2012[39]	CHS, USA	4,432	1,072	m/w	≥65*	~12	α-linolenic acid	no association to HF risk
Wilk et al., 2012[40]	PHS, USA	19,097	703	m	58.7§	~8	n3FA	no association to HF risk
Belin et al., 2011[41]	WHI, USA	84,493	1,858	w	50-79	~10	n3FA, trans fatty acids	no association to HF risk
Levitan et al., 2010[42]	SMC, Sweden	36,234	651	w	48-83	~9	n3FA	inverse association to HF risk
Dijkstra et al, 2009[43]	RS, The Netherlands	5,299	669	m	≥55*	~11	n3FA	no association to HF risk
Levitan et al., 2009[44]	CSM, Sweden	39,367	597	m	45-79	~7	n3FA	U-shaped association to HF risk
Yamagishi et al., 2008[45]	JACC, Japan	57,972	307	m/w	40-79	~13	n3FA	inverse association to fatal HF risk
Vitamins								
Cui et al., 2010[46]	JACC, Japan	58,730	318	m/w	40-79	~14$	folate, vitamin B_6, vitamin B_{12}	inverse association to fatal HF risk positive association to fatal HF risk (n.s.)
Rautiainen et al., 2013[47]	SMC, Sweden	33,713	894	w	49-83	~11	total antioxidant capacity of diet	inverse association to HF risk
Minerals								
Zhang et al., 2012[48]	JACC, Japan	58,615	431	m/w	40-79	~15$	magnesium	inverse association to fatal HF risk in women
He et al., 2002[49]	NHANES I, USA	10,362	1,092	m/w	25-74	~19	sodium	positive association to HF risk

* Minimum age; § arithmetic mean, $ median
Abbreviations: CHS, Cardiovascular Health Study; CSM, Cohort of Swedish Men; FUP, follow-up time; HF, heart failure; JACC, Japan Collaborative Cohort; n3FA, omega-3 fatty acids; NHANES, National Health and Nutrition Examination Survey; n.s., not significant; PHS, Physicians' Health Study; RS, Rotterdam Study; SMC, Swedish Mammography Cohort; WHI, Women's Health Initiative

Regarding beverages, meta-analyses have been published for alcohol intake[50] (Figure 2) and for coffee consumption[51] in relation to HF development. Both coffee and alcohol consumption turned out to be inversely associated with HF risk if consumed moderately.

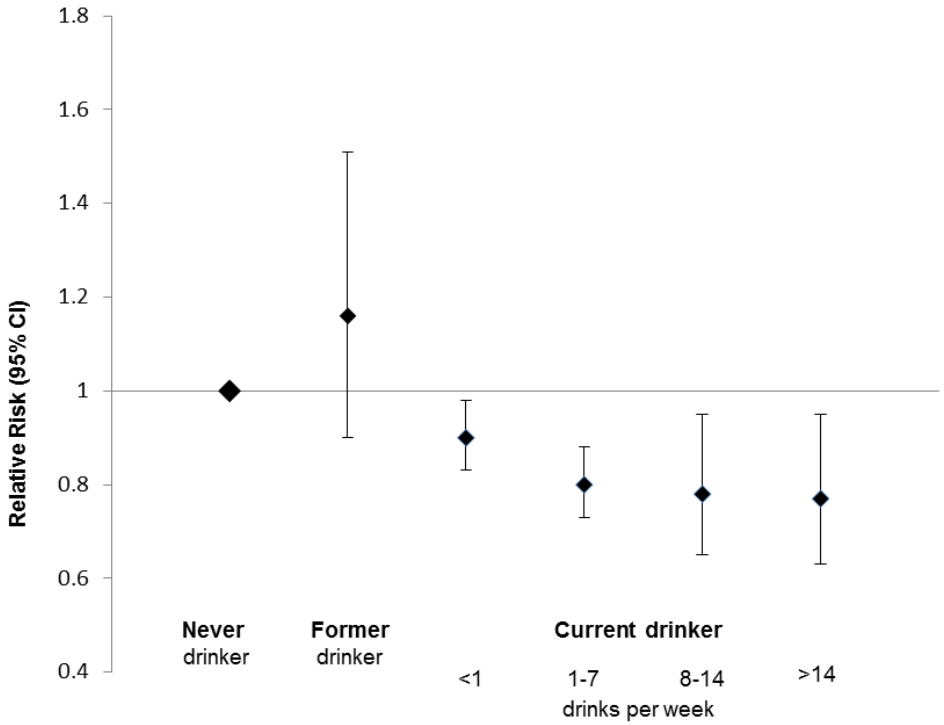

Figure 2: Results from a Meta-analysis on Alcohol Consumption and the Risk of Heart Failure

This figure is a modified version of Figure 1, Padilla, 2010[50]
Abbreviations: CI, confidence interval

Similarly, the research on dietary patterns in relation to HF development is limited to three publications.[52-54] The DASH diet, a diet rich in fruits, vegetables, nuts, legumes, low-fat dairy and whole grain, but low in sodium, sweetened beverages and red and processed meat, has potential for risk reduction of HF.[21, 22] The dietary glycemic index or glycemic load, however, seems not to influence the development of HF. [52]

Despite the growing evidence about the role of nutrition in HF development, literature is still insufficient to draw firm conclusions on the association between dietary components and the incidence of HF, even regarding the extensively examined food group fish.

Table 4: Summary of Prospective, Population-based Cohort Studies on Fish Intake and Heart Failure Risk

First author, year	Study, Country	Population					Exposure	Result
		Number	Cases	Sex	Age [range]	FUP§ [years]	Intake of…	
Mozaffarian et al., 2005[55]	Prospective cohort: CHS, USA	4,738	980	m/w	≥65*	~12	fish	inverse association to HF risk
Yamagishi et al., 2008[45]	Prospective cohort: JACC, Japan	57,972	307	m/w	40-79	~13	fish	inverse association to HF risk (n.s.)
Nettleton et al., 2008[36]	Prospective cohort: ARIC, USA	14,153	1,140	m/w	45-64	~14	fish	no association to HF risk
Dijkstra et al, 2009[43]	Prospective cohort: RS, Netherland	5,299	669	m	≥55*	~11	fish	no association to HF risk
Levitan et al., 2009[44]	Prospective cohort: CSM, Sweden	39,367	597	m	45-79	~7	fish	U-shaped association to HF risk (n.s.)
Levitan et al., 2010[42]	Prospective cohort: SMC, Sweden	36,234	651	w	48-83	~9	fish	inverse association to HF risk
Belin et al., 2011[41]	Prospective Cohort: WHI, USA	84,493	1,858	w	50-79	~10	fried fish boiled/baked fish	positive association to HF risk inverse association to HF risk
Wilk et al., 2012[40]	Prospective cohort: PHS, USA	18,968	695	m	58.7§	~8	fish	inverse association to HF risk

* Minimum age; § arithmetic mean

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; CSM, Cohort of Swedish Men; FUP, follow-up time; HF, heart failure; JACC, Japan Collaborative Cohort; n.s., not significant; PHS, Physicians' Health Study; RS, Rotterdam Study; SMC, Swedish Mammography Cohort; WHI, Women's Health Initiative

Table 5: Summary of Prospective, Population-based Cohort Studies on Different Food Groups and Heart Failure Risk

First author, year	Study, Country	Population					Exposure	Result
		Number	Cases	Sex	Age [range]	FUP[§] [years]	Intake of…	
Djoussè et al., 2007[56]	PHS, USA	21,376	1,018	m	40-86	~20	breakfast cereals	inverse association to HF risk (limited to whole grain cereals)
Djoussè et al., 2008[57]	PHS, USA	21,275	1,084	m	53.7[§]	~20	eggs	positive association to HF risk
Nettleton et al., 2008[36]	ARIC, USA	14,153	1,140	m/w	45-64	~14	whole grains, high-fat dairy, eggs fruits/vegetables nuts, red meat	inverse association to HF risk positive association to HF risk no association to HF risk
Djoussè et al., 2008[58]	PHS, USA	20,976	1,093	m	54.6[§]	~20	nuts	no association to HF risk
Ashaye et al., 2010[20]	PHS, USA	21,120	1,204	m	54.6[§]	~20	red meat	positive association to HF risk
Mostofsky et al., 2010[59]	SMC, Sweden	31,823	419	w	48-83	~9	chocolate	U-shaped association to HF risk
Kaluza J et al., 2014 [60]	CSM, Sweden	37,035	3,157	m	45-79	11.8	Processed meat Unprocessed meat	Positive association to HF risk No association to HF risk

[§] arithmetic mean

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; FUP, follow-up time; HF, heart failure; PHS, Physicians' Health Study; SMC, Swedish Mammography Cohort

1.3.3 The Mediterranean Diet

In Mediterranean countries such as Greece or Italy, a typical lifestyle and diet is common, which in parts is considerably different from the diet in other European countries due to, amongst others, closeness to the sea and the subtropical climate. Physical activity is also part of the Mediterranean lifestyle, as field and kitchen work were characteristics of the Mediterranean area in the 1960s along with low occurrence of obesity.[61] In addition, the Mediterranean diet represents a social component: meals are eaten together with family and friends and are an expression of enjoyment, stress relief and pleasure.[61]

Characteristics of the Mediterranean Diet

The Mediterranean diet is characterised by a high proportion of plant foods like vegetables, fruits, cereals, legumes, seeds and bread. Furthermore, meals are generally consumed fresh or minimally processed. The proportion of saturated fatty acids (SFAs) is usually low due to low consumption of red meat, while olive oil is the principal fat source. Intakes of fish exceed the intakes of poultry and are consumed in moderate amounts. Another component of the diet is the consumption of wine, typically in low to moderate amounts and during meals. Fresh fruit is usually eaten as dessert.

The typical Mediterranean diet reflects the nutritional pattern of Greek (especially Crete) and south Italian regions in the 1960s and was defined and operationalized by means of a Mediterranean diet pyramid by Willett et al. in 1995.[61] Figure 3 shows a similar Mediterranean diet pyramid, introduced by the Supreme Scientific Health Council of the Ministry of Health and Welfare in 1999.[62]

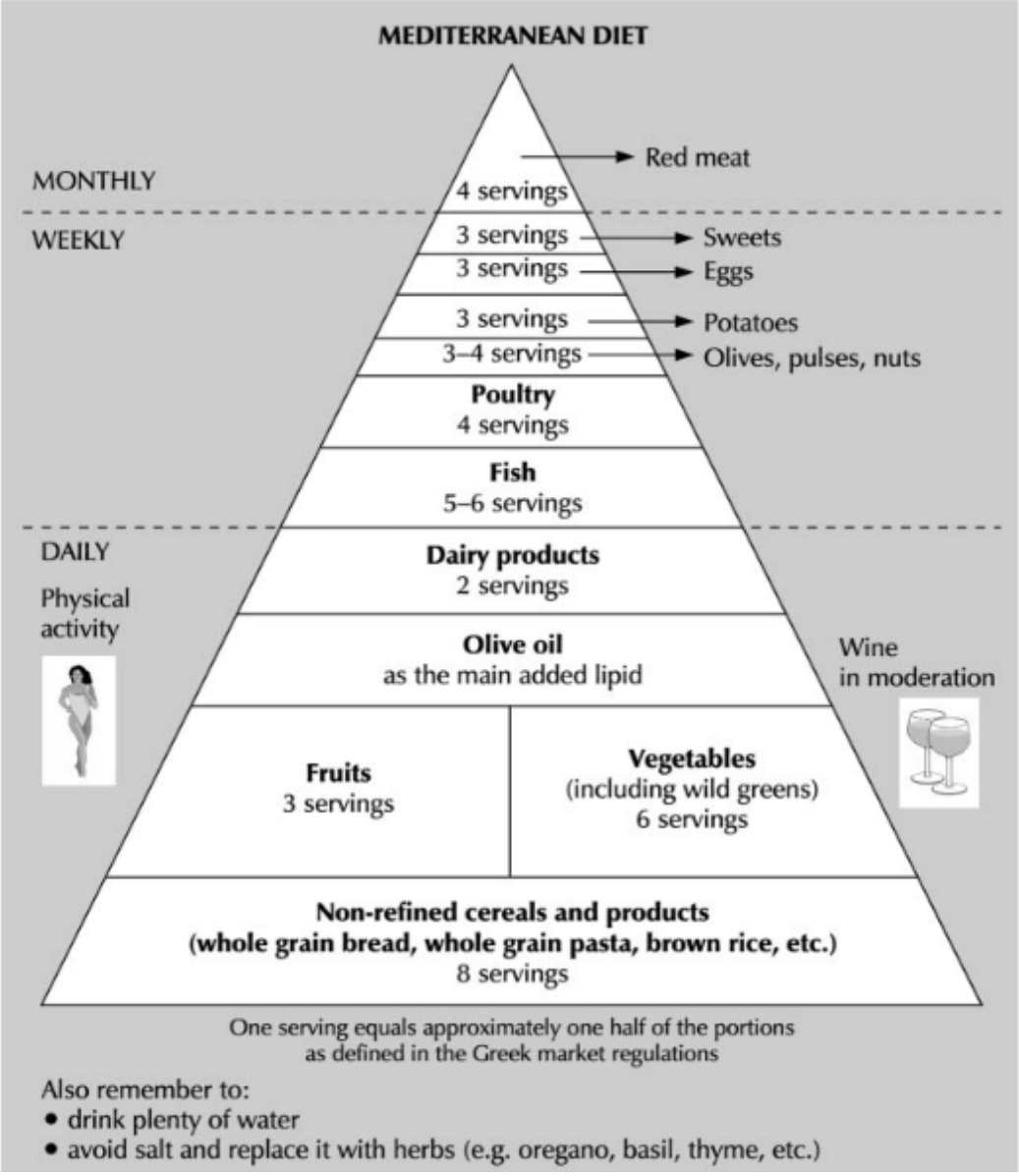

Figure 3: The Mediterranean Diet Pyramid (Source: Supreme Scientific Health Council 1999, p 519)[62]

Mediterranean Diet Scores

In the scientific literature, a vast amount of publications is available on attempts for defining and estimating adherence to the Mediterranean diet. The majority of them computed the adherence by means of *a priori* (derived from prior knowledge) defined Mediterranean diet scores.[63]

The first score, the traditional Mediterranean diet score (tMED), was introduced by Trichopoulou et al. in 1995[64] and generated by using median intakes of a Greek population to specify adherence to the diet (Table 6). Six positive (health-promoting) and two negative (detrimental) components were considered. The tMED was widely used by

other investigators, especially the one, which was revised by Trichopoulou et al.[65] in 2003 to include fish as a seventh positive component. A further modification was performed by the same author[66] to allow application of the score in non-Mediterranean populations. The main difference to the previous score was the inclusion of polyunsaturated fatty acids (PUFAs) in the numerator of the fat-ratio, since monounsaturated fatty acids (MUFAs, that represent olive oil in Mediterranean countries) originate from other - presumably unhealthy - sources in the nutrition of non-Mediterranean populations.

Besides Trichopoulou's own modifications, other investigators modified the tMED due to the type of their research question, data collection, general health recommendations, or the differing distribution of the components' intakes in the population under investigation. The main changes were the exclusion of alcohol or the use of different definitions of moderate alcohol consumption, the exclusion of nuts or dairy products from the score, and the pooling of two components (e.g. legumes with vegetables or nuts, and potatoes with cereals or vegetables). Some researchers also split meat into red meat and poultry or excluded the latter from the score. One more recent study should be mentioned here: Sofi et al.[67] combined the tMED with *a posteriori* (based on empirical data) defined cut-points. Participants were assigned 0, 1 or 2 points according to their amount of intakes (with 2 points reflecting higher adherence than 1 point). This score ranged from 0 to 18 points.

Apart from the tMED, another score was widely used in the scientific literature: the alternate Mediterranean diet score (aMED).[68] This score was generated in the Nurses' Health Study and therefore adapted to a U.S. American population. It was a modified version of the revised tMED in order to integrate associations to lower risks of chronic diseases. Therefore, only whole-grain and red meat were included, nuts were regarded as separate component and dairy products were excluded from the score. Additionally, the amount of moderate alcohol consumption was modified to fit U.S. American standard portion sizes (Table 6).

Many more investigators came up with other scores that differed in their components and weighting of these, or they used different cut-points for score construction (percentages, tertiles, or categories). However, those were not used in the present work and therefore were not further explained. An overview of the present Mediterranean scores that are used in observational studies is given in Appendix III-Appendix VI.

Table 6: The Characteristics of the Traditional and the Alternate Mediterranean Diet Score

First Author, Year	Study population	No. of components	Positive components	Negative components	Score cut points	Score range	Account for energy	Adapted or modified by
1) Traditional Mediterranean Diet Score (tMED)								
Trichopoulou 1995[64]	Residents from 3 Greek villages	8	1. MUFA/SFA-ratio 2. moderate alcohol 3. legumes 4. cereals/ potatoes 5. fruits and nuts 6. vegetables	1. meat/meat products 2. milk/milk products	Sex-specific medians*	0-8	Intakes were adjusted to 2000 kcal (women) /2500 kcal (men)	6 studies
Revised in 2003[65]	EPIC-Greece	9	***Changes:*** - Inclusion of fish as positive component - Definition of moderate alcohol consumption: women: 5-25g/d, men: 10-50g/d		Sex-specific medians*	0-9	adjusting for energy-expenditure index	70 studies
Modified in 2005[66]	EPIC-Elderly, 10 European countries	9	***Changes:*** - (PUFA+MUFA)/ SFA-ratio - fruits did not include nuts		Sex-specific medians*	0-9	adjusting for energy intake	10 studies
2) Alternate Mediterranean Diet Score (aMED)								
Fung, 2005[68]	Nurses' Health study	9	1. MUFA/SFA-ratio 2. moderate alcohol (w: 5-15g/d, m:10-25g/d) 3. legumes 4. whole-grain cereals 5. fruits 6. nuts 7. vegetables 8. fish	1. red and processed meat	Sex-specific medians*	0-9	adjusting for energy intake in the regression model	21 studies

* persons receive 0 points for intakes ≤ median and 1 point for intakes ≥ median in case of positive components and reverse for negative components

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids

The Mediterranean Diet and Heart Health

The Mediterranean diet gained notoriety ever since the protective effect against ischaemic heart disease has been recognized by Keys in the Seven Countries Study,[69] where mortality rates of CHD were compared between populations from Mediterranean countries, Japan, North European countries and the USA. The lowest death rates were observed in Greece, which was attributed to the high MUFAs and simultaneously low SFA content of their diet.[70]

Since then, much research has been conducted in this area to understand the health-promoting ability of the Mediterranean diet. Cardio-protective properties have been well documented by ecologic, cohort as well as intervention studies, and in different settings and populations of primary and secondary prevention.[71-76] The clear regional variation in cardiovascular mortality within Europe, showing a north-east to south-west gradient, is thought to be related to differing risk profiles including lifestyle and diet (together with alcohol consumption).[71] The Mediterranean diet has already been reported to be inversely associated to cardiovascular risk factors and precursors of CVD and HF.[68, 77-82] Furthermore, to incident CHD[73, 75] and CVD mortality[73, 75, 76] in the general population, and to survival after myocardial infarction[74] and HF[83] (although not significant in HF). A meta-analysis of 20 prospective cohort studies by Sofi et al.[84] that investigated the relationship between adherence to the Mediterranean diet and the incidence and mortality from CVD reported a 10% risk-reduction per two points increase in Mediterranean diet score. Recently, the CVD risk-protective effects of the Mediterranean diet have also been confirmed in the PREDIMED study (PREvención con DIeta MEDiterránea), a large randomized dietary trial in a population at high cardiovascular risk.[72] Participants who were assigned to a Mediterranean diet supplemented with either olive-oil or nuts, had an approximately 30% reduced risk of developing major cardiovascular events compared to the control group which was advised to reduce total dietary fat.[72]

Behind this background, it is not surprising that the Mediterranean diet has become an important tool of preventive measures for cardiovascular health and is part of several guidelines and recommendations for primary and secondary prevention of CVD endpoints, especially CHD.[85-87] The secondary prevention of CHD appears to be closely related to primary prevention of HF, at least of systolic nature, since HF-related deaths are quite common among persons with established CHD.[86, 88] Following a Mediterranean-style dietary pattern seems to be the most promising dietary behaviour in the primary prevention of HF as it is a recommended nutritional pattern in the secondary prevention of CHD.[86] Furthermore, it combines most of the previously identified dietary components that may be relevant in HF development as outlined in Chapter 1.3.2.

1.4 Objectives

Against the presented background, the research question of this thesis was whether the adherence to a Mediterranean-style dietary pattern is associated with the risk of developing HF in a population of apparently healthy adults, and whether this association is driven by certain components of the diet.

The objective of this thesis is therefore to evaluate associations between adherence to the Mediterranean diet and the risk of HF on different levels of nutrition. To reach this goal, a top-down approach was applied; beginning with analyses on an established Mediterranean diet score[65], continuing with the dietary components on which the score was based, up to the level of single subgroups, macronutrients and micronutrients (see Appendix II) depending on the results derived from the respective higher level. Data of a large German prospective cohort study, EPIC-Potsdam, were used for these analyses.

The top-down approach was structured into the following steps:

1. Evaluation of the association between the adherence to an *a priori* defined Mediterranean dietary pattern and the risk of HF by using a common established Mediterranean diet score
2. Analyses on components of the score to identify the main contributors to the diet-disease association, or - in case of no association with the overall score - to identify whether individual score components (and subgroups of these) are associated to HF risk
3. Evaluation of the association between the main representatives of the respective identified foods and the risk of HF on macro- and/or micronutrient level.

2. MATERIAL AND METHODS

2.1 Material

2.1.1 Study Design and Population

EPIC is a large-scale multi-center cohort study with a total of nearly 520,000 participants from ten European countries and 23 centers.[89] The German Institute of Human Nutrition is one of the two German centers and is located in Potsdam (north-east of Germany). From initially about 75,000 invited residents from Potsdam and surrounded areas, 27,548 (22.7%) agreed to participate and were recruited between 1994 and 1998.[90, 91] Participants gave their written informed consent and all study procedures were approved by the Ethics Committee of the Federal State Brandenburg.

Recruitment included physical examinations as well as personal interviews and questionnaires on lifestyle and health factors that are of interest in studies aimed to investigate the relationship between nutrition and chronic diseases, particularly cancer.[91] Every two to three years, participants were re-contacted and interviewed by questionnaires about lifestyle and newly diagnosed diseases.[92] Up to the fourth follow-up, response rates exceeded 90% at each occasion.

Some exclusion was required for the current analyses. This involved 3,540 participants (including 116 incident HF cases). In detail, 125 participants with either a prevalent/not verifiable HF at baseline, 612 participants who never filled out any follow-up questionnaire, and 135 participants with an age lower than 35 were excluded. Further exclusion criteria were missing information about covariates (n=247), and implausible energy intake (top and bottom 1% of total energy intakes) to minimize the problem of over- and underreporting (n=528). As CHD (herein angina pectoris or myocardial infarction) is a severe disease where dietary changes can be expected and it is also an important risk factor for HF, 1,863 participants (including 100 incident HF cases) with prevalent CHD were excluded. Finally, 24,008 participants (23,799 non-cases and 209 incident HF cases) remained for analyses.

2.1.2 Exposure and Covariate Assessment

Dietary Assessment

Habitual dietary intakes during the year preceding enrolment were assessed by means of a semi-quantitative self-administered FFQ. In this questionnaire it was asked about the frequencies and portion sizes (supported by photographs) of 148 food items and possible answers were scaled from 'once a month or less' to 'five times a day or more'. Food items have then been summarized into 49 food groups as described previously.[93] For each participant, intakes were converted into grams per day or milliliters per day, and various nutrients, as well as total energy intakes were calculated by a link to the German Nutrient Data Base.[94]

The FFQ data was validated by comparison to 24h dietary recalls in a subset of 104 EPIC-Potsdam participants as previously described.[95, 96] The validity of the FFQ was reported to be low for food groups consumed in low amounts and mainly at weekends (which were not covered by the 24h dietary recalls), such as legumes (Spearman correlation coefficient (r) =0.14), nuts (r=0.18) and fish (r= 0.21). Moderate validity was observed for intakes of vegetables (r=0.34), cereals (r=0.42), cheese (r=0.47), fruits (r=0.50), red meat (r=0.53), milk products (r=0.56), and processed meat (r=0.56). The relative validity of alcoholic beverages was high (r=0.90).[93] On the level of nutrients, observed Pearson correlation coefficients were moderate for intakes of total energy (r=0.59), SFAs (r=0.57), MUFAs (r=0.53), and cholesterol (r=0.51), while it was high for ethanol (r=0.88).[96]

Selection and Building of the Mediterranean Diet Score

To investigate the Mediterranean dietary pattern, in a first step, two established Mediterranean diet scores were used, namely the revised modified tMED by Trichopoulou et al.[66] and the aMED created by Fung et al.[68] (for both see Table 6). These two scores were selected because they sufficiently differed in terms of components and construction and they were both established in a wide range of previous studies. Furthermore, the revised modified tMED was generated to be applied in non-Mediterranean countries, and the aMED was constructed in line with recommendations to prevent chronic diseases and, therefore, both seemed to be the most appropriate ones.

However, after the first analyses (see Appendix VII), it was decided to change to the traditional revised tMED[65] with the initial used cut-points (median intake values of the Greek population), as this seemed to reflect the 'true' Mediterranean diet more properly. Two main issues were identified when keeping at study-specific median cut-points:

First, it was noted, that the dietary intakes according to score points in some parts did not much differ between the groups (Appendix VIII and Appendix IX). In case of the tMED this was conspicuous especially for the consumption of meat (mean intakes were equal in all three groups of adherence). With respect to the aMED, the proportion of persons receiving a point for several individual components was not differing much across the groups (e.g. 45% received a point for high vegetable intake in group 1 versus 53% in group 3 of aMED adherence). Second, great differences between the consumed intakes of the initial Greek population and the EPIC-Potsdam study participants were recognized (Table 7). By using the Greek cut-points an inverse relationship was expected which corresponded more to the 'true' effect of the Mediterranean diet.

Thus, the finally used score included nine components (for structure and composition see Appendix X) with a possible range from 0 to 9 points (minimum to maximum adherence). One point was assigned for intakes at or above the sex-specific median intakes of the Greek population (Table 7) for components considered to be healthy (vegetables, fruit and nuts, legumes, cereals, fish, and the ratio between MUFAs and SFAs). Persons received no point when the intakes were lower. In terms of components considered detrimental (meat products and milk products) the scoring was reversed. Regarding alcohol, a value of one was assigned for moderate consumption (men: ≥10 g/d – 50 g/d, women ≥ 5g/d – 25 g/d) and no point for lower and higher intakes.

Table 7: Median Dietary Intakes* (by sex) of Mediterranean Diet Score Components Comparing EPIC-Potsdam and EPIC-Greece

Component	Men		Women	
	EPIC-P	EPIC-G[65]	EPIC-P	EPIC-G[65]
Fish	23.0	23.7	16.4	18.8
Fruits and nuts	126.1	362.5	156.8	356.3
Vegetables	81.8	549.9	97.3	499.6
Legumes	23.4	9.1	14.6	6.7
MUFA/SFA-ratio	0.87	1.72	0.84	1.74
Cereals	221.6	177.7	172.9	139.7
Meat products	135.1	120.8	87.1	89.8
Milk products	154.0	196.7	190.4	191.1

* Median dietary intakes include consumers and non-consumers
Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-G, EPIC-Greece; EPIC-P, EPIC-Potsdam

Assessment of Covariates

Information on non-dietary factors such as prevalent diseases (e.g. CHD, diabetes, hypertension and hyperlipidemia), lifestyle and socio-demographic factors were obtained at baseline by computer-guided questionnaires and personal interviews.[89-91] Further, a physical examination covered, amongst others, measurements of anthropometric parameters and blood pressure. Body mass index (BMI) was calculated by dividing body weight by body height squared (kg/m^2). For the present analysis, prevalent hypertension was defined as systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg or self-reporting of a diagnosis or use of antihypertensive medication. Prevalent CHD was defined as either myocardial infarction or angina pectoris prior to baseline. The prevalence of diabetes at baseline was assessed by using information on self-reported medical diagnosis, medication records and dieting behaviour. Persons were considered to have prevalent hyperlipidemia, if they reported a diagnosis or the use of lipid lowering drugs. Physical activity was defined as the mean time spent on leisure time physical activities and cycling (hours/week) during summer and winter. All interviews and physical examinations were standardized and conducted by trained personnel.[91]

2.1.3 Outcome Ascertainment

In the present analyses only medically confirmed HF cases were used. Those were identified by several sources of information:

- Self-report
- Death certificates (diagnosis I50 of ICD-10 as underlying cause of death)
- Link to the hospital information system of the major hospital in the Potsdam area.
- Validation of participants who suffered from incident myocardial infarction or reported the use of medications typical for the treatment of HF

In the fourth follow-up round a question about HF was first incorporated in the questionnaires (see Appendix XII) to determine newly diagnosed outcomes by self-report. The participants were asked, whether they ever had been diagnosed with a weak heart or HF. If they affirmed, the date of diagnosis and the treating physician was obtained. Attending physicians were then contacted and asked to fill out a validation form (Appendix XIII), in which the diagnosis and the respective date should be confirmed.

In addition, HF cases were classified in accordance to the diagnostic criteria of the ESC Guidelines,[2] as previously described.[97] Briefly, HF cases were divided into definite, probable, possible and indefinite cases by the degree of diagnostic information (Figure 4).

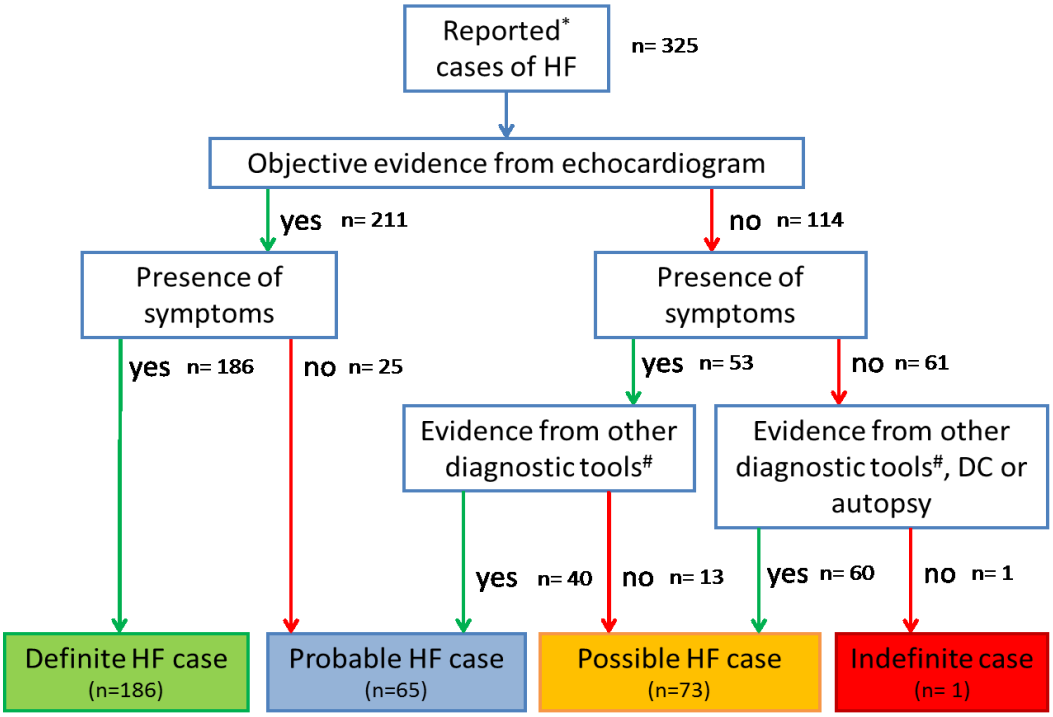

Figure 4: Flow Chart of the Validation Procedure for Heart Failure Classification, according to Diagnostic Evidence (Source: Wirth 2013[98], p. 28)

* Identified by self-report, death certificates (diagnosis ICD-10 I50 as underlying cause), and by link to the hospital information system of the major hospital in the Potsdam area. In addition, participants were validated, who suffered an incident myocardial infarction or reported the use of medications that are commonly prescribed for the treatment of HF. Only HF cases confirmed by the general practitioner are further validated for the discrimination between definite, probable or possible cases. # Evidence from electrocardiogram, x-ray or cardiac catheterization; Note that this figure includes all reported HF cases without any exclusion

Abbreviations: HF, heart failure; DC, death certificate

2.2 Methods

2.2.1 The Top-Down Approach

After selection of the final Mediterranean diet score, the overall association between the adherence to the diet and HF risk was evaluated (see the following Chapter 2.2.2, Risk Analysis for details). To decide which score components play a role for the development of HF and, therefore, should be analyzed further on lower levels of nutrition (top-down), three approaches were used:

1. HF risk analysis of each individual component on a dichotomous scale
2. Evaluation of the shape of the association between each individual component and HF risk on a continuous scale
3. A 'subtraction method', removing alternately each one component at a time as proposed by Trichopoulou et al.[99] to determine the relative impact of these components on HF risk

The components that were considered relevant according to these approaches were further studied in detail. Therefore, food subgroups and their main representatives on macro- and/or micronutrient level (taking into account the amount of substances within the food group and possible underlying mechanisms related to HF risk) were examined. In order to increase the ability to differentiate between associations of highly correlated nutrients (as a natural consequence of their common origin) these analyses were conducted both source-specific and by total nutritional intakes.

2.2.2 Statistical Analyses

All statistical analyses were performed using the SAS software package, release 9.4 (SAS Institute, Cary, NC). A p value <.05 was considered statistical significant. For investigations of interactions, a p value of 0.1 was selected to take into account large variances and resulting lower statistical power in detecting interactions.[100]

Descriptives

Baseline characteristics of the study participants were compared across categories of tMED and across intakes of selected food groups using analysis of covariance. All characteristics except participants' age and sex were calculated adjusted for age and sex. Sex-specific categories (in most cases quintiles) of food groups (e.g. total meat), subgroups (e.g. poultry, red- and processed meat) and nutrients (e.g. SFAs) were generated to investigate its association to HF risk. Analyses of alcoholic beverages were performed separately for men and women using categories defined in accordance to standard portion sizes.[101] As beer consumption was much higher in men than in women,

five and four categories were generated, respectively (men: non-consumers, consumers of less than a quarter of a glass of beer (250ml), consumers of 250ml to less than 500ml, consumers of 500ml to less than one liter, consumers of more or equal to one liter; women: non-consumers, consumers of less than 125ml, consumers of 125ml to less than 250ml, consumers of at least 250ml). The intakes of wine did not differ much between men and women, therefore both were categorized equally (non-consumers, consumers of less than one glass per week (35.7ml), consumers of more than one glass per week and less than half a glass per day (125ml), consumers of more than half a glass and less than one glass per day (250ml), consumers of one or more glasses per day). The lowest category of consumers served as reference group as non-consumers may reflect a mixture of never drinkers and former drinkers who quit drinking as a result of a disease.

Spearman partial correlation coefficients (adjusted for age and sex) were calculated to describe the correlation between nutrients and food groups.

Selection of Covariates

In the present work, directed acyclic graphs (DAGs) were implemented to identify the minimal sufficient adjustment set of covariates to investigate the association between a Mediterranean-style dietary pattern and HF risk.[102] DAGs support the user's understanding in underlying relationships (causal and non-causal) and help to distinguish between confounders and mediators (see Figure 5). The DAG program (v0.21) was used to identify minimally sufficient adjustment sets to estimate the total effect of the Mediterranean diet on HF risk.

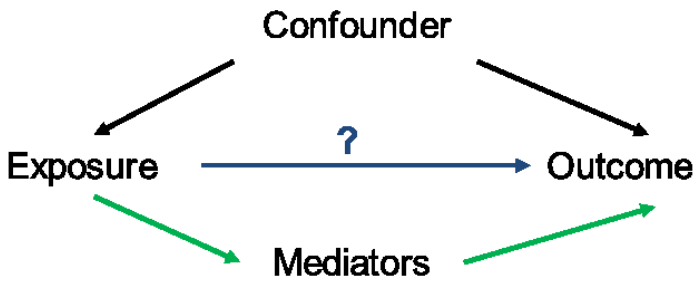

Figure 5: Graph of Exposure-Disease Associations

In green: causal pathway via mediator; black: non-causal pathway in which the confounder is influencing the relationship between exposure and outcome; blue and highlighted by question mark: the association of interest between exposure and outcome.

Two competing DAGs were generated (Figure 6 and Figure 7). Some factors, like age, sex and educational or occupational attainment are well known HF risk factors and also determinants of lifestyle habits, including diet;[103-109] e.g. in older age, health

consciousness rises and leads to greater compliance to health recommendations, including the adherence to the Mediterranean diet.[106, 108, 109] Diet in turn may be a direct cause of adiposity or comorbidities like diabetes, hypertension, and hyperlipidemia. If people do not change their dietary habits after diagnosis - probably depending on disease severity, duration from diagnosis to dietary assessment and the degree of health consciousness - associations will result in DAG 1 (Figure 6).

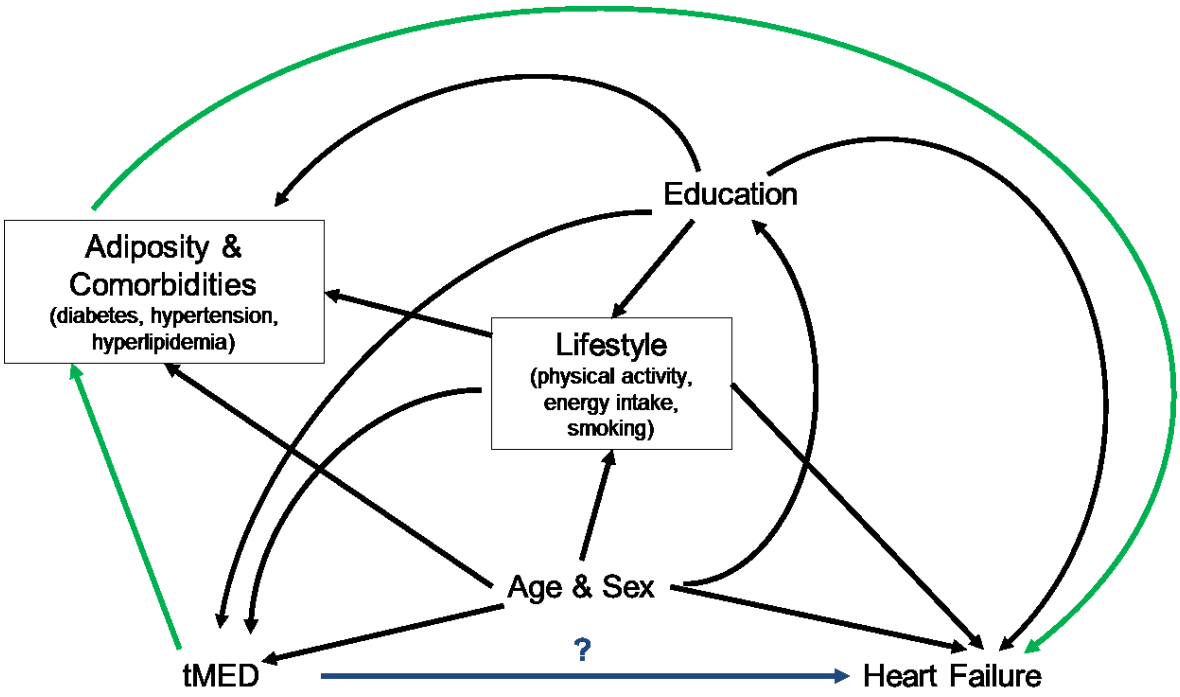

Figure 6: Directed Acyclic Graph (DAG 1) for the Association between the Mediterranean Diet and Heart Failure

Boxes include factors with similar associations to the remaining elements which were summarized for simplicity purposes. The minimal sufficient adjustment set of this DAG consists of lifestyle factors, education and age & sex. Green: the possible causal pathway from exposure to disease via mediator (comorbidities). Blue: the pathway that is to be examined
Abbreviations: tMED, traditional Mediterranean diet score

On the other hand, prevalent diseases often trigger lifestyle changes like smoking cessation, reduction of alcohol intake and dietary changes. In this case, the DAG will present like illustrated in Figure 7. Thus, it cannot be figured out with certainty, whether the mentioned prevalent diseases are confounding or mediating the association between diet and HF. Actually, it is assumed that the 'true' association between the adherence to the Mediterranean diet and the development of HF may be a mixture of both DAGs.

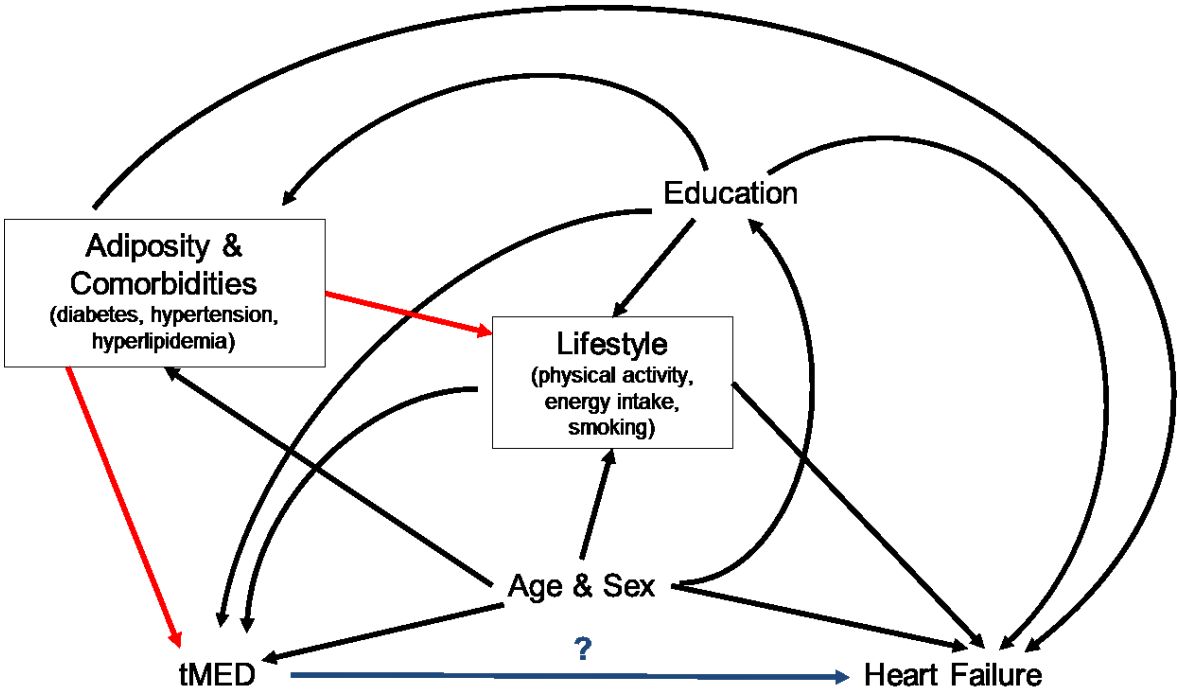

Figure 7: Directed Acyclic Graph (DAG 2) for the Association between the Mediterranean Diet and Heart Failure

Boxes include factors with similar associations to the remaining elements and which were summarized for simplicity purposes. The minimal sufficient adjustment set of this DAG consists of comorbidities, lifestyle factors, education and age & sex. Red: arrows whose direction cannot be determined unambiguously and which might run conversely (see **Figure 6**). Blue: the pathway that is to be examined
Abbreviations: tMED, traditional Mediterranean diet score

Accordingly, three statistical models were used, a basic model containing a minimum of covariates (model 1), a second model considering covariates from DAG 1 (model 2), and a third model which contains potential mediators resulting from DAG 2 (model 3):

Model 1: adjusted for sex and total energy intake (MJ/d), stratified for age

Model 2: Model 1 further adjusted for educational degree (no vocational training/vocational training (reference); technical college; university; used as indicator variables), physical activity (continuously in hours/week), smoking status (never smoker (reference); past smoker; smoker <20 cigarettes/day, smoker ≥20 cigarettes/day; used as indicator variables)

Model 3: Model 2 further adjusted for BMI and waist circumference (continuously), and prevalent diseases (diabetes mellitus, hypertension, hyperlipidemia (present/absent))

For analyses on individual food groups and nutrients covariates included all remaining score components in the model.

Risk Analysis

Cox proportional hazards regression was performed to determine the association between the adherence to the Mediterranean-style diet, the intakes of its components as well as the main representing nutrients and the risk of HF. Age was used as the underlying time variable in the counting process. Entry and exit time were defined as the participants' age at recruitment and age at time of HF diagnosis or censoring, respectively. One central assumption of Cox regression analyses is that the ratio of the hazards of exposed and non-exposed individuals remain constant over time. The proportional hazards assumption was checked with the Kolmogorov-type supremum test (based on a sample of 1,000 simulated residual patterns) and revealed no violation.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated according to categories of the Mediterranean diet score (0-2 points (reference), 3-4 points and ≥5 points) and per two units increase in the score. The presence of effect modification was explored by using cross product terms of tMED (per two units increase) and the most important risk factors for HF (age (<60 / ≥60 years), sex, current smoking (yes / no), obesity (BMI ≥ 30kg/m2) (yes / no), and prevalent diabetes, hypertension, and hyperlipidemia (yes / no)) in the final multivariable adjusted Cox regression model.

For selection of the 'relevant' score components, Cox regression analyses was performed using components on a dichotomous scale. HRs and 95% CIs of HF were calculated for persons who received one point for each of the individual components compared to the reference group (persons who did not receive a point for the respective score component). Furthermore, restricted cubic spline Cox regression analysis with three knots (5th, 50th (reference) and 95th percentile) was used to analyze the shapes of the association between the food group intakes (g/d) that are reflected by each score component and HF risk in the fully adjusted model. A third approach to select 'relevant' components was the 'subtraction method' introduced by Trichopoulou et al.[99] By using this method, HRs of HF per two unit increment in tMED were calculated for the overall score and the scores that were derived by subtracting alternately one of the components. To account for the different scaling (nine versus eight possible score points) the estimated logarithms of the HRs were multiplied by 9/10 before exponentiation. The percentage change in the estimate was calculated to assess the proportion to the overall association of each score component.[99]

HRs and 95% CIs of HF according to intakes of selected food groups/subgroups and nutrients were calculated per sex-specific categories of intakes (in most cases quintiles) using the first category as reference.

To calculate linear trends of HRs across categories (p_{trend}) ordinal variables for successive categories were used (coded 1-5). For intakes of alcoholic beverages, the p value for nonlinearity (p_{nonlin}) was obtained by the Wald chi-square test following restricted cubic spline Cox regression performed in statistical model 3.

Several sensitivity analyses were performed to deal with the remaining problems of confounding. First, as an alternative to the use of Greek medians, further cut-points were applied to classify participants in adhering or not adhering to the Mediterranean diet. Therefore, the population-specific third tertile of intake was used and, analyses were performed using the cut-off values proposed by Sofi and colleagues.[67]
Second, to cope with the problem of reverse causality, in a further analysis early HF cases (occurring within the first two years of follow-up) were excluded. These persons might have already changed lifestyle and diet as a result of first symptoms prior to recruitment. Additionally, for the same reason, persons were excluded who reported a dietary change during the year preceding the recruitment. Further, the issue of possible misclassification of cases was addressed by repeating analyses excluding both possible and probable HF cases.

Lastly, the analyses at nutrient level have, furthermore, been repeated adjusting for other nutrients to conform to most other investigations. Thus, in model 2 nutrients were mutually adjusted for intakes of total ethanol, total iron, total fiber, total cholesterol, total SFAs, and total animal protein in the overall analysis, and additionally included the respective nutrient of the other source in sub-analyses. For example intakes of cholesterol from meat were adjusted for intakes of total ethanol, total fiber, total SFAs, total animal protein, total iron and cholesterol from sources other than meat. In case of SFAs, analyses were additionally adjusted for MUFAs and PUFAs, and in case of animal protein for calcium intake. Regarding n3FAs, analyses were adjusted for total ethanol, total SFAs, total cholesterol, and total fiber intakes.

3. RESULTS

3.1 Characteristics of the Study Participants

3.1.1 Characteristics According to Heart Failure Status

After a mean follow-up period of 8.2 ± 1.6 years, 209 HF cases occurred. In Table 8, baseline characteristics of the study participants are shown regarding their disease status at follow-up. Incident HF cases were older, lower educated and more likely to be men, overweight, current smokers, and suffering from hypertension, diabetes and hyperlipidemia, than persons, who did not develop HF.

Table 8: General Baseline Characteristics of Study Participants (n=24,008) According to their Heart Failure Status at Follow-up

	Heart Failure	
Characteristics	No (n=23,799)	Yes (n=209)
n (cases)		
Gender, % female	61.8	37.8
Age, years	49.9 (8.8)	57.9 (6.8)
Body mass index, kg/m^2	26.2 (0.03)	27.4 (0.29)
Waist circumference, cm		
Men	94.5 (0.1)	97.3 (0.9)
Women	80.3 (0.1)	86.6 (1.2)
University Degree, %	40.1	34.0
Current smoking, %	21.5	34.4
Physical activity, hrs/wk	2.78 (0.02)	2.68 (0.23)
Total Energy Intake, MJ,d	9,072 (16)	8,986 (162)
Alcohol intake, g/d	15.6 (0.1)	12.5 (1.1)
Medical History, %		
Prevalent hypertension	46.3	60.6
Prevalent diabetes	4.4	15.8
Prevalent hyperlipidemia	27.2	34.8

Baseline characteristics are expressed as age- and sex-adjusted mean (standard error) or percentages, age and sex are unadjusted means (standard deviation) or percentages, respectively

More than half of the cases fulfilled the ESC criteria and were regarded as definite HF. In Table 9, clinical characteristics that were used for case classification are summarized.

Table 9: Clinical Characteristics of Heart Failure Cases in EPIC-Potsdam According to Definite, Probable and Possible Heart Failure

		DIAGNOSTIC CATEGORY		
	All cases	**Definite**	**Probable**	**Possible**
No. of events (%)	209	118 (57)	40 (19)	51 (24)
Symptoms n (%)	152 (73)	118 (100)	22 (55)	12 (24)
Pathological finding n (%)				
Echocardiogram	136 (65)	118 (100)	18 (45)	0 (0)
Cardiac catheterization	75 (36)	65 (55)	7 (18)	3 (6)
Chest x-ray	92 (44)	71 (60)	21 (53)	0 (0)
Electrocardiogram	101 (48)	80 (68)	20 (50)	1 (2)
NYHA classification n (%)				
I	29 (14)	13 (11)	10 (25)	6 (12)
II	53 (25)	41 (35)	10 (25)	2 (4)
III	25 (12)	22 (19)	3 (8)	0 (0)
IV	13 (6)	12 (10)	0 (0)	1 (2)
unknown	89 (43)	30 (25)	17 (43)	37 (73)
Function of HF n (%)				
Diastolic	15 (7)	10 (8)	5 (13)	0 (0)
Systolic	56 (27)	47 (40)	9 (23)	0 (0)
Both	32 (15)	24 (20)	5 (13)	3 (6)
Unknown	68 (33)	37 (31)	21 (53)	48 (94)

For NYHA classification see Table 2
Abbreviations: HF, heart failure; NYHA, New York Heart Association

Beside the necessary information (presence of symptoms and objective evidence from echocardiogram), for most definite cases information on at least one other diagnostic tool was present. Most cases where information was available were classified as NYHA II (25%). Furthermore, more systolic (27%) than diastolic (7%) HF was diagnosed. However, Information about severity and function of the disease were available more often for definite compared to probable and possible cases. Possible ones, however, were mainly fatal events (41 of 51 cases) that have been ascertained from death certificates. Therefore, information on NYHA classification and diagnostic procedures were frequently missing.

3.1.2 Baseline Characteristics According to the Mediterranean Diet

Using the median intake values of the Greek population resulted in a tMED score ranging from 0 to 7 (of 9 possible points), and an average score of 3.5 points in EPIC-Potsdam. The distribution of the scoring is illustrated in Figure 8.

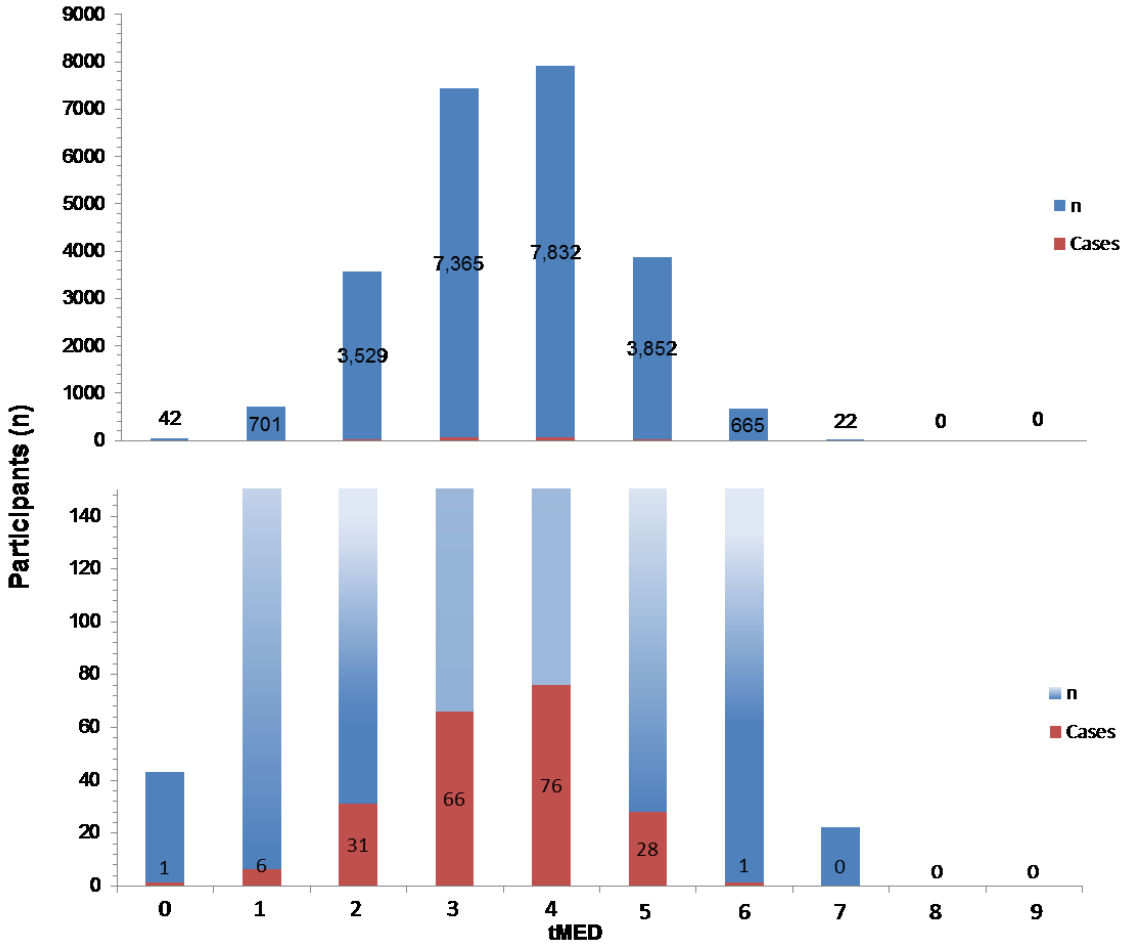

Figure 8: Panel Chart of the Scoring Distribution among Participants who did and did not Develop Incident Heart Failure during Follow-up

The upper panel shows the entire graph, while the bottom panel depicts a section of low values for better illustration.
Abbreviation: tMED, traditional Mediterranean diet score

Distribution of Nutritional Parameters

In Table 10, the consumptions of seven tMED components and the food groups to which each of them belong are listed. The components comprise one to five food groups, as summarized previously.[93]

The intakes of the components *fruits and nuts*, *vegetables*, and *milk and milk products* were in general higher in women, while *cereals*, *meat and meat products*, *fish* and *legumes* were consumed in greater amounts by men. This is partly different regarding the individual subgroups. For example, within the cereals component male intakes were higher only for *other bread*, while the remaining food groups were consumed in similar amounts in both sexes. The same was observed for *milk and milk products*, where a higher intake in women is only seen for *low-fat dairy products*.

Table 10: Daily Consumption of Components of the Traditional Mediterranean Diet Score and its Food Groups and Subgroups among Men and Women (n=24,008)

tMED component Food group	Men (n=9,225)				Women (n=14,783)			
	Non-consumers	Consumers			Non-consumers	Consumers		
	n (%)	Mean (SD)	Median [IQR]	1st p / 99th p	n (%)	Mean (SD)	Median [IQR]	1st p / 99th p
Fruits and nuts	**0 (0.00)**	**125.2(89.2)**	**97.0 [69.1-169.4]**	**13.3 / 446.0**	**3 (0.02)**	**156.4 (97.2)**	**133.9 [91.1-198.5]**	**22.7/ 473.4**
Fresh fruits	3 (0.03)	121.6 (88.6)	94.2 [66.6-163.3]	12.5 / 442.5	5 (0.03)	153.6 (96.6)	131.0 [89.5-195.6]	20.8/ 469.3
Nuts	1,241 (13.5)	4.3 (8.6)	0.8 [0.4-4.1]	0.4 / 35.6	2,129 (14.4)	3.3 (7.2)	0.8 [0.4-4.1]	0.4 / 35.6
Vegetables	**1 (0.01)**	**90.0 (49.5)**	**81.3 [57.0-111.1]**	**17.5 / 256.8**	**0 (0.0)**	**107.8 (56.3)**	**96.9 [71.9-132.0]**	**24.2 / 305.5**
Raw vegetables	9 (0.1)	47.6 (39.1)	37.9 [23.2-64.1]	4.2 / 200.6	8 (0.1)	61.7 (46.8)	52.0 [32.5-71.7]	6.6 / 231.8
Cooked vegetables	3 (0.03)	27.2 (17.1)	23.6 [15.8-35.1]	3.4 / 78.3	2 (0.01)	29.9 (18.4)	26.1 [17.6-37.9]	4.8 / 89.0
Mushrooms	410 (4.4)	2.0 (2.4)	1.2 [0.6-2.5]	0.1 / 11.1	667 (4.5)	2.1 (2.4)	1.3 [0.7-2.8]	0.1 / 10.9
Cabbage	33 (0.4)	13.4 (13.4)	9.4 [4.8-17.1]	0.5 / 64.2	27 (0.2)	14.2 (14.2)	10.4 [5.6-18.1]	0.6 / 65.9
Garlic	4,861 (52.7)	0.24 (0.48)	0.08 [0.02-0.28]	0.02 / 2.14	7,355 (49.8)	0.28 (0.65)	0.14 [0.03-0.28]	0.02 / 2.14
Cereals	**—**	**232.3 (86.4)**	**223.2 [173.3-283.9]**	**63.9 / 480.0**	**—**	**178.6 (65.0)**	**173.2 [131.6-217.2]**	**54.6 / 358.1**
Whole-grain bread	1,397 (15.1)	48.0 (59.0)	24.2 [8.4-65.0]	0.6 / 269.2	948 (6.4)	51.5 (52.8)	34.2 [12.2-75.3]	0.7 / 233.2
Other bread	49 (0.5)	169.8 (86.7)	163.3 [106.7-220.7]	8.7 / 412.2	149 (1.0)	107.6 (62.8)	99.1 [62.0-146.4]	3.6 / 281.2
Grain flakes	6,189 (67.1)	14.3 (23.6)	4.1 [0.8-17.8]	0.4 / 100.0	7,378 (49.9)	11.9 (18.7)	4.1 [0.8-17.8]	0.4 / 100.0
Cornflakes	6,661 (72.2)	5.0 (9.2)	1.6 [0.7-5.7]	0.3 / 40.0	8,801 (59.5)	4.8 (8.4)	1.6 [0.7-5.7]	0.3 / 40.0
Pasta and rice	229 (2.5)	17.1 (15.1)	13.5 [6.3-22.8]	0.7 / 73.9	120 (0.8)	16.2 (14.5)	12.5 [6.6-21.3]	0.8 / 70.1
Meat and meat products	**19 (0.2)**	**147.6 (71.5)**	**136.2 [98.3-183.5]**	**28.5 / 373.4**	**70 (0.5)**	**94.2 (48.3)**	**87.3 [61.5-118.2]**	**13.2 / 244.9**
Red meat	37 (0.4)	54.2 (34.3)	47.1 [31.6-69.8]	6.1 / 168.4	127 (0.9)	34.7 (22.6)	30.7 [19.5-44.7]	2.6 / 112.9
Processed meat	41 (0.4)	78.9 (51.3)	65.7[44.7-101.1]	8.2 / 250.4	139 (0.9)	48.4 (33.1)	43.3 [25.8-59.7]	3.7 / 161.9
Poultry	210 (2.3)	15.0 (13.7)	11.0 [5.5-20.2]	1.0 / 65.6	252 (1.7)	11.6 (11.1)	8.3 [4.2-15.4]	0.8 / 52.3
Fish	**223 (2.4)**	**28.4 (28.8)**	**23.0 [11.5-33.9]**	**1.6 / 135.3**	**333 (2.3)**	**21.4 (21.3)**	**16.4 [9.9-28.5]**	**1.6 / 99.7**
Canned fish	572 (6.2)	14.7 (23.0)	8.2 [4.1-14.2]	0.8 / 100.0	1,193 (8.1)	9.6 (15.9)	8.2 [1.6-14.2]	0.8 / 71.2
Baked, fried fish	369 (4.0)	14.5 (13.3)	14.8 [3.0-20.5]	1.6 / 64.1	502 (3.4)	12.5 (11.4)	8.2 [3.0-14.8]	1.6 / 64.1
Milk and milk products	**10 (0.1)**	**213.8 (218.2)**	**153.2 [81.3-265.1]**	**12.3 / 1,066**	**13 (0.1)**	**241.0 (211.5)**	**190.1 [108.7-304.0]**	**19.9 / 1,037**
High-fat dairy products	359 (3.9)	101.9 (164.4)	51.6 [12.8-128.7]	0.1/ 753.0	519 (3.5)	104.5 (146.9)	57.3 [12.8-150.3]	0.1 / 665.8
Low-fat dairy products	3,484 (37.8)	126.2(193.8)	53.4[12.3-158.2]	1.2 / 912.3	3,647 (24.7)	141.8 (197.8)	74.8 [21.4-176.7]	1.2 / 907.0
High-fat cheese	515 (5.6)	33.3 (27.6)	30.7 [13.2-39.2]	0.4 / 122.5	952 (6.4)	28.5 (23.2)	26.2 [11.6-36.9]	0.2 / 107.5
Low-fat cheese	6,687 (72.5)	20.4 (22.6)	12.5 [4.8-28.9]	0.3 / 99.4	9,374 (63.4)	18.0 (17.9)	12.5 [5.0-26.5]	0.3 / 78.2
Legumes	**22 (0.2)**	**28.9 (23.2)**	**23.3 [11.6-40.0]**	**2.1 / 106.2**	**62 (0.4)**	**19.3 (15.7)**	**14.6 [8.1-27.0]**	**1.1 / 72.2**

Daily consumption is expressed in grams per day;
Abbreviations: IQR, interquartile range; p, percentile; SD, standard deviation; tMED, traditional Mediterranean diet score

As shown in Table 10, the proportion of non-consumers is very low at the individual components, but for some food groups (*garlic*, *grain flakes*, *cornflakes* and *low-fat cheese*) it exceeds 50%, particularly in men. Additionally, the intakes of some food groups were very low (median ≤10 g/day), such as *nuts*, *mushrooms*, *cabbage*, *garlic*, *grain flakes*, *cornflakes* and *poultry* (women).

In Table 11 the contents and sources of the two remaining macronutrient components of the tMED (alcohol and fat-ratio) are shown. Among consumers, the main source of fat (disregarding indirect sources such as meat) is margarine, while the intakes of vegetable and other fats (including olive oil) are negligible. Regarding alcoholic beverages, beer is consumed in higher amounts by men when compared to women, while the consumption of wine is more common in women than beer but is in a comparable range for both sexes. Both beer and wine represent the main source of daily ethanol intake (~80%).

Table 11: Daily Consumption of Components of the Traditional Mediterranean Diet Score and its Subgroups and Main Sources among Men and Women (n=24,008)

tMED component Source	Men (n=9,225) Non-consumers n (%)	Consumers Mean (SD)	Consumers Median [IQR]	Consumers 1st p / 99th p	Women (n=14,783) Non-consumers n (%)	Consumers Mean (SD)	Consumers Median [IQR]	Consumers 1st p / 99th p
Fat-ratio	—	**0.87 (0.11)**	**0.86 [0.79-0.94]**	**0.65 / 1.17**	—	**0.84 (0.11)**	**0.84 [0.77-0.90]**	**0.63 / 1.15**
Monounsaturated fat	—	33.3 (11.5)	31.4 [25.1-39.3]	14.0 / 68.9	—	25.5 (8.7)	24.2 [19.3-30.2]	10.8 / 51.8
Polyunsaturated fat	—	16.6 (6.3)	15.5 [12.2-19.8]	6.6 / 37.3	—	13.3 (5.0)	12.4 [9.7-15.9]	5.2 / 28.8
Saturated fat	—	38.9 (14.3)	36.6 [28.6-46.6]	15.5 / 84.1	—	30.8 (11.4)	29.1 [22.6-36.9]	12.1 / 65.6
Butter	1,418 (15.4)	12.4 (15.0)	6.1 [1.4-20.0]	0.1 / 70.2	1,904 (12.9)	9.0 (11.3)	4.3 [1.2-11.5]	0.1 / 52.5
Margarine	990 (10.7)	20.2 (16.7)	20.0 [7.1-30.3]	0.2 / 72.3	1,555 (10.5)	15.8 (13.3)	11.3 [5.3-20.9]	0.2 / 56.4
Vegetable fat	709 (7.7)	3.26 (3.04)	2.51 [1.25-4.33]	0.08 / 14.46	768 (5.2)	3.83 (3.44)	2.99 [1.56-4.99]	0.14 / 16.69
Other fat	7,037 (76.3)	1.45 (1.17)	1.17 [0.55-2.08]	0.04 / 5.20	11,931 (80.7)	1.18 (0.90)	0.98 [0.54-1.58]	0.05 / 4.14
Ethanol	**286 (3.1)**	**23.3 (21.7)**	**18.3 [8.3-31.7]**	**0.4 / 91.9**	**387 (2.6)**	**8.6 (10.6)**	**5.3 [2.1-10.5]**	**0.2 / 50.2**
Beer	686 (7.4)	422 (478)	356 [82-500]	4.1 / 2,000	5,801 (39.2)	77.6 (153.8)	20.5 [8.2-71.2]	4.1 / 712.3
Wine	1,551 (16.8)	60.4 (107.4)	20.5 [8.2-71.2]	2.1 / 500	1,244 (8.4)	57.9 (88.2)	35.6 [8.2-71.2]	2.1 /500
Spirits	1,810 (19.6)	6.3 (14.0)	2.8 [0.7-5.7]	0.2 / 60	7.123 (48.2)	2.1 (5.1)	0.3 [0.3-1.6]	0.1 /21.4
Other	1,383 (15.0)	13.0 (20.7)	6.6 [2.5-16.4]	0.8 / 95.9	916 (6.2)	15.1 (24.7)	8.2 [3.3-17.3]	0.8 / 106.8

Daily consumption is expressed in grams per day, except for the fat-ratio which has no measurement unit;
Abbreviations: IQR, interquartile range; p, percentile; SD, standard deviation; tMED, traditional Mediterranean diet score

Table 12 depicts the distribution of each score component according to categories of adherence to the Mediterranean-style diet.

Table 12: Daily Intake of Score Components across the Traditional Mediterranean Diet Score using Greek Cut-points

	tMED		
CHARACTERISTICS	0-2	3-4	≥ 5
n (cases)	4,272 (38)	15,197 (142)	4,539 (29)
Total energy intake, MJ/d	8,990 (36)	9,108 (19)	9,023 (35)
Scored Components			
Alcohol intake, g/d#	13.2 (0.2)	15.6 (0.1)	17.4 (0.2)
Moderate*, %	14.9	48.4	86.6
Fruits and nuts intake, g/d#	127 (1.4)	139 (0.8)	160 (1.4)
≥ Greek Median, %	0.6	2.7	9.2
Vegetable intake, g/d#	92.8 (0.8)	98.9 (0.4)	104.4 (0.8)
≥ Greek Median, %	0.0	0.1	0.2
Cereals intake, g/d#	178 (1.1)	208 (0.6)	223 (1.1)
≥ Greek Median, %	43.2	73.5	92.6
Fish intake, g/d#	15.6 (0.4)	23.7 (0.2)	34.2 (0.4)
≥ Greek Median, %	12.9	40.7	78.5
Legumes intake, g/d#	18.4 (0.3)	24.5 (0.2)	27.0 (0.3)
≥ Greek Median, %	56.2	84.4	96.4
Fat-ratio#	0.84 (0.0)	0.86 (0.0)	0.87 (0.0)
≥ Greek Median, %	0.0	0.0	0.1
Meat intake, g/d#	131.0 (0.9)	122.7 (0.5)	104.7 (0.9)
< Greek Median, %	29.7	46.6	70.1
Milk products intake, g/d#	316 (3.2)	223 (1.7)	160 (3.1)
< Greek Median, %	24.3	55.2	82.0

intakes are expressed as age- and sex-adjusted mean (standard error) or percentages; Greek medians are used for score building: fruits: men= 362.5 g, women= 356.3 g; vegetables: men= 549.9 g, women= 499.6 g; cereals: men= 177.7 g, women= 139.7 g; legumes: men= 9.1 g, women= 6.7 g; fish: men= 23.7 g, women= 18.8 g; ratio of monounsaturated to saturated fat: men= 1.72, women= 1.74; meat products: men= 120.8, women= 89.8; milk products: men= 196.7, women= 191.1.
* low: men <10g/d, women <5 g/d; moderate: men ≥10 g/d – 50 g/d, women ≥ 5g/d – 25 g/d; high: men >50 g/d, women > 25 g/d
Abbreviation: tMED, traditional Mediterranean diet score

The contribution to the overall score differs for individual food groups. The components *fat-ratio*, *vegetables* and *fruits and nuts* counted towards zero to the overall score because very few persons consumed amounts higher than the Greek medians (*fat-ratio*: men=0.01%, women=0.03%; *vegetables*: men=0.04%, women=0.1% and *fruits and nuts*: men=2.5%, women=4.3%). On the other hand many persons received points for components like *legumes*, *milk and milk products* and *cereals* even in the lowest category of adherence (persons who received a point for *legumes*: men=83%, women=81%, *cereals*: men=73%, women=71% and *milk products*: men=61%, women=50%). Nevertheless, age- and sex-adjusted mean intakes of *fruits and nuts*, *vegetables* and the

fat-ratio showed slightly higher mean intakes in the highest adherence group compared to the lowest. This was also true for *meat and meat products* (overall 41% of men and 53% of women received a point), which is in contrast to the first analyses that used median intakes of EPIC-Potsdam study participants (see Appendix VIII). The number of persons achieving one point was moderate regarding high fish intakes (men=43%, women=44%) and moderate alcohol consumption (men=57%, women=44%).

Demographics, Lifestyle, and Health status

The distribution of non-dietary parameters according to categories of adherence to the Mediterranean-style diet is shown in Table 13. Persons with scorings equal to or above five points were more likely to be male, non-smokers and had a higher educational attainment. Regarding prevalent diseases, the proportion of diabetics was slightly lower in the highest adherence group, while hypertension and hyperlipidemia were equally distributed across the categories.

Table 13: Baseline Characteristics of Study Participants (n= 24,008) According to Achieved Points in the Traditional Mediterranean Diet Score

	tMED		
Characteristics	0-2	3-4	5-7
n (cases)	4,272 (38)	15,197 (142)	4,539 (29)
Gender, % female	66.6	61.2	57.0
Age, mean, years	49.5 (8.8)	50.0 (8.8)	50.3 (8.8)
Body mass index, kg/m^2	26.3 (0.1)	26.3 (0.0)	26.0 (0.1)
Waist circumference, cm			
Men	94.8 (0.3)	94.6 (0.1)	94.1 (0.2)
Women	80.5 (0.2)	80.5 (0.1)	79.8 (0.2)
University Degree, %	34.7	40.0	45.1
Current smoking, %	24.3	21.3	20.2
Physical activity, hours/week	2.52 (0.1)	2.79 (0.0)	2.98 (0.1)
Medical History, %			
Prevalent hypertension	45.5	46.8	45.9
Prevalent diabetes	5.8	4.5	3.4
Prevalent hyperlipidemia	27.5	27.4	26.5

Baseline characteristics are expressed as age- and sex-adjusted mean (standard error) or percentages, age and sex are unadjusted means (standard deviation) or percentages, respectively.
Abbreviation: tMED, traditional Mediterranean diet score

3.2 The Mediterranean Diet, its Components and the Risk of Heart Failure

3.2.1 Dietary Pattern Analysis

Association between the Mediterranean Diet and Heart Failure Risk

Table 14 shows prospective associations between the adherence to the Mediterranean-style diet and the risk of developing HF. Persons who were assigned a tMED score of 5 or more points had an about 40% decreased risk to develop HF compared to participants with zero to two points. However, this association was attenuated after adjustment for smoking, education and physical activity. Adjustment for potential mediators (model 3) further weakened the diet-disease relationship.

Table 14: Association between the Adherence to the Mediterranean Diet and the Risk of Heart Failure

	tMED				
	0-2	**3-4**	**5-7**		**per 2 units**
n (cases)	4,272 (38)	15,197 (142)	4,539 (29)		
Person-years	35,310	125,266	37,458		
	HR	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**	**HR (95%CI)**
Model 1	1	0.95 (0.67-1.37)	0.59 (0.36-0.96)	0.03	0.76 (0.60-0.97)
Model 2	1	0.99 (0.69-1.41)	0.63 (0.39-1.02)	0.06	0.80 (0.62-1.02)
Model 3	1	1.00 (0.70-1.43)	0.66 (0.41-1.08)	0.10	0.82 (0.64-1.05)

Model 1: adjusted for sex and energy intake, stratified for age; Model 2: further adjusted for lifestyle (smoking, education, physical activity); Model 3: further adjusted for anthropometry (BMI and waist circumference) and prevalent comorbidities (diabetes, hypertension and hyperlipidemia)
Abbreviations: CI, confidence interval; HR, hazard ratio; tMED, traditional Mediterranean diet score

Analyses performed using the third tertile of the study-specific intakes or using cut-points suggested by Sofi et al.[67] (Appendix XI) to define adherence to the Mediterranean diet did not show a diet-disease association.

Sensitivity analyses that took into account the problem of reverse causality (exclusion of either cases that occurred within the first two years of follow-up, or persons that reported a dietary change during the year preceding recruitment) yielded minor attenuations of the association but did not change the results substantially (data not shown). The exclusion of probable and possible cases, however, attenuated the association (HRs and 95% CIS across categories: 1 (reference), 1.04 (0.64-1.71), 0.78 (0.42-1.47), p_{trend}=0.43). No significant interaction was observed between tMED scoring and various risk factors (all p values >0.3)

Selection of Relevant Components for Further Analysis

To choose potentially relevant score components, three approaches were conducted: First, for each single component HRs and 95% CIs of HF were calculated for persons who received a point compared to those who did not. Results are outlined in Table 15. This analysis led to significant inverse associations with HF risk only by moderate alcohol consumption and low meat intake after multivariable adjustment.

Table 15: Association between the Adherence to Individual Traditional Mediterranean Diet Score Components and the Risk of Heart Failure

	Model 1		Model 2	
	<Median intake	≥Median intake	<Median intake	≥Median intake
Score component	**HR**	**HR (95%CI)**	**HR**	**HR (95%CI)**
Alcohol*	1	0.67 (0.51-0.89)	1	0.73 (0.55-0.97)
Fish	1	0.88 (0.67-1.17)	1	0.86 (0.65-1.14)
Vegetables#	1	n.e.	1	n.e.
Fruits and nuts	1	0.86 (0.38-1.96)	1	0.97 (0.43-2.21)
Cereals	1	0.96 (0.70-1.31)	1	0.99 (0.73-1.36)
Legumes	1	1.18 (0.80-1.75)	1	1.09 (0.73-1.62)
Fat-ratio#	1	n.e.	1	n.e.
Milk products	1.23 (0.92-1.65)	1	1.18 (0.88-1.58)	1
Meat products	0.64 (0.47-0.86)	1	0.72 (0.54-0.98)	1

Model 1: Adjusted for sex and total energy intake, stratified by age; Model 2: Further adjusted for education, smoking, physical activity, BMI, waist circumference, comorbidities (diabetes, hyperlipidemia, hypertension) and all other tMED components;
* in case of alcohol consumption, moderate consumption (women: 5-25g/d, men=10-50g/d) was compared to non-moderate consumption (including low and high intakes)
# the number of participants who received a point was too low to calculate risk estimates
Abbreviation: BMI, body mass index; CI, conficence interval; HR, hazard ratio; n.e., not evaluable

A second approach was the performance of restricted cubic spline Cox regression analysis for intakes of all score components on a continuous scale to investigate the shape of the association to HF risk. This analysis identified two relevant components: fish and ethanol intake, both showing significant inverse linear associations with HF risk (Figure 9). On the other hand, meat intake was positively associated with HF risk. However, this association lost statistical significance after adjustment for comorbidities (model 3). Graphs of all remaining score components are provided in Appendix XIV.

The third method to derive potentially relevant food groups of the tMED, the subtraction method according to Trichopoulou et al.,[99] resulted in minor changes of the overall risk estimate. The exclusion of e.g. *ethanol*, *meat and meat products*, *fish* shifted the estimates towards the 1, therefore these food groups contributed to the overall inverse tendency between the adherence to the Mediterranean-style diet and the risk of HF. Conversely, factors that shifted the estimates away from the 1 might be not or positively related to HF risk (e.g. *legumes* and *milk and milk products*).

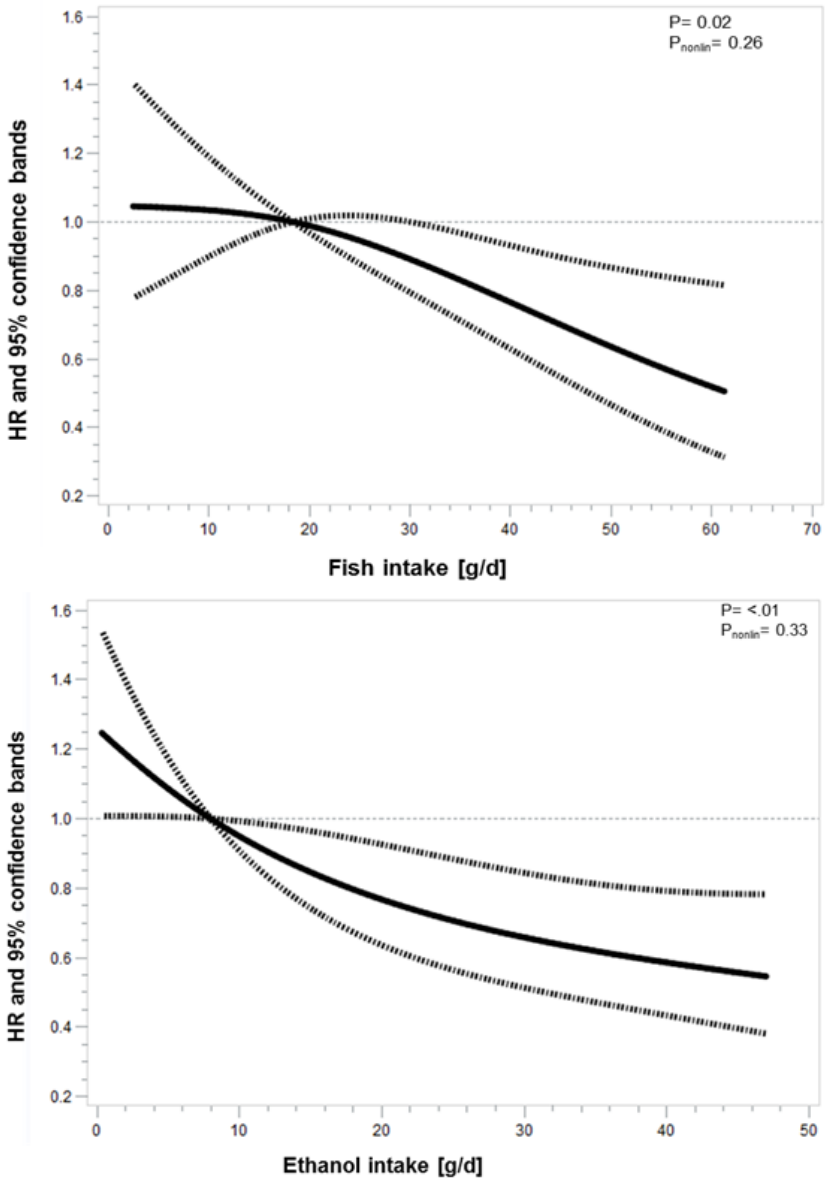

Figure 9: Graphs of Fish Consumption and Ethanol Intake and Heart Failure Risk Derived by Restricted Cubic Spline Cox Regression Analysis

Restricted cubic spline regression analysis was performed using knots at the 5th, 50th (reference) and 95th percentile. Hazard ratios and 95% confidence bands (dotted lines) are stratified by age and adjusted for sex, total energy intake, education, smoking, physical activity, BMI, waist circumference, prevalent comorbidities (diabetes, hypertension, hyperlipidemia) and all remaining tMED score components (continuously). P for nonlinearity was computed by Wald chi-square test.

Abbreviations: BMI, body mass index; HR, hazard ratio; tMED, traditional Mediterranean diet

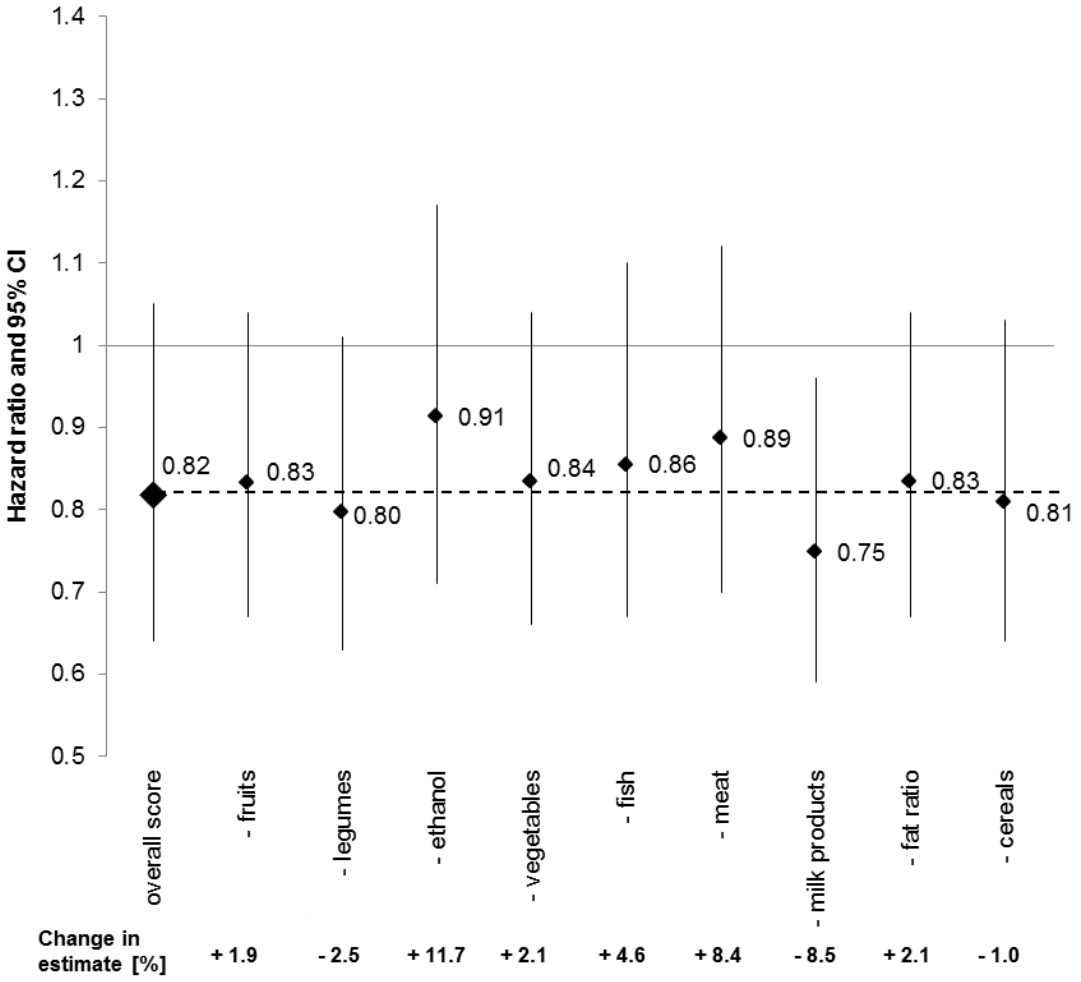

Figure 10: Hazard Ratios and 95% Confidence Intervals for a Two Unit Increment in Mediterranean Diet Score (tMED) and after Subtracting each of its Components

Hazard ratios and 95% confidence intervals are stratified by age and adjusted for sex, total energy intake, education, smoking, physical activity, body mass index, waist circumference, prevalent comorbidities (diabetes, hypertension, hyperlipidemia) and corresponding subtracted component (dichotomous).
The estimated logarithms of the hazard ratios were multiplied by 9/10 before exponentiation to correct for the nine point scale of the overall score[99]

The contributions of the individual tMED components to the overall association were highest for moderate ethanol intake (11.7 %), low meat intake (8.4 %) and high fish intake (4.6 %) as depicted in Figure 10. Noteworthy, the exclusion of milk products led to a lower HF risk which was statistically significant even in the multivariable adjusted model.

Based on the results of these different approaches, three components of the tMED were considered relevant for HF development and selected for further analyses at the level of food groups, subgroups and nutrients: *meat and meat products*, *fish*, and moderate *ethanol intake*.

3.2.2 Analysis of Food Groups and Subgroups

To follow the *top-down* approach, the associations between *fish*, *meat and meat products* and *ethanol*, and the risk of HF were further analyzed. In terms of *meat and meat products*, total meat intake was investigated as well as its subgroups *poultry*, *red meat* and *processed meat*. For *fish*, the subgroups *canned fish* and *baked, cooked and fried fish* were examined in addition to total fish intake. As *ethanol* was already studied on the level of nutrients, the two major contributors to total ethanol intake have been investigated, namely beer and wine.

Meat and Meat Products

In general, women had lower meat intakes than men and persons in higher quintiles of meat consumption were younger than in the lower ones. After adjustment for age and sex, participants with higher meat intake had generally poorer health conditions: they were more likely to be overweight, smokers, less physically active and less educated. Besides, prevalent diabetes and hypertension were more frequently present (data not shown). With approximately 50%, the food group *processed meat* contributes most to total meat consumption. Poultry was consumed in lower amounts in the study population (Table 16).

Table 16: Age- and Sex-adjusted Intakes of Selected Food Groups and Nutrients according to Quintiles of Total Meat Consumption

	Quintiles of Total Meat Intake				
Total Meat Intake*	1	2	3	4	5
Men [g/d] Women [g/d]	65.7 (19.9) 37.1 (14.0)	105.5 (8.6) 66.4 (6.1)	136.1 (9.3) 86.9 (5.9)	172.6 (12.9) 110.8 (8.8)	256.4 (62.9) 167.4 (41.9)
n (cases)	4801 (27)	4803 (49)	4802 (41)	4800 (42)	4802 (50)
Poultry*	6.3 (6.0)	9.4 (7.8)	12.0 (9.3)	14.5 (11.4)	21.1 (17.8)
Red meat*	18.3 (12.0)	31.0 (14.7)	39.4 (17.7)	49.7 (23.4)	71.2 (38.7)
Processed meat*	23.5 (14.9)	41.0 (17.6)	54.4 (22.4)	70.3 (29.5)	109.4 (58.5)
Total energy, [MJ/d]	7831 (31)	8382 (31)	8852 (31)	9564 (31)	10711 (31)
Intake of tMED Components					
Alcohol intake	13.5 (0.2)	14.8 (0.2)	15.4 (0.2)	16.6 (0.2)	17.3 (0.2)
Fruits and nuts intake	146.7 (1.4)	138.7 (1.4)	137.9 (1.4)	137.0 (1.4)	142.7 (1.4)
Vegetable intake	95.4 (0.8)	93.7 (0.8)	96.0 (0.8)	99.7 (0.8)	109.5 (0.8)
Cereals intake	194 (1.1)	198 (1.1)	202 (1.1)	210 (1.1)	224 (1.1)
Fish intake	22.4 (0.4)	22.6 (0.4)	23.5 (0.4)	25.2 (0.4)	27.7 (0.4)
Legumes intake	19.7 (0.3)	21.8 (0.3)	23.7 (0.3)	25.8 (0.3)	28.8 (0.3)
Fat-ratio	0.82 (0.00)	0.84 (0.00)	0.85 (0.00)	0.87 (0.00)	0.89 (0.00)
Milk products intake	254 (3.1)	230 (3.1)	218 (3.1)	219 (3.1)	215 (3.1)

Intakes are expressed as age- and sex-adjusted means (standard error) and shown in grams per day (or as otherwise indicated). The fat-ratio is the ratio between monounsaturated and saturated fat and has no unit.
* Meat subgroups are presented as unadjusted means (standard deviation)
Abbreviations: tMED, traditional Mediterranean diet score

As outlined in Table 16, total energy intake and the intakes of most other score components were positively associated with total meat intake. One exception was the group *milk and milk products* that showed lower intakes with higher intakes of meat.

In Table 17, associations between intakes of total meat and meat subgroups and the risk of HF are shown. Total meat intake was positively associated with HF risk after multivariable adjustment.

Table 17: Associations between the Consumption of Total Meat and Different Meat sources and the Risk of Heart Failure

	Quintiles of Meat Intake			
Total Meat	**1**	**3**	**5**	
Men [g/d]	65.7 (19.9)	136.1 (9.3)	256.4 (62.9)	
Women [g/d]	37.1 (14.0)	86.9 (5.9)	167.4 (41.9)	
Person-years	39,754	39,693	39,510	
n (cases)	4801 (27)	4802 (41)	4802 (50)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.67 (1.02-2.72)	3.04 (1.83-5.07)	<.01
Model 2	1	1.60 (0.97-2.63)	2.50 (1.44-4.33)	<.01
Model 3	1	1.40 (0.85-2.31)	2.04 (1.17-3.55)	0.01
Poultry	**1**	**3**	**5**	
Men [g/d]	2.5 (1.3)	10.8 (1.6)	36.2 (15.0)	
Women [g/d]	2.0 (1.0)	8.2 (1.2)	28.4 (13.1)	
n (cases)	4,825 (40)	4,803 (39)	4,794 (42)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.02 (0.66-1.59)	1.16 (0.75-1.79)	0.69
Model 2*	1	1.01 (0.65-1.58)	1.10 (0.69-1.75)	0.80
Model 3*	1	1.03 (0.66-1.61)	1.07 (0.67-1.71)	0.93
Red Meat	**1**	**3**	**5**	
Men [g/d]	17.6 (7.2)	46.9 (4.1)	107.4 (32.6)	
Women [g/d]	9.5 (3.9)	30.3 (2.8)	69.5 (21.2)	
n (cases)	4,801 (35)	4,801 (46)	4,802 (48)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.35 (0.87-2.10)	1.54 (0.99-2.42)	<.01
Model 2*	1	1.20 (0.77-1.89)	1.15 (0.71-1.86)	0.18
Model 3*	1	1.14 (0.73-1.78)	1.01 (0.62-1.64)	0.42
Processed Meat	**1**	**3**	**5**	
Men [g/d]	26.6 (10.7)	66.3 (6.9)	157.7 (52.1)	
Women [g/d]	13.3 (6.3)	42.9 (3.2)	98.5 (35.3)	
n (cases)	4,801 (37)	4,801 (42)	4,802 (49)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.24 (0.79-1.93)	2.12 (1.33-3.37)	<.01
Model 2*	1	1.14 (0.72-1.81)	1.82 (1.09-3.03)	<.05
Model 3*	1	1.05 (0.67-1.66)	1.56 (0.93-2.61)	0.16

Model 1: stratified by age, adjusted for sex and energy intake; Model 2: further adjusted for education, smoking, physical activity and all remaining score components (continuously) like listed in Table 16; Model 3: further adjusted for anthropometry (BMI and waist circumference) and prevalent comorbidities (diabetes, hypertension and hyperlipidemia); * the adjustment set includes each of the other two meat subgroups (continuously); for simplicity reasons only quintiles 1, 3 and 5 are shown. **Abbreviations**: HR, hazard ratio; CI, confidence interval

Analyses based on different meat sources showed significant positive associations only for the food groups *red meat* and *processed meat*. However, after adjusting for lifestyle factors and the prevalence of comorbidities the associations were no longer significant for both *red meat* and *processed meat*.

To better account for the higher consumption of processed meat, a sensitivity analysis was performed with standardized portion sizes for all meat subgroups (Table 18). Although not significant, in this analysis higher risk estimates were observed per each 50g of poultry consumption. Nevertheless, the results of total and processed meat consumption were similar and statistically significant in models 1 and 2, whereas the association between red meat consumption and HF risk was only present in the basic adjustment model.

Table 18: Hazard Ratios per Portion Sizes of Different Meat Sources

	MODEL 1 HR (95% CI)	MODEL 2 HR (95% CI)	MODEL 3 HR (95% CI)
Total meat (per 50g)	1.25 (1.12-1.40)	1.16 (1.02-1.32)	1.09 (0.95-1.24)
Poultry (per 50g)	1.48 (0.92-2.37)	1.40 (0.85-2.32)#	1.27 (0.78-2.08)#
Red meat (per 50g)	1.31 (1.06-1.63)	1.07 (0.85-1.36)#	1.00 (0.79-1.27)#
Processed meat (per 50g)	1.26 (1.09-1.46)	1.18 (1.00-1.39)#	1.12 (0.94-1.32)#

Model 1: stratified by age, adjusted for sex and energy intake; Model 2: further adjusted for education, smoking, physical activity and all remaining score components (continuously) like listed in Table 16; Model 3: further adjusted for anthropometry (BMI and waist circumference) and prevalent comorbidities (diabetes, hypertension and hyperlipidemia); # the adjustment set includes each of the other two meat subgroups (continuously)
Abbreviations: HR, hazard ratio; CI, confidence interval

In a further analysis, it was investigated whether the association between total meat intake and HF risk was depending on the individual meat subgroups. Therefore, meat consumption was investigated by subtracting alternately each of the three subgroups. The exclusion of *red meat* and *poultry* resulted in slightly attenuated risk estimates of HF across quintiles of total meat intake that, however, remained significant in the higher intake group. On the other hand, the exclusion of *processed meat* attenuated the association and lost its statistical significance across all quintiles (Figure 11).

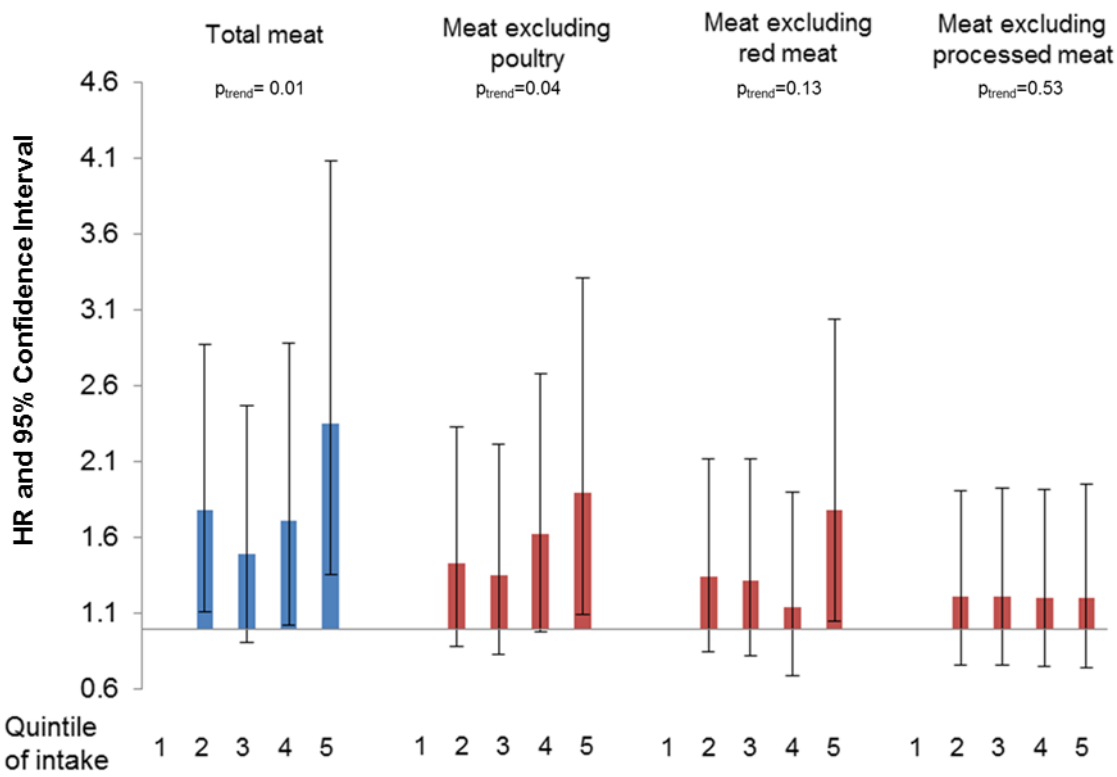

Figure 11: Association between Total Meat Intake and the Risk of Heart Failure and after Subtracting each of the Meat Subgroups

Hazard ratios and 95% confidence intervals are stratified for age and adjusted for sex, total energy intake, education, smoking, physical activity, body mass index, waist circumference, comorbidities (diabetes, hypertension, hyperlipidemia), and other score components including the subtracted food group (continuously).
Abbreviation: HR, hazard ratio

Overall, total meat intake was associated with an increased risk of HF, but this association seemed to be mainly driven by the intake of processed meat, the main contributor to total meat consumption in EPIC-Potsdam.

Furthermore, the intakes of animal protein, cholesterol, iron and SFAs were selected in the context of the *top-down* approach to further investigate the association with HF risk at the level of macro- and micronutrients (see Chapter 3.2.3). These nutrients are the main representatives of meat consumption and may be responsible for the risk-increase of HF due to total meat consumption.

Alcoholic Beverages

Beer and wine were the main contributors of total ethanol consumption in the EPIC-Potsdam cohort (Figure 12)

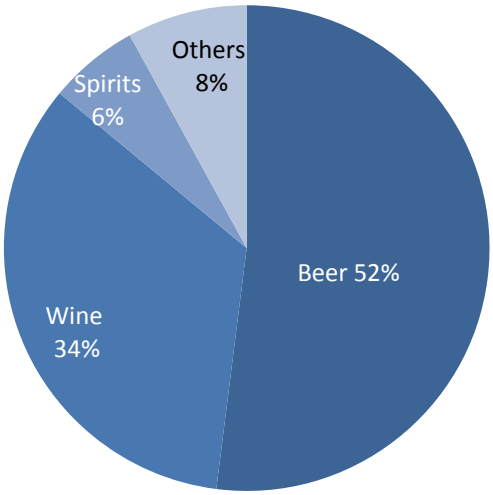

Figure 12: Percentage of Total Ethanol Intake by Alcoholic Beverages in EPIC-Potsdam

Percentages are approximates and calculated from mean intake values of the total EPIC-Potsdam cohort (n=24,008). Beer was equivalent to 4g ethanol/100ml, wine: 9g ethanol/100ml, spirits: 32g ethanol/100ml and other alcoholic beverages: 5-24g ethanol/100ml according to the German Nutrient Data Base[94]
Abbreviation: EPIC, European Prospective Investigation into Cancer and Nutrition

Baseline characteristics according to beer and wine intakes differed substantially: Wine intake was associated to a more prudent lifestyle (less smoking, more physical activity), a higher education and a lower presence of overweight and prevalent diseases. However, in the highest intake group there were more smokers and diabetics compared to the second highest group. Furthermore, with higher consumptions of wine a more 'healthy' diet was present (Appendix XV and Appendix XVI). On the contrary, beer consumption was associated with a less favorable risk profile, especially in men: a lower physical activity, more overweight, more prevalent diseases and a higher consumption of meat with simultaneously lower intake of fruits. With higher intakes of beer, more current smoking was present, but the non-consumers smoked most. These were also more often diabetics (Appendix XVII and Appendix XVIII).

Tables 19 and 20 show the associations between wine and beer consumption and the risk of HF in men and women.

In men, the consumption of both wine and beer was significantly associated with a decreased risk of HF (Table 19). This was more pronounced in case of wine intake but followed a U-shaped tendency, while the association appeared linear with beer consumption. For women, results showed the same tendency but were less pronounced than in men and did not reach statistical significance (Table 20).

Table 19: Association between Intakes of Wine and Beer and the Risk of Heart Failure in Men

	Categories of Intake*						
Wine	**1**	**2**	**3**	**4**	**5**		
Intake, ml	0	1-<35.7*	35.7*-<125	125-<250	≥ 250		
n (cases)	1,511 (40)	4,491 (69)	2,243 (13)	542 (2)	398 (6)		
Person-years	12,299	37,046	18,773	4,448	3,236		
	HR (95%CI)	**HR**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**	**p_{nonlin}**
Model 1	1.61 (1.09-2.38)	1	0.38 (0.21-0.69)	0.27 (0.07-1.09)	1.10 (0.47-2.55)	<.01	<.01
Model 2	1.35 (0.90-2.03)	1	0.42 (0.23-0.76)	0.29 (0.07-1.17)	1.13 (0.48-2.65)	<.01	0.01
Model 3	1.27 (0.85-1.91)	1	0.42 (0.23-0.76)	0.28 (0.07-1.15)	1.20 (0.51-2.84)	<.01	0.03
Beer	**1**	**2**	**3**	**4**	**5**		
Intake, ml	0	1-<250	250-<500	500-<1000	≥1000		
n (cases)	686 (13)	4,155 (62)	1,270 (19)	1,643 (23)	1,471 (13)		
Person-years	5,444	34,280	10,526	13,572	11,981		
	HR (95%CI)	**HR**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**	**p_{nonlin}**
Model 1	1.32 (0.72-2.40)	1	1.13 (0.67-1.89)	0.97 (0.60-1.57)	0.66 (0.36-1.21)	0.15	0.77
Model 2	0.99 (0.54-1.82)	1	1.11 (0.66-1.88)	0.89 (0.55-1.46)	0.53 (0.28-1.00)	0.10	0.47
Model 3	0.94 (0.51-1.74)	1	1.10 (0.66-1.86)	0.86 (0.52-1.41)	0.45 (0.24-0.86)	0.04	0.39

Model 1: stratified by age, adjusted for energy intake; Model 2: further adjusted for education, smoking, physical activity and the remaining score components (continuously) including ethanol from other alcoholic beverages, Model 3: further adjusted for BMI, waist circumference and prevalent comorbidities (diabetes, hypertension and hyperlipidemia), p_{nonlin} was calculated by restricted cubic spline Cox regression analyses (Wald chi-square test) with continuous intake of the respective alcoholic beverage (g/d) and 3 knots (5th, 50th (ref) and 95th percentile);
* Categories of intakes based on standard portion sizes in Germany (wine=250ml, beer=500ml), 35.7ml of wine reflect an intake of one glass per week
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; p_{nonlin}, p value for nonlinearity; SD, standard deviation

Table 20: Association between Intakes of Wine and Beer and the Risk of Heart Failure in Women

	Categories of Intake*						
Wine	**1**	**2**	**3**	**4**	**5**		
Intake, ml	0	1-<35.7*	35.7*-<125	125-<250	≥ 250		
n (cases)	1,244 (13)	7,624 (44)	4,325 (18)	966 (2)	624 (2)		
Person-years	10,003	63,215	35,891	8,022	5,100		
	HR (95%CI)	**HR**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**	**p_{nonlin}**
Model 1	1.45 (0.78-2.71)	1	0.81 (0.47-1.41)	0.50 (0.12-2.08)	0.68 (0.16-2.84)	0.08	0.20
Model 2	1.41 (0.75-2.65)	1	0.83 (0.48-1.46)	0.54 (0.13-2.26)	0.70 (0.17-2.97)	0.12	0.26
Model 3	1.02 (0.53-1.96)	1	0.87 (0.50-1.53)	0.56 (0.13-2.36)	0.67 (0.16-2.88)	0.37	0.58
Beer	**1**	**2**	**3**	**4**			
Intake, ml	0	1-<125	125-<250	≥250			
n (cases)	5,801 (40)	7,469 (34)	845 (3)	668 (2)			
Person-years	47,503	62,170	7,020	5,538			
	HR (95%CI)	**HR**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**	**p_{nonlin}**	
Model 1	1.35 (0.85-2.15)	1	0.88 (0.27-2.87)	0.81 (0.19-3.39)	0.18	<.05	
Model 2	1.27 (0.79-2.04)	1	0.87 (0.26-2.84)	0.71 (0.17-3.01)	0.22	0.09	
Model 3	1.04 (0.64-1.68)	1	0.91 (0.27-2.99)	0.71 (0.17-3.04)	0.62	0.37	

Model 1: stratified by age, adjusted for energy intake; Model 2: further adjusted for education, smoking, physical activity and the remaining score components (continuously) including ethanol from other alcoholic beverages, Model 3: further adjusted for BMI, waist circumference and prevalent comorbidities (diabetes, hypertension and hyperlipidemia), p_{nonlin} was calculated by restricted cubic spline Cox regression analyses (Wald chi-square test) with continuous intake of the respective alcoholic beverage (g/d) and 3 knots (5th, 50th (ref) and 95th percentile);
* Categories of intakes based on standard portion sizes in Germany (wine=250ml, beer=500ml), 35.7ml of wine reflect an intake of one glass per week
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; p_{nonlin}, p value for nonlinearity; SD, standard deviation

To sum up, a lower HF risks was observed in relation to beer (linear relationship) and wine (U-shaped relationship) consumption. Components of wine (polyphenols) other than ethanol might explain the observed protective effects on HF risk. However, it was not possible to test this hypothesis as the dietary assessment did not allow the differentiation between white and red wine.

Fish

The consumption of fish was related to a slightly more unfavorable HF risk profile. The proportion of current smokers and persons with overweight and prevalent diseases (diabetes, hypertension and hyperlipidemia) was higher among participants of the highest group of consumption compared to the lowest. However, persons within the fifth quintile of fish consumption were more physically active and more educated compared to participants in quintile 1 (data not shown). The intakes of all score components showed a positive association with fish intake (Table 21).

Table 21: Age- and Sex-adjusted Baseline Characteristics according to Quintiles of Fish Consumption

	Quintiles of Fish Intake				
Fish Intake	**1**	**2**	**3**	**4**	**5**
Men [g/d]	5.0 (3.1)	14.7 (2.4)	22.3 (2.2)	31.7 (3.2)	66.3 (43.1)
Women [g/d]	3.0 (1.6)	10.3 (1.9)	16.9 (1.6)	25.1 (2.8)	50.4 (31.1)
n (cases)	5,084 (48)	4,609 (40)	4,786 (39)	4.824 (51)	4,705 (31)
Canned fish	1.7 (2.0)	5.1 (4.1)	6.6 (4.8)	11.2 (6.1)	29.6 (34.8)
Baked, cooked and fried fish	2.1 (1.6)	6.9 (4.4)	12.4 (5.3)	16.4 (6.0)	27.0 (17.4)
Total energy intake, MJ/d	8,484 (32)	8,761 (34)	8,909 (33)	9,315 (33)	9,928 (33)
Medical History, %					
Prevalent hypertension	45.6	45.3	46.0	47.0	48.2
Prevalent diabetes	4.3	4.7	4.1	4.6	4.9
Prevalent hyperlipidemia	26.5	27.5	27.0	27.4	27.8
Intake of tMED Components					
Alcoholic intake	13.9 (0.2)	15.0 (0.2)	15.3 (0.2)	16.4 (0.2)	17.2 (0.2)
Fruits and nuts intake	131 (1.3)	137 (1.4)	140 (1.4)	145 (1.4)	152 (1.4)
Vegetable intake	89.3 (0.7)	94.9 (0.8)	98.3 (0.8)	102.5 (0.8)	110.1 (0.8)
Cereal intake	205 (1.0)	205 (1.1)	203 (1.1)	206 (1.1)	210 (1.1)
Meat intake	113 (0.8)	115 (0.9)	120 (0.8)	125 (0.8)	131 (0.9)
Legumes intake	21.2 (0.3)	22.5 (0.3)	23.5 (0.3)	25.8 (0.3)	26.9 (0.3)
Fat-ratio	0.84 (0.00)	0.84 (0.00)	0.85 (0.00)	0.86 (0.00)	0.89 (0.00)
Milk products intake	206 (3.0)	220 (3.2)	221 (3.1)	233 (3.1)	258 (3.1)

Baseline characteristics are expressed as age- and sex-adjusted mean (standard error) or percentages, age and sex are unadjusted means (standard deviation) or percentages, respectively. The fat-ratio is the ratio between monounsaturated and saturated fat and has no unit.
* Fish subgroups are presented as unadjusted means (standard deviation)
Abbreviations: tMED, traditional Mediterranean diet

The contribution of *baked, cooked and fried fish* to total fish intake was slightly higher compared to *canned fish*. The relation between the consumptions of total fish and the fish subgroups to the risk of HF is shown in Table 22. High fish intake was associated with lower HF risk. This association did not reach statistical significance across categories of total fish and *baked, cooked and fried fish*, but for *canned fish* in model 3.

Table 22: Association between Fish Intake and the Risk of Heart Failure

	Quintiles of Fish Intake			
Total Fish	**1**	**3**	**5**	
Men, mean (SD), [g/d]	5.0 (3.1)	22.3 (2.2)	66.3 (43.1)	
Women, mean (SD), [g/d]	3.0 (1.6)	16.9 (1.6)	50.4 (31.1)	
n (cases)	5,084 (48)	4,786 (39)	4,705 (31)	
Person-years	41,725	39,568	38,812	
	HR	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	0.81 (0.53-1.25)	0.62 (0.39-0.99)	0.14
Model 2	1	0.83 (0.54-1.28)	0.63 (0.39-1.01)	0.17
Model 3	1	0.84 (0.55-1.29)	0.59 (0.36-0.95)	0.11
Canned Fish	**1**	**3**	**5**	
Men, mean (SD), [g/d]	1.06 (0.68)	8.07 (0.44)	39.06 (38.17)	
Women, mean (SD), [g/d]	1.01 (0.63)	8.03 (0.46)	36.57 (33.65)	
n (cases)	8,120 (69)	6,453 (62)	3,617 (24)	
Person-years	66,480	53,377	29,799	
	HR	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.02 (0.72-1.45)	0.59 (0.37-0.95)	0.06
Model 2	1	1.04 (0.74-1.48)	0.59 (0.36-0.96)	0.07
Model 3	1	1.04 (0.73-1.48)	0.56 (0.35-0.92)	0.05
Baked, Cooked and Fried Fish	**1**	**3**	**5**	
Men, mean (SD), [g/d]	2.11 (1.02)	14.73 (0.18)	33.32 (17.01)	
Women, mean (SD), [g/d]	1.87 (0.89)	14.64 (0.25)	31.67 (14.29)	
n (cases)	7,306 (60)	7,255 (57)	4,026 (35)	
Person-years	60,272	59,964	33,076	
	HR	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	0.79 (0.55-1.14)	0.82 (0.53-1.25)	0.43
Model 2	1	0.81 (0.56-1.17)	0.85 (0.55-1.30)	0.48
Model 3	1	0.80 (0.56-1.16)	0.81 (0.52-1.25)	0.32

Model 1: stratified by age, adjusted for sex and energy intake; Model 2: further adjusted for education, smoking, physical activity, and all remaining score components (continuously) like listed in Table 21; Model 3: further adjusted for anthropometry (BMI and waist circumference) and prevalent comorbidities (diabetes, hypertension and hyperlipidemia

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid and HR, hazard ratio; CI, confidence interval; SD, standard deviation

In summary, these findings support an inverse relationship between fish intake, especially *canned fish*, and HF risk, at least at high fish consumptions. To continue the *top-down* approach, marine n3FAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) were further investigated and presented in Chapter 3.2.3.

3.2.3 Analyses of Macro- and Micronutrients

In the following chapter the selected components *fish* and *meat and meat products* are examined further regarding their most representative compounds on the level of macro- and/or micronutrients. The association between ethanol intake and HF risk has already been presented in Chapter 3.2.1.

Saturated Fatty Acids, Cholesterol, Iron and Animal Protein from Meat

To continue the *top-down* approach with main representatives of *meat and meat products*, animal protein, cholesterol, iron and SFAs were selected to further investigate the association to HF risk on the level of macro- and micronutrients, because of their high content in meat and the potential of these nutrients to influence the overall HF risk-increasing effect of total meat consumption demonstrated in Chapter 3.2.1.

Intakes of nutrients exclusively derived from meat were highly correlated with each other (Table 23, upper part). Total meat intake and animal protein from meat were nearly perfectly direct correlated (partial Spearman r = 0.99). Regarding total nutrient intakes, correlations were lower (Table 23, lower part). Analyses on nutrient level were, therefore, investigated for total intake and source-specific intakes of the respective nutrient, to be less prone to the problem of multicollinearity.

Table 23: Crude and Partial Spearman Correlation Coefficients for Nutrients from Meat and from the Whole Diet

Nutrient / Food Group	SFA*	Cholesterol*	Iron*	Animal protein*	Total meat	Poultry	Red meat	Proc. meat
SFA*		0.90	0.84	0.88	0.92	0.29	0.51	0.90
Cholesterol*	0.91		0.91	0.97	0.97	0.47	0.71	0.76
Iron*	0.87	0.93		0.86	0.87	0.33	0.64	0.72
Animal protein*	0.90	0.97	0.89		0.99	0.48	0.74	0.76
Total meat	0.93	0.97	0.89	0.99		0.45	0.71	0.80
Poultry	0.31	0.46	0.35	0.49	0.46		0.38	0.13
Red meat	0.58	0.75	0.69	0.77	0.75	0.40		0.27
Processed meat	0.92	0.79	0.75	0.79	0.83	0.17	0.36	
Nutrient / Food Group	**SFA#**	**Cholesterol#**	**Iron#**	**Animal protein#**	**Total meat**	**Poultry**	**Red meat**	**Proc. meat**
SFA#		0.83	0.59	0.67	0.45	0.14	0.28	0.42
Cholesterol#	0.84		0.60	0.74	0.56	0.28	0.44	0.44
Iron#	0.63	0.64		0.63	0.49	0.24	0.32	0.41
Animal protein#	0.70	0.76	0.67		0.69	0.38	0.48	0.54
Total meat	0.51	0.62	0.55	0.73		0.45	0.71	0.80
Poultry	0.17	0.30	0.26	0.40	0.46		0.38	0.13
Red meat	0.35	0.49	0.40	0.54	0.75	0.40		0.27
Processed meat	0.49	0.50	0.48	0.60	0.83	0.17	0.36	

Values are all significant (<.01) and expressed as crude Spearman correlation coefficients (highlighted in blue), and partial Spearman correlation coefficients (adjusted for age and sex); * only nutrients from meat are shown; # Total nutrients from all food sources are shown
Abbreviation: SFA, saturated fatty acid

Meat contributed to 23-44% to the average overall intakes of SFAs, cholesterol, iron and animal protein that were present in the EPIC-Potsdam cohort as shown in Figure 13.

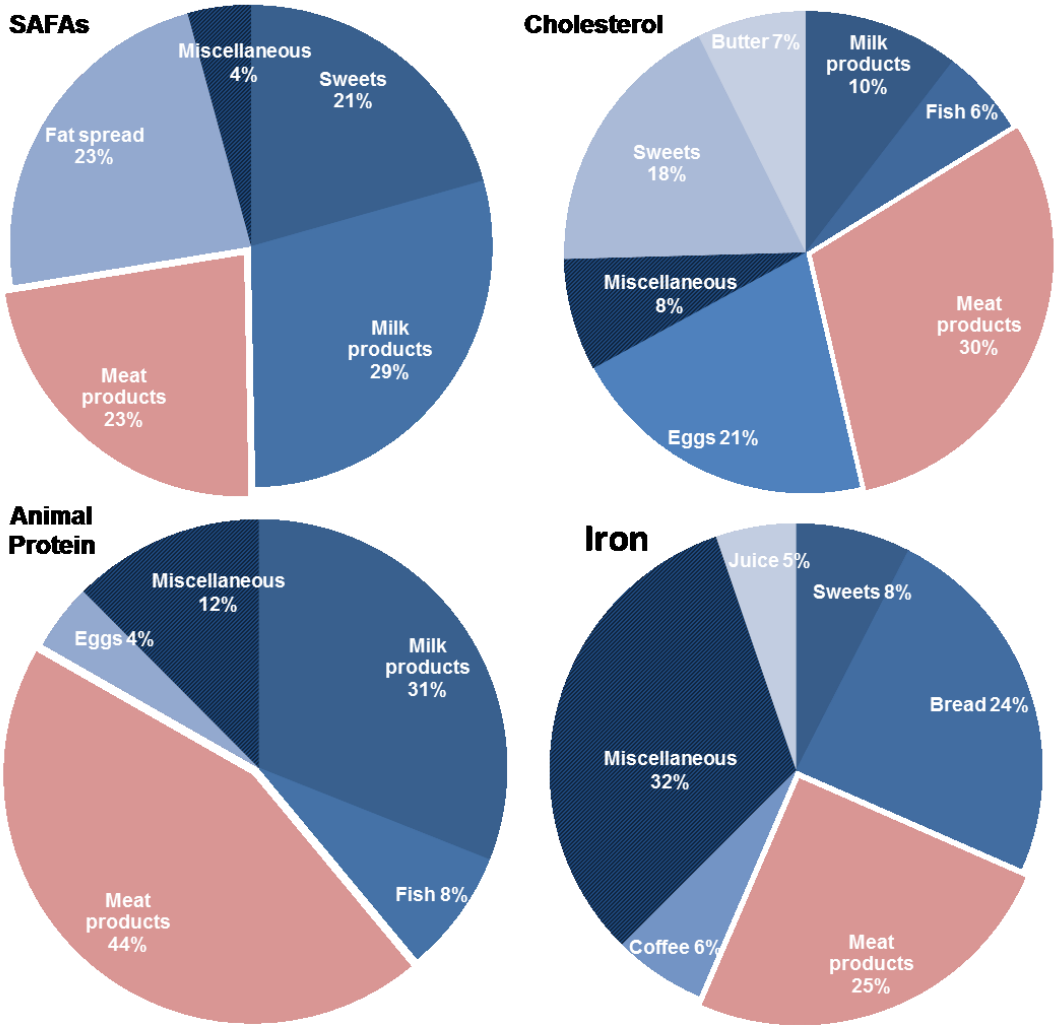

Figure 13: Main Contributing Food Sources to Total Intakes of Saturated Fatty Acids, Cholesterol, Iron and Animal Protein in EPIC-Potsdam

Percentages are approximates calculated by multiplying nutrient content of the food group (mg/g or g/g)[94] with average food group intake in EPIC-Potsdam (g/d) relative to the average total nutrient amount derived from the whole diet (mg/d or g/d)
Abbreviation: SFA, Saturated fatty acid

The associations between the intakes of total SFAs, SFAs from meat and SFAs from other sources and the risk of HF are depicted in Table 24. All investigated SFA sources showed significantly positive associations with HF risk across all adjusted models.

Table 24: Relationship between the Intakes of Total Fat and Overall and Meat-Specific Saturated Fatty Acids and the Risk of Heart Failure

	Quintiles of Fat intake					
Total SFAs	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [g/d]	22.3 (3.6)	30.2 (1.8)	36.6 (1.9)	44.3 (2.7)	61.1 (10.9)	
Women, mean (SD), [g/d]	17.5 (2.8)	23.9 (1.5)	29.1 (1.5)	35.1 (2.1)	48.4 (8.5)	
n (cases)	4,810 (36)	4,797 (39)	4,803 (44)	4,797 (47)	4,801 (43)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.39 (0.87-2.22)	1.83 (1.12-2.98)	2.42 (1.42-4.12)	3.26 (1.68-6.29)	<.01
Model 2	1	1.25 (0.78-2.01)	1.59 (0.96-2.61)	1.96 (1.13-3.41)	2.34 (1.14-4.81)	<.01
Model 3	1	1.33 (0.82-2.13)	1.81 (1.09-2.99)	2.39 (1.36-4.20)	2.85 (1.38-5.89)	<.01
SFAs from Meat	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [g/d]	3.5 (1.2)	5.8 (0.5)	7.7 (0.6)	10.1 (0.8)	16.0 (4.7)	
Women, mean (SD), [g/d]	1.8 (0.7)	3.5 (0.4)	4.7 (0.4)	6.1 (0.5)	9.7 (3.1)	
n (cases)	4,801 (29)	4,806 (44)	4,798 (42)	4,801 (45)	4,802 (49)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.61 (1.01-2.58)	1.60 (0.99-2.59)	1.89 (1.16-3.06)	2.77 (1.67-4.60)	<.01
Model 2	1	1.56 (0.97-2.50)	1.47 (0.90-2.38)	1.68 (1.03-2.75)	2.33 (1.39-3.92)	<.01
Model 3	1	1.41 (0.88-2.26)	1.27 (0.78-2.06)	1.40 (0.85-2.28)	1.79 (1.06-3.03)	0.06
SFAs from other Sources	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [g/d]	16.0 (2.9)	22.6 (1.6)	28.1 (1.6)	34.7 (2.3)	49.8 (10.2)	
Women, mean (SD), [g/d]	13.8 (2.4)	19.4 (1.3)	23.9 (1.3)	29.4 (2.0)	41.8 (8.0)	
n (cases)	4,801 (38)	4,802 (45)	4,801 (37)	4,802 (45)	4,802 (44)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.30 (0.84-2.03)	1.18 (0.73-1.92)	1.65 (1.00-2.73)	2.00 (1.10-3.65)	0.02
Model 2	1	1.30 (0.83-2.04)	1.18 (0.72-1.95)	1.71 (1.00-2.91)	2.06 (1.06-4.02)	0.04
Model 3	1	1.36 (0.87-2.14)	1.37 (0.83-2.27)	2.11 (1.22-3.64)	2.63 (1.34-5.17)	<.01

Model 1: stratified by age, adjusted for sex and energy intake; Model 2: further adjusted for education, smoking, physical activity, and all remaining score components (continuously), except 'meat and meat products', 'milk and milk products' and the ratio between monounsaturated and saturated fatty acids (milk products were included in analyses of SFA from meat and meat was included in analyses on SFA from other sources); Model 3: further adjusted for anthropometry (BMI and waist circumference), and prevalent comorbidities (diabetes, hypertension and hyperlipidemia)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SD; standard deviation; SFA, saturated fatty acid

Regarding cholesterol, the results were similar to those observed for SFAs. Both total and source-specific cholesterol intake were positively related to the risk of HF. However, risk estimates comparing the highest versus the lowest intakes of cholesterol from other sources than meat were significant only in model 3 (Table 25).

For total animal protein intake, a significant positive association was observed, which, however, disappeared after adjustment for prevalent diseases and anthropometry (Table 26). Animal protein from meat sources showed significantly higher HRs across all quintiles of intake compared to the first, and remained significant in all applied statistical models.

Table 27 shows the results of the analyses on total and source-specific iron intake and the risk of HF. Overall, the intake of total iron showed no clear association with HF risk. But contradictory associations can be noticed when considering the different iron sources. Iron from meat was positively associated with HF risk, while the intake of iron from other sources appeared to be inversely associated. However, regarding iron from meat the association was attenuated and lost its significance after multivariable adjustment.

Sensitivity analyses that were adjusted for nutrients did not substantially alter the results (data not shown).

Table 25: Relationship between Cholesterol Intake and the Risk of Heart Failure

	Quintiles of Cholesterol intake					
Total Cholesterol	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d] Women, mean (SD), [mg/d]	202.6 (34.3) 157.2 (27.6)	276.7 (15.8) 216.6 (13.1)	331.8 (17.0) 261.2 (13.4)	399.5 (23.7) 314.7 (18.1)	546.9 (102.7) 428.3 (91.3)	
n (cases)	4,802 (36)	4,802 (40)	4,805 (43)	4,804 (52)	4,795 (38)	
Person-years	39,320	39,650	39,692	39,805	39,567	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.28 (0.81-2.02)	1.63 (1.01-2.61)	2.23 (1.37-3.63)	2.08 (1.14-3.78)	<.01
Model 2	1	1.26 (0.79-2.00)	1.56 (0.96-2.52)	2.01 (1.21-3.33)	1.72 (0.90-3.27)	0.02
Model 3	1	1.23 (0.78-1.96)	1.54 (0.95-2.49)	2.07 (1.24-3.44)	1.65 (0.86-3.19)	0.02
Cholesterol from Meat	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d] Women, mean (SD), [mg/d]	48.9 (15.1) 27.5 (10.5)	78.4 (6.4) 49.5 (4.5)	101.3 (6.9) 64.9 (4.4)	128.9 (9.8) 82.8 (6.3)	192.1 (47.1) 125.4 (3.1)	
n (cases)	4,801 (28)	4,802 (43)	4,802 (49)	4,801 (42)	4,802 (47)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.56 (0.97-2.51)	1.89 (1.18-3.02)	1.85 (1.13-3.03)	2.44 (1.48-4.04)	<.01
Model 2	1	1.52 (0.94-2.46)	1.80 (1.12-2.88)	1.65 (1.00-2.73)	2.01 (1.20-3.39)	0.01
Model 3	1	1.37 (0.85-2.22)	1.54 (0.96-2.47)	1.42 (0.85-2.35)	1.55 (0.92-2.61)	0.15
Cholesterol from other sources	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d] Women, mean (SD), [mg/d]	124 (25) 108 (21)	181 (13) 155 (11)	224 (13) 192 (11)	277 (18) 237 (15)	402 (90) 336 (87)	
n (cases)	4,801 (46)	4,802 (39)	4,801 (40)	4,802 (42)	4,802 (42)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	0.92 (0.60-1.42)	1.01 (0.65-1.57)	1.20 (0.75-1.90)	1.29 (0.76-2.20)	0.23
Model 2	1	0.95 (0.61-1.46)	1.08 (0.69-1.68)	1.27 (0.79-2.04)	1.43 (0.82-2.47)	0.13
Model 3	1	1.00 (0.65-1.55)	1.19 (0.76-1.88)	1.45 (0.90-2.33)	1.66 (0.95-2.91)	0.04

Model 1: stratified by age, adjusted for sex and energy intake; Model 2: further adjusted for education, smoking, physical activity, and all remaining score components (continuously), except meat, and the ratio between MUFAs and SFAs (milk products were not included and meat was included in analyses of cholesterol from other sources); Model 3: further adjusted for anthropometry (BMI and waist circumference), and prevalent comorbidities (diabetes, hypertension and hyperlipidemia)
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SD; standard deviation; SFA, saturated fatty acid

Table 26: Relationship between Animal Protein Intake and the Risk of Heart Failure

	Quintiles of Animal Protein Intake					
Total Animal Protein	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [g/d]	33.5 (5.3)	45.0 (2.5)	53.5 (2.6)	63.9 (3.5)	86.0 (15.4)	
Women, mean (SD), [g/d]	26.3 (4.4)	35.3 (2.0)	42.0 (2.0)	50.0 (2.7)	67.3 (13.1)	
n (cases)	4,801 (36)	4,802 (34)	4,801 (50)	4,802 (53)	4,802 (36)	
Person-years	39,328	39,554	39,643	39,835	39,675	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.01 (0.63-1.63)	1.53 (0.97-2.40)	1.79 (1.11-2.87)	1.54 (0.87-2.73)	0.02
Model 2	1	1.05 (0.65-1.69)	1.58 (0.99-2.50)	1.82 (1.12-2.96)	1.57 (0.86-2.87)	0.02
Model 3	1	0.96 (0.59-1.54)	1.39 (0.88-2.21)	1.48 (0.91-2.41)	1.12 (0.61-2.06)	0.23
Animal Protein from Meat	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [g/d]	12.5 (3.8)	20.1 (1.7)	26.0 (1.8)	32.9 (2.5)	48.9 (11.7)	
Women, mean (SD), [g/d]	7.1 (2.7)	12.7 (1.2)	16.6 (1.1)	21.1 (1.7)	32.0 (7.8)	
n (cases)	4,801 (27)	4,802 (47)	4,801 (42)	4,802 (42)	4,802 (51)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.79 (1.11-2.88)	1.71 (1.05-2.79)	1.91 (1.16-3.14)	2.97 (1.79-4.93)	<.01
Model 2	1	1.76 (1.09-2.84)	1.66 (1.01-2.73)	1.73 (1.04-2.89)	2.44 (1.42-4.19)	<.01
Model 3	1	1.61 (1.00-2.60)	1.44 (0.87-2.36)	1.51 (0.90-2.53)	1.99 (1.15-3.43)	<.05
Animal Protein from other sources	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [g/d]	14.5 (3.0)	21.0 (1.5)	26.0 (1.6)	32.3 (2.2)	47.5 (12.1)	
Women, mean (SD), [g/d]	13.9 (2.7)	19.8 (1.3)	24.3 (1.3)	29.8 (2.0)	43.5 (11.7)	
n (cases)	4,801 (51)	4,802 (36)	4,801 (40)	4,802 (44)	4,802 (38)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	0.65 (0.42-1.00)	0.72 (0.47-1.11)	0.77 (0.50-1.19)	0.69 (0.42-1.13)	0.29
Model 2	1	0.70 (0.45-1.09)	0.82 (0.53-1.28)	0.93 (0.59-1.49)	0.93 (0.53-1.61)	0.88
Model 3	1	0.64 (0.41-0.99)	0.75 (0.48-1.18)	0.80 (0.50-1.28)	0.70 (0.40-1.22)	0.45

Model 1: stratified by age, adjusted for sex and energy intake; Model 2: further adjusted for education, smoking, physical activity and the remaining score components (continuously), except 'meat and meat products'(milk products were included in analyses of animal protein from meat and meat was included in analyses on animal protein from other sources) ; Model 3: further adjusted for anthropometry (BMI and waist circumference), and prevalent comorbidities (diabetes, hypertension and hyperlipidemia),
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SD, standard deviation

Table 27: Relationship between Iron Intake and the Risk of Heart Failure

	Quintiles of Iron Intake					
Total Iron	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d]	10.0 (1.2)	12.5 (0.5)	14.3 (0.5)	16.4 (0.7)	20.8 (2.9)	
Women, mean (SD), [mg/d]	8.5 (0.9)	10.5 (0.4)	12.0 (0.4)	13.6 (0.6)	16.9 (2.1)	
n (cases)	4,802 (38)	4,802 (51)	4,800 (43)	4,802 (46)	4,802 (31)	
Person-years	39,478	39,688	39,757	39,507	39,605	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	p_{trend}
Model 1	1	1.26 (0.81-1.94)	1.03 (0.64-1.67)	1.12 (0.67-1.89)	0.77 (0.39-1.51)	0.53
Model 2	1	1.16 (0.74-1.80)	0.88 (0.53-1.44)	0.90 (0.52-1.56)	0.50 (0.23-1.06)	0.12
Model 3	1	1.18 (0.76-1.83)	0.85 (0.52-1.40)	0.86 (0.50-1.50)	0.44 (0.20-0.95)	0.07
Iron from Meat	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d]	1.33 (0.44)	2.25 (0.20)	2.98 (0.23)	3.95 (0.35)	6.62 (2.22)	
Women, mean (SD), [mg/d]	0.70 (0.28)	1.31 (0.13)	1.77 (0.14)	2.36 (0.21)	3.89 (1.23)	
n (cases)	4,802 (27)	4,801 (37)	4,801 (51)	4,802 (47)	4,802 (47)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	p_{trend}
Model 1	1	1.39 (0.85-2.30)	1.95 (1.22-3.13)	1.85 (1.13-2.98)	1.91 (1.16-3.15)	<.01
Model 2	1	1.31 (0.79-2.16)	1.75 (1.09-2.83)	1.63 (1.00-268)	1.54 (0.92-2.60)	0.08
Model 3	1	1.22 (0.74-2.01)	1.60 (0.99-2.59)	1.41 (0.86-2.32)	1.32 (0.78-2.24)	0.30
Iron from other sources	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d]	7.6 (1.0)	9.6 (0.4)	11.0 (0.4)	12.6 (0.6)	16.0 (2.1)	
Women, mean (SD), [mg/d]	7.1 (0.8)	8.8 (0.4)	10.0 (0.4)	11.4 (0.5)	14.3 (1.8)	
n (cases)	4,801 (46)	4,802 (49)	4,801 (44)	4,802 (41)	4,802 (29)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	p_{trend}
Model 1	1	0.95 (0.63-1.44)	0.81 (0.52-1.28)	0.73 (0.45-1.21)	0.50 (0.26-0.95)	0.04
Model 2	1	0.93 (0.61-1.42)	0.79 (0.49-1.27)	0.70 (0.40-1.20)	0.45 (0.21-0.96)	0.06
Model 3	1	0.93 (0.60-1.42)	0.76 (0.47-1.23)	0.66 (0.38-1.15)	0.38 (0.18-0.83)	0.03

Model 1: stratified by age, adjusted for sex and energy intake; Model 2: further adjusted for education, smoking, physical activity and the remaining score components (continuously), except 'meat and meat products' and cereals (cereals were included in analyses iron from meat and meat was included in analyses iron from other sources); Model 3: further adjusted for anthropometry (BMI and waist circumference), and prevalent comorbidities (diabetes, hypertension and hyperlipidemia)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SD, standard deviation

Marine Omega-3 Fatty Acids from Fish

EPA and DHA were further investigated as the most representative components in fatty fish to follow the *top-down* approach. Unlike the nutrients shown before, the intakes of EPA and DHA are mainly depending on fish consumption (Figure 14).

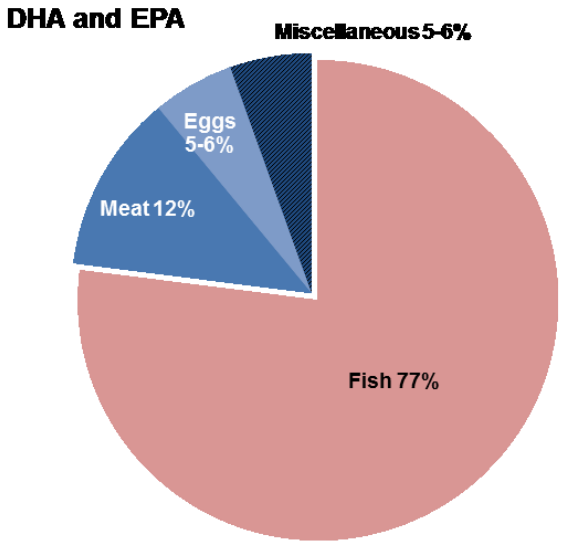

Figure 14: Main Contributing Food Sources to Total Marine Omega-3 Fatty Acids in EPIC-Potsdam
Percentages are approximates calculated by multiplying nutrient content of the food group (mg/g)[94] with average food group intake in EPIC-Potsdam (g/d) relative to the total nutrient amount derived from the whole diet (mg/d)
Abbreviation: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Canned fish contributes to marine n3FAs about double compared to *baked, cooked and fried fish.* That is also reflected by higher correlations (Table 28).

Table 28: Crude and Partial Spearman Correlation Coefficients for Omega-3 Fatty Acids and Fish

Nutrient / Food Group	Total DHA and EPA	DHA and EPA from fish	Total fish	Canned fish	Baked fish
Total DHA and EPA		0.97	0.95	0.86	0.68
DHA and EPA from fish	0.97		0.97	0.89	0.68
Total fish	0.95	0.97		0.76	0.83
Canned fish	0.86	0.89	0.76		0.34
Baked fish	0.68	0.69	0.83	0.35	

Values are all significant (<.01) and expressed as crude Spearman correlation coefficients (highlighted in blue), and partial Spearman correlation coefficients (adjusted for age and sex);
Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Table 29 shows the associations between total and source-specific marine n3FAs intake and the risk of HF. An inverse association was observed for DHA and EPA from fish and all sources but not from other sources than fish. Persons in the fifth quintile of total marine n3FAs intake had only half the risk of developing HF compared to persons in the lowest category. For DHA and EPA from other sources, a risk increase was observed which, however, remained significant after multivariable adjustment but showed no linear trend.

Table 29: Association between Intakes of Total Omega 3 Fatty Acids and Omega 3 Fatty Acids from Fish and Other Sources and the Risk of Heart Failure

	Quintiles of Omega-3-Fatty Acids Intake					
Total DHA+EPA	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d] Women, mean (SD), [mg/d]	122 (35) 87 (24)	226 (26) 161 (21)	315 (25) 231 (22)	418 (37) 316 (30)	878 (602) 623 (426)	
n (cases)	4,801 (45)	4,802 (42)	4,801 (48)	4,802 (49)	4,802 (25)	
Person-years	39,477	39,427	39,790	39,695	39,644	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	0.90 (0.59-1.37)	1.03 (0.68-1.55)	1.03 (0.68-1.56)	0.54 (0.32-0.89)	0.09
Model 2	1	0.89 (0.58-1.36)	1.03 (0.68-1.56)	0.98 (0.64-1.50)	0.50 (0.30-0.84)	0.06
Model 3	1	0.87 (0.57-1.34)	1.01 (0.66-1.53)	0.97 (0.63-1.48)	0.46 (0.27-0.78)	0.03
DHA+EPA from Fish	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d] Women, mean (SD), [mg/d]	42.8 (27.1) 33.7 (19.8)	141.3 (20.1) 102.1 (18.8)	227.8 (19.8) 162.0 (21.1)	327.1 (37.7) 243.9 (28.3)	815.4 (620.9) 539.1 (424.9)	
n (cases)	5,264 (47)	4,616 (43)	4,720 (45)	4,808 (50)	4,600 (24)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	0.91 (0.60-1.37)	0.96 (0.64-1.45)	0.98 (0.66-1.47)	0.52 (0.32-0.86)	0.06
Model 2	1	0.94 (0.62-1.43)	0.98 (0.65-1.48)	1.02 (0.68-1.54)	0.52 (0.31-0.87)	0.07
Model 3	1	0.94 (0.62-1.43)	0.98 (0.64-1.48)	1.00 (0.66-1.50)	0.50 (0.30-0.83)	0.04
DHA+EPA from other sources	**1**	**2**	**3**	**4**	**5**	
Men, mean (SD), [mg/d] Women, mean (SD), [mg/d]	49.0 (9.9) 36.1 (7.9)	70.3 (4.7) 53.5 (4.1)	87.1 (4.8) 66.9 (3.9)	106.6 (6.9) 82.2 (5.4)	151.2 (31.9) 116.3 (28.4)	
n (cases)	4,801 (31)	4,802 (52)	4,801 (46)	4,802 (43)	4,802 (37)	
	HR	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**p_{trend}**
Model 1	1	1.97 (1.26-3.10)	1.88 (1.18-3.00)	2.08 (1.28-3.39)	2.12 (1.24-3.64)	0.01
Model 2*	1	1.93 (1.23-3.03)	1.79 (1.12-2.88)	1.87 (1.13-3.09)	1.76 (1.00-3.09)	0.09
Model 3*	1	1.88 (1.20-2.97)	1.74 (1.08-2.80)	1.76 (1.07-2.91)	1.57 (0.88-2.80)	0.21

Model 1: stratified by age, adjusted for sex and energy intake; Model 2: further adjusted for education, smoking physical activity, and all remaining score components (continuously), except 'fish'; Model 3: further adjusted for anthropometry (BMI and waist circumference), and prevalent comorbidities (diabetes, hypertension and hyperlipidemia),
* fish was included in the adjustment
Abbreviations: BMI, body mass index; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio

4. DISCUSSION

The aim of the present study was to examine the association between the adherence to the Mediterranean diet and the risks of HF. Data of a prospective non-Mediterranean cohort study (EPIC-Potsdam) were used to pursue this goal. By means of a *top-down* approach, it was explored whether a Mediterranean-style diet as a whole, in its individual components, and at micro- and macronutrient level was associated with the risk of HF. Thereby, the most important elements of this diet with respect to HF risk were identified and examined in detail.

4.1 Interpretation of Results

4.1.1 Dietary Pattern Analysis and Selection of Relevant Components

In the present work, a higher adherence to the Mediterranean-style diet was associated with a lower risk of HF. EPIC-Potsdam participants who received five or more score points had an about 40% decreased HF risk compared to participants who were assigned a score of zero to two points. However, this relationship was attenuated after multivariable adjustment and was further weakened after adjustment of prevalent comorbidities and anthropometric measurements. Moreover, the exclusion of probable and especially possible cases attenuated the association notably.
Nevertheless, this result is considered to be likely reliable for the following reasons:

First, as addressed in Chapter 2.2.2 (Selection of Covariates), comorbidities and anthropometric measurements are suspected mediators within the causal pathway between diet and HF development and, therefore, more emphasis may be given to model 2 that was borderline significant ($p = 0.06$). Furthermore, risk estimates across categories of tMED remained rather stable in all applied statistical models. Third, possible cases consisted mainly of fatal events that suggest more severe endpoints and/or farther disease progression. An effect might be stronger in those participants and thus may explain the attenuation of risk estimates after exclusion of these cases. Fourth, the effectiveness of the Mediterranean diet on mortality has been reported to be higher in Mediterranean countries than in non-Mediterranean ones.[99] This might also be true concerning HF.

In the present work, of the nine components that were used in the tMED, only three were identified to play a major role in the investigated population with respect to HF risk reduction. These were: low intakes of meat and meat products, moderate consumption of

alcohol and a high intake of fish. The observed finding is quite similar to one of an investigation in a Greek population. In this study, low meat and moderate alcohol consumption were identified as the first two main contributors to the overall inverse association between the Mediterranean diet and mortality.[99] However, with regards to HF, studies on dietary patterns are very scarce. So far, only the consistency with the DASH diet has been reported to be associated with a decreased risk of HF in men and women.[52, 53] The DASH diet shares a number of tMED components and was associated with a 22% lower risk of HF in men[52] and a 37% lower risk in women[51] comparing the highest versus the lowest adherence groups. However, the DASH diet score differed from the tMED in the fact that sodium and sweetened beverages were included, while fish, alcohol and the fat-ratio were not. In addition, low-fat dairy products were considered as positive component, cereals were limited to whole grains and poultry was excluded from total meat.

4.1.2 Analysis of Food Groups and Subgroups

The components identified as being the main contributors to the overall inverse diet-disease relationship were further analyzed according to relevant food subgroups of which they were composed.

Total meat consumption was related to a two to three-fold increased risk of developing HF comparing persons in the highest versus those in the lowest quintile of consumption. In fact, all meat subgroups (processed meat, red meat and poultry) contributed to a certain extent to this overall association (Figure 11), but processed meat was the crucial factor in the investigated population. Men and women who consumed at least ~150g and ~100g of processed meat per day had an 82% higher risk to develop HF compared to men and women with lowest intakes (27g and 13g per day, respectively). For red meat and poultry no independent association was observed but exclusion of these from total meat attenuated the positive association to HF risk.

So far, three investigations studied the impact of red and processed meat consumption on the risk of HF.[36, 60, 110] Nettleton et al.[36] did not observe any association in a cohort of men and women (ARIC), while two investigations in men are in accordance to the results of the present thesis. Both Ashaye et al.[117] and Kaluza and colleagues[61] observed significantly higher risks of HF with higher intakes of red and processed meat. In one of those studies the risk increase was restricted to processed meat consumption.[61] This is in line with the results of the present thesis. None of the mentioned studies investigated the intake of poultry. However, the association between poultry intake and CHD risk seems to be negligible, although studies including consumers of high amounts are lacking.[111]

As a second component of the tMED, fish consumption was inversely associated with HF risk. This was particularly true for canned fish (containing mainly fatty fish such as tuna or pickled herring) but not baked, fried or cooked fish. This finding is in agreement to most of the previous ones, although results were somewhat conflicting. Three meta-analyses have addressed this topic recently, all drawing different conclusions.[33-35] Two of them summarized results from the same studies but differed in the comparison groups. Djoussé et al.[35] reported a 15% (95% CI: 27%-1%) lower HF risk for persons in the highest versus the lowest category of consumption, while Li and colleagues[34] computed HRs of HF according to specific frequencies of consumption and reported a HR of 0.91 (95% CI: 0.84-0.99) comparing one serving of fish per week with lower or equal to one serving per month. These analyses contrasted with the meta-analysis of Hou et al.[34] who included the null finding of Nettleton et al.[36] and observed no association between fish consumption and HF risk (HR (95% CI): 1.00 (0.81-1.24) for the highest versus the lowest quartile of consumption). On the contrary, in a second analysis limited to fried fish, the same authors observed an increase in HF risk with higher consumption (HR (95% CI): 1.40 (1.22-1.61). This analysis included only two studies but, however, could be an explanation for the lack of an inverse association with *baked, fried and cooked fish* observed in the present work. Two further studies are published on that topic, both not covered by any of the mentioned meta-analyses. Both Wilk et al.[41] and Yamagishi et al.[46] observed an inverse association between fish intake and HF risk, although the latter was not significant and only included fatal HF events. Overall, evidence of an inverse association between fish consumption and HF risk is growing and now supported also by the present study.

Ethanol intake was inversely associated with the risk of HF in EPIC-Potsdam. As shown in Figure 9, this relationship appeared quite linear rather than U-shaped assuming a benefit in terms of HF risk no matter how high the intakes were. Apart from the potential increased risk of some cancers according to high ethanol consumption,[112] it must be noted that among EPIC-Potsdam participants a quite moderate intake of ethanol was present (see Table 11). Most participant were far away from the reported amount of <90g ethanol per day that induces cardiomyopathies (median intake [interquartile range] of ethanol in consumers: men 18.3 [8.3-31.7] and women: 5.3 [2.1-10.5]).[4] The consumed amounts of the study participants were, thus, in a range in which the second half of a probable U-shape might not yet have been detectable. The ‘sick quitters bias’ might furthermore explain the especially higher risk of HF observed with lowest intakes.

The overall protective effect of ethanol consumption on the risk of HF has been summarized earlier in a meta-analysis of six prospective studies and is in line with the results of the present thesis.[50] The authors observed an inverse association that was not

U-shaped either, and they argued with the lack of adequate data on heavy drinkers. Reported cardio-protective properties of moderate ethanol consumption are manifold and well documented. Ethanol has been linked to improved insulin sensitivity, increased plasma HDL cholesterol,[113] and reduced inflammation and platelet aggregation.[114] Additionally, a 'fish-like' effect of ethanol was proposed, as alcohol intake was observed to increase concentrations of marine n3FAs in plasma and blood.[115, 116]

So far, there are few insights to what extent the association with HF risk might differ between types of alcoholic beverages. One of the studies included in the meta-analysis of Padilla et al.[50] addressed this subject and found no association between liquor intakes and HF risk, but similar risk reductions due to wine and beer consumption.[117] However, this was only seen in men and HF that was related to CHD. In the present thesis, the analyses of wine and beer revealed that the intakes of both were associated with reduced HF risk. In agreement with the result of Klatsky et al,[117] this was more pronounced and significant only in men. Men in the highest intake group of beer had approximately half the risk of developing HF compared to drinkers in the lowest category. The corresponding HR in women was 0.71 (95% CI: 0.17-3.01). Men who drank between half and one glass of wine per day even had an about 70% lower risk of HF compared to wine consumers drinking a maximum of one glass a week (~50% in women). A possible additional protective effect of wine compared to other alcoholic beverages might be explained by its high antioxidant capacity, especially due to polyphenols in red wine.[118] The observed sex-differences might be due to lower consumption of alcohol and lower HF incidence rates in women compared to men and, thus, lower power in detecting significant associations.

Interestingly, wine consumption showed the expected U-shaped association with HF risk, while beer intakes showed a linear relationship with HF risk. Unmeasured confounding might have impacted these differences. Persons who preferably drink beer appeared very different to persons who favor wine. This might also be reflected in drinking behavior. Daily moderate consumption of alcohol and *binge drinking* have been associated with opposing cardiovascular effects.[119] While *binge drinking* is associated to an increased risk of cardiovascular outcomes even in generally moderate consumers, regular (daily) but responsible alcohol consumption is reported to be beneficial. Although speculative, beer drinkers in the highest group of consumption might have taken advantage of a regular and responsible consumption rather than a very high consumption on a few days per week or months.[114 120, 121] However, this could not be answered in the present study.

4.1.3 Analysis of Macro- and Micronutrients

The main nutrients of *meat and meat products* and *fish*, which were presumably responsible for the overall association with HF risk, have been further investigated.

In case of *meat and meat products*, analyses were conducted for SFAs, cholesterol, iron and animal protein.

Intakes of SFA and cholesterol showed quite similar trends. For both, a positive association to HF risk was observed regardless of the source that was studied. Persons with the highest intakes of total SFAs, SFAs from meat and SFAs originating from other foods showed a more than two-fold increased HF risk relative to persons in the lowest intake group. These associations remained significant even after adjustment for potential mediators.

Regarding cholesterol, similar risk-increasing trends were observed for total and source-specific cholesterol intakes. However, an increase in HF risk was more pronounced for cholesterol from meat than cholesterol from other sources.

Few prospective studies investigated the impact of nutrients on HF risk (Table 3). As far as known, none of them included the intakes of SFAs or dietary cholesterol. Nevertheless, a sufficient body of evidence exists that supports the present findings, although this mostly refers to the impact on CHD risk.[70, 122, 123] The main adverse effect of dietary cholesterol and SFAs on heart health is suggested to be the LDL cholesterol-increasing effect due to the inhibition of the LDL receptor activity.[122] It is furthermore discussed that a high intake of SFAs and cholesterol simultaneously might exacerbate this effect.[122]

Concerning animal protein, inconsistent results were observed for intakes calculated from meat and other sources. Total animal protein intake was associated with an increased risk of HF. However, this association seemed to depend on the risk increase due to animal protein from meat, while animal protein derived from other sources was not associated with HF risk. As illustrated in Table 23, animal protein from meat was highly correlated to total meat consumption and, therefore, might simply replicate the findings observed for total meat. HRs of HF calculated for animal protein were very similar to those observed for total meat consumption. The scientific evidence on the relation between animal protein intake and the risk of CVD endpoints is very scarce. In the Nurses' Health Study no association was observed between overall animal protein intake and CHD, which is in contrast with the present findings.[124] However, an increase in risk due to protein from meat rather than milk products (as the main source of other animal protein) may be explained by different preparation techniques. Meat is typically eaten baked, grilled, fried or cooked, while milk products like yogurt are normally not heated before consumption. Heating processes alter the protein structure and induce the production of detrimental

compounds like heterocyclic aromatic amines during Maillard reaction. The carcinogenic effect of these amines is well known and the impact on heart health is yet not clear.[125]
A similar pattern of association was seen for iron intake. Iron from meat appeared to be positively related to HF risk, whereas the intake of iron from other sources showed an inverse association to HF development. Some investigations support an adverse effect of heme iron that might explain these differences.[126-128] Heme iron was reported to increase the risk of e.g. gallstones[128] and diabetes,[129] which both might be intermediates of CVD and thus HF.[130] One possible explanation might be that heme iron - that is only present in animal products - may act pro-oxidative and therefore induce damages to organ tissues, for instance the pancreas.[129, 131] However, both the association between intakes of iron from meat and from other sources were not significant after multivariable adjustment, suggesting that probably iron intake does not contribute to the risk-increasing association observed between meat intake and HF risk.
Although a 'true' positive association between iron or animal protein from meat and HF risk cannot be ruled out, less emphasis is given to these results as the mentioned pathways are mainly speculative and adequate evidence from other studies is lacking.

Marine n3FAs were examined as fat source driving the inverse association observed between fatty fish intake and HF risk. As expected, high intakes of DHA and EPA were associated with a decreased risk of HF. However, as the correlation between n3FAs and total fish consumption was very high, risk estimates were very similar to the ones observed in the analyses of fish consumption. Total and fish-specific DHA and EPA consumption were associated with a decreased risk of HF when consumed in high amounts. Regarding DHA and EPA from other sources no clear picture was observed, though HRs tended to a rather risk-increasing effect. Nevertheless, marine n3FAs from other sources than fish contributed only about 20% to total marine n3FA intakes and were mainly derived from meat and egg consumption. Residual confounding and correlations to detrimental components (like SFAs and cholesterol) might have impacted this finding.
The observed results are in agreement with the results from previous studies that examined the intakes of marine n3FAs and the risk of HF.[42, 44, 45 35] However, in the present work, a significant lower risk of HF was only observed in the highest versus the lowest quintile of intake. The general mechanisms behind the cardio-protective effect of EPA and DHA have been well explored. Marine n3FAs are reported to have anti-inflammatory, anti-thrombotic and anti-arrhythmic properties. Furthermore, the lipid-lowering effect of n3FAs has been described.[132, 133]

4.2 Critical Appraisal of Methods

In the present thesis, a dietary pattern has been identified *a priori* that seemed to be most promising to reduce the risk of HF: The Mediterranean diet. This diet has been related to heart health in ecologic, interventional and observational studies.

For analyses of the relationship between the adherence to the Mediterranean diet and the risk of HF a well-established Mediterranean diet score was used, the tMED. However, it was assumed that using the Greek median intake values as cut-points to separate participants into adherent and non-adherent to the diet, would increase the validity of the score to measure the Mediterranean diet in this non-Mediterranean population more accurately. The question arises whether this change of cut-points is somewhat arbitrary or justified. To answer this question, it is important to understand the consequences of this change: By using the median intakes of EPIC-Potsdam participants all tMED components were equivalent; for each component 50% of the population received either one or no point, respectively. One might think that, thus, all components contributed equally to the overall score. But not only is the percentage of persons that scored in a component of interest, it is rather the gradient of this percentage across the score categories. The first analyses (using the revised modified tMED with median values of EPIC-Potsdam as cut-points) demonstrated that the proportion of persons that received one point for a component was higher with higher overall scores, except for meat that was consumed in similar amounts in all categories. With the change to the Greek cut-points two main things happened: First, the uniform distribution of zeros and ones in each score component was abolished. Henceforth, in some components participants scored more and in some less frequently. Practically speaking, the contribution of *vegetables*, *fat-ratio* and *fruits and nuts* to the overall score was very low, since few participants received one point. Conversely more than 70% of the population scored in the groups of *legumes* and *cereals*. Second, the proportions of participants who were assigned one point for a certain component were redistributed across score categories. As a result, particularly the components *meat and meat products*, *alcohol* and *fish* experienced a considerably steeper slope across score categories, i.e. a more sufficient exposure gradient, compared to the first analysis using EPIC-Potsdam median intakes to generate the tMED. For instance, before changing to the Greek cut-points, 42% and 58% of persons received one point for the meat component in the lowest and highest tMED category, respectively. With the use of the Greek medians the respective proportions were 30% and 70%.

To sum up, there has thus been a shift of contributions of score components and the question remains whether this shift is justified or arbitrary. Actually, the change to the Greek median cut-points has led to a better discrimination of intakes of the food groups

that were identified as being the most important contributors to the inverse effect of the dietary pattern. In fact, the equalization of all score components without considering the scientific evidence and the components' proportions in the diet has already been criticized in the use of Mediterranean diet scores.[63] Furthermore, the identification of the most contributing components was independent of the analysis of the overall score and three methods were applied. One of these methods has previously been performed in the Greek population and moderate alcohol consumption and low intake of meat and meat products appeared to be the most contributing factors of the Mediterranean diet regarding mortality risk reduction, underlying the fact that a higher weighting of these food groups may be reasonable.[99]

However, until now the scientific literature revealed no clear picture of how to evaluate the Mediterranean diet properly. Many Mediterranean diet scores have been generated and at least as many changes have been made to the existing ones. There is no consensus about which components should be included in a score, and which not. Similarly, there are many approaches on appropriate cutoff values. However, so far the use of the Greek median values to define adherence was used only cross-sectionally.[134, 135]

In the present thesis, two main reasons were figured out that might have impacted the effectiveness of the Mediterranean diet defined by this score:

1. *Adherence to the Mediterranean Diet was too low among EPIC-Potsdam Participants to Provide a Sufficient Exposure Gradient*

The present study population generally showed a low adherence to the Mediterranean-style diet. The average score was 3.5 and score values reached only a maximum of seven out of nine possible points. Few participants achieved a score of more than 5 points (n = 687). On the other hand, similarly few people were assigned a scoring of zero or one point (n = 743). The comparison between the highest and the lowest adherence group was, thus, mainly a comparison between persons with two and persons with five score points. Taking this into account, it is not surprising that the overall diet-disease association narrowly missed the significance level. Despite these circumstances, a fairly strong association was observed, supporting the overall protective effect of the Mediterranean diet.

2. *Low Feasibility to Depict the 'Real' Mediterranean Diet in Non-Mediterranean Populations*

Only three out of nine Mediterranean diet score components were identified to play a role for HF development in the present study. However, it was assumed that an inverse

relationship between intakes of other score components and the risk of HF probably may exist, but that this could not sufficiently been demonstrated by the score.

The ratio between MUFAs and SFAs did not show a beneficial effect in terms of the risk of HF (see Appendix XIV and Figure 10). Even the inclusion of PUFAs in the numerator of the ratio did not alter this result (data not shown). Beside the generally low MUFA/SFA ratio in EPIC-Potsdam compared to the Greek population (on average <0.9 versus >1.7) it is believed that this lack of association arises from low comparability between fat sources of non-Mediterranean populations and the ones of Mediterranean countries.[136] In EPIC-Potsdam the fat-ratio reflected to a large extent the ratio between margarine and butter intake and was, furthermore, positively associated with meat consumption (data not shown). Thus, this component has little resemblance to the fat-ratio in Mediterranean countries where olive oil is the main source of fat. Margarine from mostly hydrogenated fats hardly contains essential fatty acids but may be a source of trans-fats that are related to adverse effects on the heart.[137] On the other hand, olive oil is rich in MUFAs (especially oleic acid) and thus may be a very important contributor to the cardio-protective effects of the Mediterranean diet.[109] A recent primary prevention trial demonstrated the preventive potential (regarding CVD morbidity and mortality) of a Mediterranean diet enriched with extra-virgin olive oil.[72]
Vegetable fat (including olive oil) was consumed in small amounts in EPIC-Potsdam. Therefore, in the current work the component *fat-ratio* was actually not present and, hence, the potential of the overall protective effect of the Mediterranean diet was weakened.

For similar reasons, the expected HF risk-lowering association might not have been confirmed in analyses of *fruits and nuts* and *vegetables* (Appendix XIV). The average daily intakes of these foods were very low compared to intakes of the Greek population (Table 7) and only few participants reached the German national recommended daily intakes of 650g of fruits and vegetables.[138] Besides the amount of intakes, food diversity and preparation methods may influence the heart health-promoting properties of these food groups. On the one hand, vitamins from vegetables may be lost due to cooking or discarding of washing water.[136] Furthermore, the proportion of raw consumed vegetables is higher in Mediterranean countries compared to non-Mediterranean ones. On the other hand, fruits in Mediterranean countries are presumably consumed more ripe and are richer in vitamins than the ones from non-Mediterranean countries.[136] Moreover, the proportion of tree nuts to peanuts might influence possible salutary effect of nut consumption (raw tree nuts eaten with skin in Mediterranean countries versus consumption of roasted and salted peanuts eaten in Western populations).[136] Therefore,

the tMED components *fruits and nuts* and *vegetables* might have shown no association to HF risk.[136] However, in line with the present study the few U.S. American studies that examined the association between these food groups and the risk of HF did not observe an association either, suggesting that there might be only a minor impact on heart health according to the consumption of vegetables, nuts and fruits.[36, 58]

In case of the components *cereals* and *legumes* risk-lowering associations might be masked due to putative harmful agents that are often consumed in parallel: The largest proportion of cereals came from bread, which might be salted or sweetened and consumed together with fat spread and sausage.[136] Sodium was reported to be positively associated to HF risk.[49] Furthermore, intakes of whole grain products were low, and especially consumption of these types of cereals have previously been associated to reduce HF risk.[36, 56] Legumes, interestingly eaten in higher amounts in EPIC-Potsdam compared to EPIC-Greece (see Table 7), might also be prepared in combination with fatty meat and salt.[136]

Moreover, there is a debate on how to include dairy products into Mediterranean diet scores. Of the 15 scores shown in Table 6 and Appendix III - Appendix VI, seven did not use this food group like initially suggested by Trichopoulou et al.[64]: two studies excluded milk products entirely from the score,[70, 139] in two investigations milk products were assessed as positive component,[140, 141] and another three research groups used whole-milk but not skimmed milk products as negative element of the score.[142-144] Actually, results of the present thesis indicate a HF risk-lowering tendency rather than a risk increase with higher intakes of milk products (Appendix XIV). Excluding milk products from the overall score even strengthened the inverse association between the adherence to the Mediterranean-style diet and HF risk (Figure 10). The intake of dairy products may imply a cardiovascular risk in Mediterranean populations but not in non-Mediterranean ones probably due to the higher fat content of dairy products in Mediterranean countries.[136] So far, only high-fat dairy products have been linked to increased HF risk.[36]

Despite these mentioned issues, an inverse relationship was observed between the adherence to the Mediterranean-style diet and the risk of HF that nearly reached the significance level. By means of a *top-down* approach, the main contributors of the inverse effect have been identified and with the further step on the nutrient level, possible agents have been detected that may have triggered these associations.

4.3 Limitations and Strengths

4.3.1 Limitations

The major limitation of the analysis on dietary pattern level was the low feasibility of the score to depict the Mediterranean diet properly in this non-Mediterranean population. At the level of nutrients, the ability to provide valid results was reduced due to the problem of multicollinearity. Compared to the analyses conducted at nutrient or dietary pattern level, those performed at the level of food group might, therefore, be considered more reliable.

Further limitations of this study warrant discussion:

First, in the present work diet was assessed by FFQ and nutrient intake was estimated by a link to the German Nutrient Data Base.[94] Thus, recall bias and measurement errors cannot be ruled out. However, the FFQ was validated by comparison with repeated 24h dietary recalls and due to the prospective study design, misclassification of exposure is supposed to be non-differential.[95] However, some food groups were not evaluated thoroughly enough to draw conclusions on their nutrient contents. For example, no distinction was made between tree nuts and peanuts or the varieties of fish species to assess precisely the intake of fatty fish. In addition, the validity of the FFQ data was relatively low for fish, nuts and legumes but might be underestimated as data of weekend consumption have not been considered in the validation study.[95] The questions included in the FFQ did also not allow distinguishing between red and white wine consumption. Furthermore, it was not possible to examine the influence of eating or drinking patterns over the day or week and a possible dietary change during follow-up. Also, reporting bias cannot be excluded though it is considered relatively low due to the generally high educational attainment of the study participants and the exclusion of implausible high or low energy intakes.

Second, the present study cannot prove causality. With the analyses at nutrient level it was possible to get more insights on the putative pathophysiological mechanisms underlying the results at higher nutritional levels (food groups), but to proof causality the conduction of interventional trials is necessary.

Third, HF cases were identified by self-report during the fourth follow-up wave. The possibility of false-positive and false-negative cases cannot be ruled out. However, due to the larger sample size of non-cases compared to cases, the impact of false-positives on the results is considered much stronger than that of false-negative ones. Many efforts

have been made to exclude false-positive cases, including validation by the study physician and application of ESC criteria. Moreover, agreement between case ascertainment by self-reporting and by physician diagnosis is supposed to be very high (sensitivity: 88.5%).[145] Therefore, the possibility of false-positive cases is considered relatively low.

Fourth, the study did not provide sufficient cases of each type of HF to allow these to be examined separately. Less diastolic than systolic HF cases have been diagnosed in the analyses, although it was suggested that incidence rates of both types might be similar.[4] Results may, therefore, be more representative for systolic HF. However, as the diagnosis of diastolic HF appears to be more critical, the proportion of diastolic HF cases among 'unknown' cases might be larger compared to systolic HF cases.

Furthermore, like all prospective observational studies, also the present one was prone to potential uncontrolled or imperfectly measured confounders. Similar to the 'sick quitters bias', where results may be distorted due to misclassification and misinterpretation of an alleged non-smoker or non-drinker, who has actually desisted from smoking / drinking due to an onset of illness, this 'sick quitters bias' may also be relevant for nutritional behaviour and a change in the diet (e.g. quitting meat consumption or starting vegetable consumption). However, sensitivity analyses excluding persons that reported a dietary change in the previous years and the exclusion of cases that occurred during the first two years did not change the result.

Lastly, the effectiveness of the Mediterranean diet in Mediterranean countries is thought to be not only influenced by diet, but also by other lifestyle factors (siesta, sociability) and the exposure to sun. All factors which were less important in Western populations and were not assessed in the present study. Furthermore, other parts of the Mediterranean diet – not included in the used score - might be important for heart health. The literature research revealed possible health-promoting effects of moderate coffee consumption that is also common practice in Mediterranean countries.[146, 147] On the other hand, consumption of eggs has been found to be positively associated to HF risk in two studies.[36, 57] Three servings of eggs per week is the amount of intake suggested in the Mediterranean diet pyramid (Figure 3). Similarly the role of salt/sodium might be important which could not be investigated in the present study.[49, 52, 53]

4.3.2 Strengths

Major strengths of the present study include the prospective design and the large sample size based on a general population. Furthermore, it was possible to adjust for a various set of covariates. Moreover, a *top-down* approach is regarded as a useful method to illustrate comprehensively the relationships between diet and disease outcomes on the basis of hypotheses drawn upon prior knowledge. Thereby, it was possible to identify most important factors of the Mediterranean diet (regarding the prevention of HF) on the basis of evidence-based hypotheses with the public health goal to contribute to specific recommendations in a still little explored area of research.

4.4 Conclusions

The present work is the first to report on the association between the adherence to a Mediterranean-style dietary pattern and the development of HF in a non-Mediterranean population of apparently healthy adults. Furthermore, it is the first investigation that systematically examined aspects of the diet on different levels of nutrition on the basis of prior knowledge, thereby offering key factors that contribute most to the overall effect of the dietary pattern. This allows deeper insights in possible underlying mechanisms linking diet to the risk of HF.

The results indicate that the adherence to a Mediterranean-style diet may play an important role in the prevention of HF. So far, a number of studies have investigated possible relationships between some of the single food groups included in the Mediterranean diet score and HF risk. However, in most investigations single food groups were examined without being able to compare the impact of single dietary components in a context of a diet. In the present work it was possible to draw conclusions about the relative importance of the intake of individual food groups within a Mediterranean-style dietary pattern. The results suggest that the cardio-protective effect essentially relies on three factors of the diet, namely moderate alcohol consumption, low consumption of meat and meat products and high fish intake. Beside the moderate consumption of beer and especially wine, particularly fatty fish was inversely and processed meat was positively associated with the risk of developing HF. The fat quality was identified as a possible reason for these findings.

To investigate the Mediterranean diet in a non-Mediterranean country was quite challenging. There is still a need for a more precise and quantified definition of the Mediterranean dietary pattern. The present work has dealt particularly with the feasibility of Mediterranean diet scores and provides useful information to improve applicability in

non-Mediterranean countries. Considered problematic were particularly the lack of consumption of some Mediterranean components (e.g. olive oil), the very divergent median intakes of the present population compared to that of Mediterranean countries (e.g. fruits and vegetables), and the different foods reflected by some components (e.g. cooked vegetables in non-Mediterranean countries versus mainly raw vegetables, like salads in Mediterranean ones).

The assessment of compliance by means of population-specific median values might not be appropriate to depict the 'true' Mediterranean diet in non-Mediterranean countries. The use of Greek median values seems superior, but seems not applicable for some elements of the diet. However, changing the cut-points alone may not be sufficient enough to improve the validity of the score. It might be reasonable to think of a proper way to weight the score components according to the importance of the effects on health outcomes.

Based on the presented results, it is suggested that a change from the commonly used fat-ratio to the amount / proportion of SFA in the diet might be reasonable, at least in a non-Mediterranean country where olive oil is hardly consumed.

Findings of the present thesis might be of great public health relevance, as HF is an outcome that covers several sorts of heart disorders more comprehensively than CHD, for instance. Health promoting strategies for HF prevention, therefore, might be more effective to improve general heart health. The intakes of specific foods are most appropriate to communicate public health recommendations. Thus, the presented results could be translated in the public health message that a moderate change of dietary habits may have strong impact on heart health, when primarily the three identified factors are involved: lowering the intakes of meat (particularly processed meat), increasing the intake of fatty fish, and consuming moderate amounts of alcoholic beverages, mainly in form of red wine. However, it should not be recommended to non-drinkers to drink alcohol only for the suspected health benefits, and those drinking excessively it should be recommended to stop as the risks of abuse and / or addiction may exceed the protective potential of a moderate and responsible alcohol use.

The identified food groups might also be included in HF risk prediction models, in addition to the already established conventional risk factors to improve HF risk stratification.

However, further studies are warranted to replicate and validate the findings observed in this thesis.

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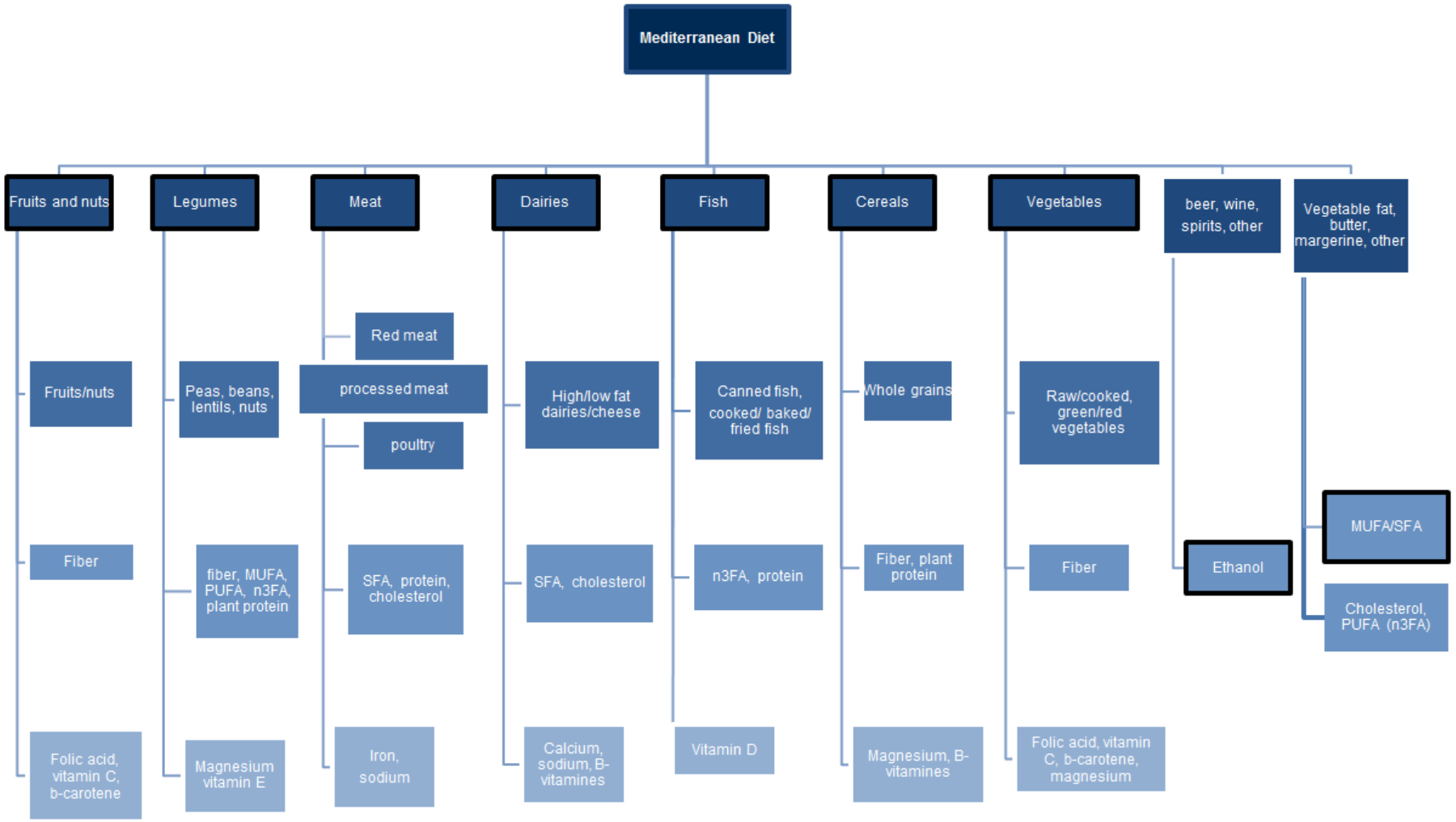
INDEX OF APPENDICES

Appendix I: ACC/AHA Classification of Heart Failure (Source: ACC/AHA Guidelines, p. 1981) [6]

STAGE	DESCRIPTION
A	High risk for HF but no structural heart disease or symptoms of HF (e.g. patients with hypertension, diabetes, obesity, …)
B	Structural heart disease but no signs* or symptoms* of HF (e.g. patients with previous myocardial infarction, asymptomatic valve disease, …)
C	Structural heart disease with prior or current symptoms of HF (e.g. patients with known structural heart disease and shortness of breath or reduced exercise tolerance, …)
D	Refractory HF requiring specialized intervention (e.g. patients with symptoms at rest despite maximal medical therapy, …)

*symptoms and signs of HF are described in in Chapter 1.2.2
Abbreviation: ACC, American College of Cardiology; AHA, American Heart Association; HF, heart failure

Appendix II: Component Levels of the traditional Mediterranean Dietary Pattern



Black outlines are the components of the Mediterranean diet score like proposed by Trichopoulou et al.[65]
Abbreviations: MUFA; monounsaturated fatty acids; n3FA, omega-3 fatty acid; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids

Appendix III: Mediterranean Diet Scores Based on Medians as Cut Point for Adherence and Non-Adherence to the Mediterranean Dietary Pattern

First Author Year	Study Population	No. of Components	Positive Components	Negative Components	Score Cut Points	Score Range	Account for Energy	Adapted or Modified by
3) Adapted Mediterranean Diet Score (AMED)								
Van Staveren 2002[141]	SENECA-study, 12 European countries	7	1. MUFA/SFA-ratio 2. Moderate alcohol 3. Legumes/nuts/seeds 4. Cereals 5. Fruits/vegetables 6. Moderate milk/milk products	1. Meat/meat products	Sex-specific medians* $p25^{th}$-$p75^{th}$ for dairy, $\geq p75^{th}$ for alcohol in women	0-7	Intakes were adjusted to 2000 kcal (women) /2500 kcal (men)	–
4) Mediterranean Diet (MD)								
Issa 2011[143]	Random sample of residents from Mount Lebanon	11	1. Olive oil/SFA ratio 2. Legumes 3. Total cereals 4. Whole grains 5. Fruits 6. Vegetables 7. Fish	1. Meat/poultry 2. Whole milk/dairy products 3. Sweetened beverages 4. Refined grains	Sex-specific medians*	0-11	Not accounted for	–
5) Mediterranean Diet Scale (MDS)								
Asghari 2012[148]	Teheran Lipid and Glucose Study (TLGS)	10	1. PUFA/SFA ratio 2. Legumes 3. Whole grains 4. Fruits 5. Nuts 6. Vegetables 7. Fish	1. Ratio of red and processed to white meat 2. Dairy products 3. Refined grains	Medians*	0-10	Adjusted for total energy intake	1 study

* persons receive 0 points for intakes ≤ median and 1 point for intakes ≥ median in case of positive components and reverse for negative components, Please note that names and abbreviations of the scores are partly arbitrary chosen and not used by the authors who generated them

Abbreviations: MUFA, monounsaturated fatty acids; p, percentile; PUFA, polyunsaturated fatty acids; SENECA, Survey in Europe on Nutrition and the Elderly; a Concerted Action; SFA, saturated fatty acids

Appendix IV: Mediterranean Diet Scores Based on Tertiles as Cut Point for Adherence and Non-Adherence to the Mediterranean Dietary Pattern

First Author Year	Study Population	No. of Components	Positive Components	Negative Components	Score Cut Points	Score Range	Account for Energy	Adapted or Modified by
6) Mediterranean Diet Score (Mediscore)								
Schröder 2004[142]	Spanish men and women from the province of Girona	9	1. Moderate red wine (>0g-20g/d=3, otherwise=1) 2. Legumes 3. Cereals 4. Fruits 5. Vegetables 6. Nuts 7. Fish	1. Meat/meat products 2. High-fat dairy	T1=1, T2=2, T3=3 points for positive components, vice versa for negative	9-27	Adjusted for total energy intake	1 study
7) Relative Mediterranean Diet Score (rMED)								
Buckland 2009[149]	EPIC-Spain	9	1. Olive oil 2. Moderate alcohol (w: 5-25g/d, m=10-50g/d) 3. Legumes 4. Cereals 5. Fruits/seeds/nuts 6. Vegetables 7. Fish	1. Meat/meat products 2. Milk/milk products	T1=0, T2=1, T3=2 points for positive components, vice versa for negative	0-18	All components were expressed as energy density (g/1000kcal/d or g/2000kcal/d))	8 studies
8) Italian Mediterranean Index (IMI)								
Agnoli 2011[139]	EPICOR, cohort of Italian volunteers from EPIC-Italy	11	1. Olive oil 2. Moderate alcohol (>0-≤12g/d) 3. Legumes 4. Pasta 5. Fruits 6. Typical Italian vegetables 7. fish	1. Red meat 2. Butter 3. Soft drinks 4. Potatoes	T1&T2=0, T3=1 point for positive components, vice versa for negative	0-11	Adjusted for total energy intake	—

Please note that names and abbreviations of the scores are partly arbitrary chosen and not used by the authors who generated them
Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; T, tertile

Appendix V: Mediterranean Diet Scores Based on Percentages of Adherence and Non-Adherence to the Mediterranean Dietary Pattern

First Author Year	Study Population	No. of Components	Positive Components	Negative Components	Score Cut Points	Score Range	Account for Energy	Adapted or Modified by
9) Mediterranean Adequacy Index (MAI)								
Alberti-Fidanza & Fidanza 2004,[150] (also see Fidanza 2004[151])	different areas of Italy	18	1. Vegetable oil 2. Red wine 3. Legumes 4. Cereals 5. Fruits 6. Vegetables 7. Fish 8. Bread 9. Potatoes	1. Milk 2. Cheese 3. Eggs 4. Animal fats 5. Margarine 6. Sweet beverages 7. Cakes 8. Pies and cookies 9. Sugar	% of total energy from positive components divided by % of total energy from negative components	No finite range, higher scores reflect higher adherence (normal: 4-8 points)	Intakes expressed as % of total energy intake	6 studies
10) Mediterranean-style Dietary Pattern Score (MSDPS)								
Rumawas 2009[140]	Framingham Offspring Study	13	1. Olive oil (exclusive) 2. Moderate alcohol (w:1.5, m:3/d) 3. Olives/legumes/nuts (4 s/wk) 4. Whole grains (8 s/d) 5. Fruits (3 s/d) 6. Vegetables (6 s/d) 7. Dairy products (2 s/d) 8. Fish (6 s/wk) 9. Poultry (4 s/wk)	1. Meat (1 serving/week) 2. Sweets (3 s/wk) 3. Potatoes/starchy roots (3 s/wk) 4. Eggs (3 s/wk)	% of achieved recommendation 100%=10 points 60%/140%=6 points	0-100	Weighted by the proportion of energy consumed from Mediterranean diet foods	5 studies
11) Mediterranean Dietary Pattern (MDP)								
Sanchez-Villegas 2002[152]	Cohort of alumni of university of Navarra	9	1. MUFA/SFA ratio 2. Moderate alcohol (w: 20g/d, m: 30g/d) 3. Legumes 4. Cereals/potatoes 5. Fruits 6. Vegetables	1. Meat/meat products 2. Milk/milk products 3. Trans fat	Standardized to SD, converted to relative %, score= sum of standardized components	0-100	Energy-adjusted values of intake	1 study

Please note that names and abbreviations of the scores are partly arbitrary chosen and not used by the authors who generated them
Abbreviations: MUFA, monounsaturated fatty acid; s/d, serving per day; s/wk, servings per week; SD, standard deviation; SFA, saturated fatty acid

Appendix VI: Mediterranean Diet Scores Based on Frequencies and other Cut Points

First Author Year	Study population	No. of components	Positive components	Negative components	Score cut points	Score range	Account for energy	Adapted or modified by
12) Mediterranean Diet Quality Index (MDQI)								
Scali 2001[108]	Random sample, Southern France	7	1. Olive oil 2. Cereals 3. Fruits/vegetables 4. Fish	1. Meat 2. Cholesterol 3. % SFA	Points (0-2) possible depending on specific cut points	0-14 Lower= healthier	Not further accounted for (but in SFA included)	1 study
13) Mediterranean Diet Score (MED)								
Panagiotakos 2004[144]/2006[153]	ATTICA, Greece	11	1. Olive oil 2. Moderate alcohol 3. Legumes 4. Non-refined cereals 5. Fruits 6. Vegetables 7. Fish 8. Potatoes	1. Red and processed meat 2. Poultry 3. Full-fat dairy products	Frequencies 0-5 points for no to almost daily consumption	0-55	Not accounted for in 2004 In 2006 regression models were adjusted for energy intake	11 studies
14) Modified Traditional Score (MTS)								
Bertoia 2014[154]	WHI, USA	10	1. % fat from PUFA+MUFA 2. Legumes/nuts 3. Whole grains 4. Fruits 5. Vegetables 6. Fish	1. Red meat 2. Poultry 3. Dairy products	<25th percentile =1, 25th-75th=2, >75th=3	0-40	Adjusted for total energy intake	–
15) Modified Mediterranean Diet Score (mMEDI)								
Yang 2014	Cohort of firefighters, US Midwest	10	1. Olive oil/others (0-4 points) 2. Moderate alcohol (0-4 points) 3. Wine (2 points) 4. Type of drinks (0-4 points) 5. Type of cereals (0-4 points) 6. Fruits/vegetables (0-8 points) 7. Fish (0-4 points)	1. Fast/take-out food (4-0 points) 2. Sweet dessert (4-0 points) 3. Fried foods (4-0 points)	Depending on category/ frequency	0-42	Not accounted for	–

Please note that names and abbreviations of the scores are partly arbitrary chosen and not used by the authors who generated them

Abbreviations: ATTICA, region in Greece; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; WHI, Women's Health Initiative

Appendix VII: Association between the Revised Modified tMED Score and the aMED Score and the Risk of Heart Failure

	tMED score*				
	0-3	4-5	6-9		
n (cases)	6,307 (53)	11,172 (113)	6,529 (43)		
Person-years	52,038	92,073	53,923		
	HR	**HR (95% CI)**	**HR (95% CI)**	**p for trend**	**per 2 units increase**
Model 1	1	1.31 (0.82-2.12)	0.96 (0.65-1.41)	0.07	0.83 (0.70-0.99)
Model 2	1	1.21 (0.75-1.96)	0.89 (0.60-1.32)	0.22	0.87 (0.73-1.04)
Model 3	1	1.30 (0.80-2.09)	0.93 (0.63-1.38)	0.10	0.84 (0.71-1.00)
	aMED score#				
	0-3	4-5	6-9		
n (cases)	4,272 (38)	15,197 (142)	4,539 (29)		
Person-years	35,310	125,266	37,458		
	HR	**HR (95% CI)**	**HR (95% CI)**	**p for trend**	**per 2 units increase**
Model 1	1	1.03 (0.75-1.41)	0.69 (0.47-1.01)	0.07	0.89 (0.75-1.04)
Model 2	1	1.10 (0.80-1.51)	0.79 (0.53-1.16)	0.27	0.94 (0.80-1.11)
Model 3	1	1.07 (0.78-1.46)	0.75 (0.51-1.10)	0.17	0.92 (0.78-1.08)

Model 1: adjusted for sex and energy intake, stratified for age; Model 2: further adjusted for lifestyle (smoking, education, physical activity); Model 3: further adjusted for anthropometry (BMI and waist circumference) and prevalent comorbidities (diabetes, CHD, hypertension and hyperlipidemia); *based on the score by Trichopoulou et al.[66]; # based on the score by Fung et al.[68]

Appendix VIII: Baseline Characteristics* of the Study Population according to Scoring of the Revised traditional Mediterranean Diet Score (tMED) using EPIC-Potsdam Median cut-off Values

	tMED score§		
Characteristics	0-3	4-5	6-9
n (cases)	6,307 (53)	11,172 (113)	6,529 (43)
Demographics, Lifestyle and Medical History			
Gender, % female	63.8	61.5	59.6
Age, mean, years	49.5 (8.8)	50.1 (8.8)	50.2 (8.8)
Body mass index, kg/m^2	26.2 (0.1)	26.3 (0.0)	26.3 (0.1)
Waist circumference, cm			
Men	94.3 (0.2)	94.6 (0.2)	94.8 (0.2)
Women	80.1 (0.2)	80.5 (0.1)	80.4 (0.2)
University Degree, %	36.1	39.7	44.4
Current smoking, %	16.6	15.0	13.7
Physical activity, hrs/wk	2.46 (0.04)	2.72 (0.03)	3.19 (0.04)
Medical History, %			
Prevalent hypertension	44.8	46.7	47.3
Prevalent diabetes	4.7	4.3	4.7
Prevalent hyperlipidemia	26.2	26.8	28.9
Total energy intake, MJ/d	8,850 (30)	9,054 (22)	9,310 (29)
Scored Components			
Alcohol intake, g/d	14.5 (0.2)	15.4 (0.2)	16.8 (0.2)
Moderate intake§	28.3	51.7	72.8
Fruits and nuts intake, g/d	100 (1.1)	140 (0.9)	180 (1.1)
≥ Median, %	23.0	49.3	76.4
Vegetables intake, g/d	72.7 (0.6)	97.6 (0.5)	125.9 (0.6)
≥ Median, %	20.6	49.1	79.1
Cereal intake, g/d	184 (0.9)	206 (0.7)	225 (0.9)
≥ Median, %	30.2	49.9	69.3
Fish intake, g/d	16.7 (0.3)	23.8 (0.2)	32.3 (0.3)
≥ Median, %	25.7	51.4	76.8
Legumes intake, g/d	17.5 (0.2)	23.8 (0.2)	30.3 (0.2)
≥ Median, %	26.3	49.7	72.5
Fat-ratio	1.19 (0.00)	1.31 (0.00)	1.43 (0.00)
≥ Median, %	22.1	50.3	76.7
Meat products intake, g/d	122 (0.7)	121 (0.6)	118 (0.7)
< Median, %	42.4	49.2	58.1
Milk products intake, g/d	283 (2.7)	222 (2.0)	183 (2.6)
< Median, %	32.4	50.3	66.4

*Baseline characteristics are expressed as age- and sex-adjusted means (standard error) or percentages, age and sex are unadjusted means (standard deviation) or percentages; § tMED was calculated according to Trichopoulou et al.[66] using median values of the EPIC-Potsdam population: fruits: men= 94.2 g, women= 130.9 g; vegetables: men= 81.3 g, women= 96.9 g; cereals: men= 223.2 g, women= 173.2 g; legumes: men= 23.2 g, women= 14.5 g; fish: men= 23.0 g, women= 16.4 g; (MUFA+PUFA)/SFA-ratio: men= 1.32, women= 1.29; meat: men= 136.0, women= 87.0; milk: men= 152.9, women= 189.9 g; § moderate consumption is defined as follows: men ≥10 g/d – 50 g/d, women ≥ 5g/d – 25 g/d

Abbreviations: MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; tMED, traditional Mediterranean diet score

Appendix IX: Baseline Characteristics* of the Study Population according to Scoring of the Alternate Mediterranean Diet Score (aMED)

	aMED score§		
Characteristics	0-3	4-5	6-9
n (cases)	4,272 (38)	15,197 (142)	4,539 (29)
Demographics, Lifestyle and Medical History			
Gender, % female	66.6	61.5	57.0
Age, mean, years	49.5 (8.8)	50.0 (8.8)	50.3 (8.8)
Body mass index, kg/m^2	26.3 (0.1)	26.3 (0.0)	26.0 (0.1)
Waist circumference, cm			
Men	94.8 (0.3)	94.6 (0.1)	94.1 (0.2)
Women	80.5 (0.2)	80.5 (0.1)	79.8 (0.2)
University Degree, %	34.7	40.0	45.1
Current smoking, %	16.2	14.7	15.3
Physical activity, hrs/wk	2.52 (0.05)	2.79 (0.03)	2.98 (0.05)
Medical History, %			
Prevalent hypertension	45.5	46.8	45.9
Prevalent diabetes	5.8	4.5	3.4
Prevalent hyperlipidemia	27.5	27.4	26.5
Total energy intake, MJ/d	8,990 (36)	9,108 (19)	9,023 (35)
Scored Components			
Alcohol intake, g/d	13.3 (0.2)	15.6 (0.1)	17.4 (0.2)
Moderate intake§	10.1	33.1	59.4
Fruits intake, g/d	124 (1.4)	135 (0.8)	156 (1.4)
≥ Median, %	46.3	49.6	54.2
Vegetables intake, g/d	92.8 (0.8)	98.9 (0.4)	104.4 (0.8)
≥ Median, %	44.9	50.2	53.4
Whole grain Cereal intake, g/d	40.0 (0.9)	50.0 (0.5)	58.0 (0.9)
≥ Median, %	42.7	50.0	56.6
Fish intake, g/d	15.6 (0.4)	23.7 (0.2)	34.2 (0.4)
≥ Median, %	24.7	50.1	81.5
Legumes intake, g/d	18.4 (0.3)	24.5 (0.2)	27.0 (0.3)
≥ Median, %	34.3	51.7	58.1
Fat-ratio	0.84 (0.00)	0.86 (0.00)	0.87 (0.00)
≥ Median, %	42.8	50.7	54.8
Nuts intake, g/d	2.92 (0.1)	3.30 (0.1)	3.67 (0.1)
≥ Median, %	53.6	59.7	64.2
Red and processed Meat intake, g/d	118 (0.8)	110 (0.4)	92 (0.8)
< Median, %	34.7	48.4	68.3

*Baseline characteristics are expressed as age- and sex-adjusted means (standard error) or percentages, age and sex are unadjusted means (standard deviation) or percentages; § aMED was calculated according to Fung et al.[68] using median values of the EPIC-Potsdam population: fruits: men= 94.2 g, women= 130.9 g; vegetables: men= 81.3 g, women= 96.9 g; whole grain cereals: men= 19.9 g, women= 36.6 g; legumes: men= 23.2 g, women= 14.5 g; fish: men= 23.0 g, women= 16.4 g; MUFA/SFA-ratio: men= 0.86, women= 0.84; red and processed meat: men= 122.3 g, women= 75.7 g; nuts: men= 0.82 g, women= 0.82 g; § moderate consumption was defined as follows: men ≥10 g/d – 25 g/d, women ≥ 5g/d – 15 g/d

Abbreviations: aMED, alternate Mediterranean diet score; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid

Appendix X: The traditional revised Mediterranean diet according to Trichopoulou et al. 65 and its components and composition of food items as used in EPIC-Potsdam

MEDITERRANEAN FOOD COMPOUND (LOADING)	CONTAINING FOOD GROUPS	CONTAINING FOOD ITEMS (LIKE IN THE FFQ)
Vegetables (+)	Raw vegetables	1. Head, endive, lettuce, Chinese cabbage and / or lettuce 2. Mixed salad 3. Carrots 4. Seeds, sprouts 5. Raw peppers, chili pepper 6. Cucumber 7. Radish, radishes, cabbage salad 8. Red tomato 9. Raw onion
	Cabbage	1. Cauliflower, red cabbage, white cabbage, kohlrabi, broccoli or other cruciferous vegetables
	Cooked vegetables	1. Tomato vegetables, tomato sauce 2. Cooked pepper 3. Zucchini, eggplant or other fruit vegetables 4. Spinach 5. Cooked carrots 6. Leek 7. Salsify, celeriac 8. Asparagus 9. Cooked peas and carrots, 'Leipziger Allerlei', Ratatouille 10. Pickled cabbage
	Garlic	1. Cooked/roasted garlic
	Mushrooms	1. Meals with mushrooms 2. Fresh mushrooms (not canned mushrooms)
Fruits and nuts (+)	Fresh fruit	1. Apple (winter and summer) 2. Pear 3. Peach, nectarine 4. Cherries, prunes, mirabelles or other stone fruit 5. Grapes 6. Strawberries 7. Currants, raspberries, blackberries, or other berry fruits 8. Kiwi, fresh pineapple, mango (in summer) 9. Banana 10. Orange and grapefruit 11. Mandarins
	Nuts	1. Nuts (like peanuts, walnuts, Brazil nuts, ...)
Legumes (+)	Legumes	1. Green pea 2. Green beans 3. Lentil, pea, bean stew
Fish (+)	Fish	1. Canned fish, smoked fish (e.g. tuna, pickled herring, salmon, smoked trout) 2. Fish (e.g. fish fillet natural or breaded, fish sticks, ...)
alcohol from beverages (+/-)	1. Beer	2. Beer
	2. Wine	1. Wine
	3. Spirits	1. Spirits (e.g. brandy, whiskey, fruit brandy, rum, ...)
	4. Other alcoholic beverages	1. Fruit wine (e.g. apple cider, ...) 2. Sparkling wine 3. Aperitif, dessert wine, liqueurs (e.g. sherry, port)

Abbreviations: FFQ, food frequency questionnaire

Appendix X continued

MEDITERRANEAN FOOD COMPOUND (LOADING)	CONTAINING FOOD GROUPS	CONTAINING FOOD ITEMS (LIKE IN THE FFQ)
Meat (-)	1. Red meat	1. Beef steak, tenderloin, loin 2. Roast beef, boiled meat 3. beef rolls 4. Beef stew, beef strips 5. Pork goulash, Strips of pork 6. Smoked pork, pork ribs 7. Boiled pork, pork knuckle, knuckle 8. Pork belly 9. Meatball, hamburger, meatloaf 10. Meat sauce, hash 11. Liver 12. Veal, lamb, rabbit
	2. Processed meat	1. Fried sausage 2. 'Wieners', ‚Frankfurters', bockwurst, knackwurst, German meatloaf
	3. Poultry	1. Broiler 2. Sliced turkey, turkey cutlets, chicken fricassee, duck, goose
Fat-ratio (+) MUFA/SFA		1. Butter 2. Margarine 3. Other vegetable fat 4. Other fat 5. Fat from all other sources*
Cereals (+)	1. Whole grain bread	1. Whole grain bread 2. Dark and whole meal rolls
	2. Other bread	1. Brown bread, rye bread, rye bread 2. White bread, wheat bread, toast 3. Bread roll 4. Croissants, pretzels
	3. Grain flakes	1. Cereal flakes, grains, muesli
	4. Cornflakes	1. Cornflakes, crisps,…
	5. Pasta and rice	1. Pasta (e.g. spaghetti, ravioli, lasagna, ... main dish or side order) 2. Rice (risotto, paella, ... main dish or side order)
Dairy products (-)	1. Low fat dairies	1. Milk, milk drink (≤1.5% fat) 2. Yogurt (natural) (1.5% fat or less) 3. Yoghurt (fruit) (1.5% fat or less) 4. Soured milk, kefir 5. Curd, curd cheese with herbs (no fruit curd) (low fat)
	2. High fat dairies	1. High fat curd (natural/with herbs), milk, milk drink (3.5% fat) 2. Yogurt (natural) (3.5% fat or more) 3. Yoghurt (fruit) (3.5% fat or more) 4. Whipped cream
	3. Low fat cheese	1. Cream cheese (low fat) 2. Hard cheese (low fat) 3. Soft cheese (low fat)
	4. High fat cheese	1. Cream cheese (high fat) 2. Hard cheese (high fat) 3. Soft cheese (high fat) 4. Cheese spread

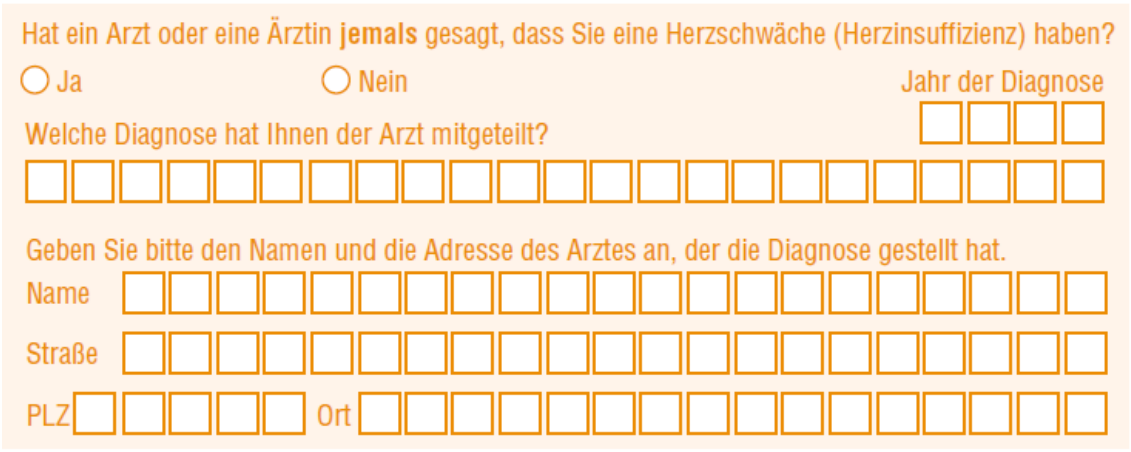
Abbreviations: FFQ, food frequency questionnaire; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid

Appendix XI: Association between the Modified tMED Score using Cut-Points Proposed by Sofi et al. and the Risk of Heart Failure

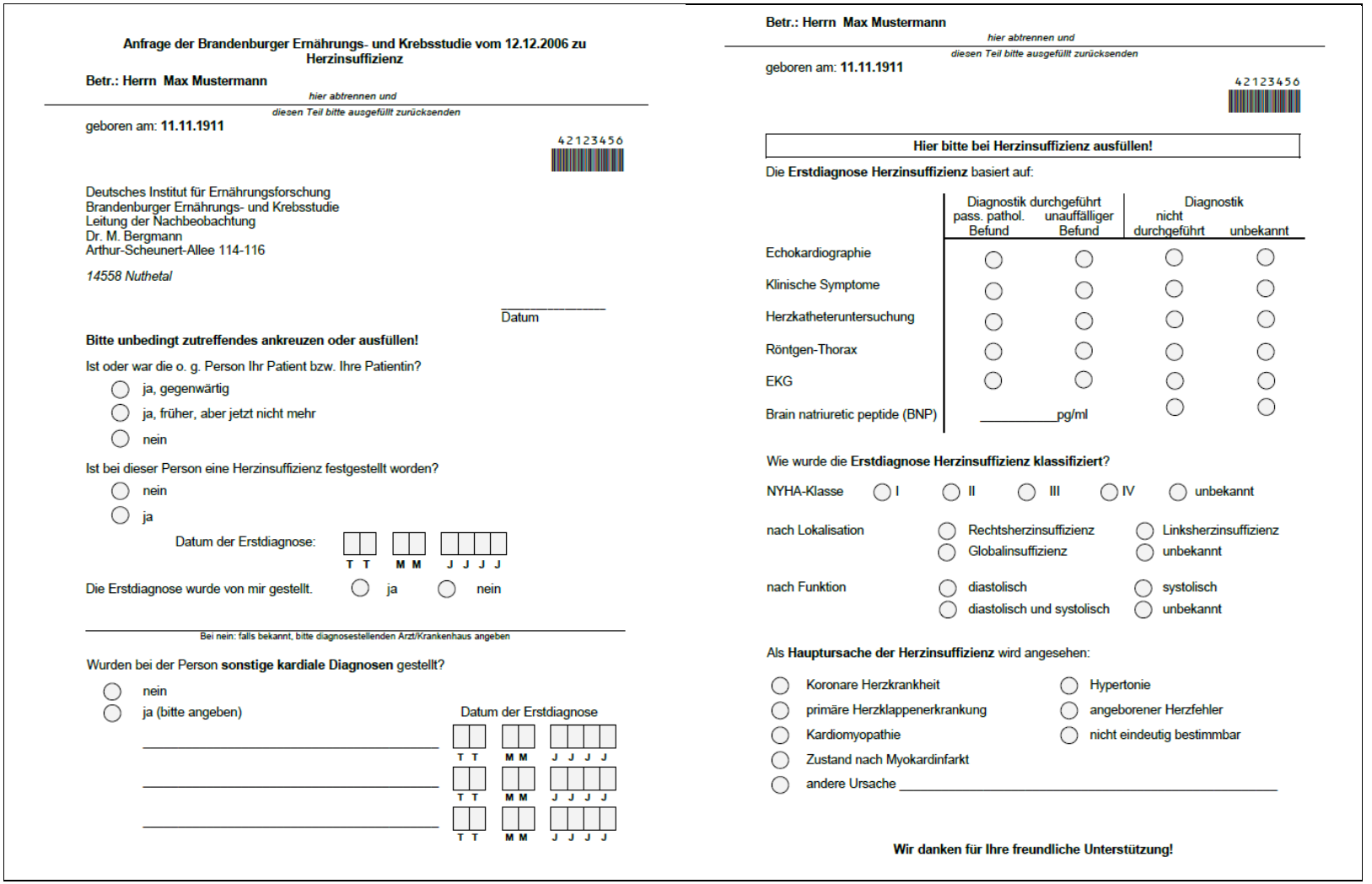
	tMED*				
	0-5	**6-8**	**9-13**		**per 2 units**
n (cases)	2,850 (20)	12,253 (93)	8,905 (96)		
Person-years	23,515	101,258	73,261		
	HR	**HR (95%CI)**	**HR (95%CI)**	**p for trend**	**HR (95%CI)**
Model 1	1	0.88 (0.54-1.43)	1.09 (0.67-1.77)	0.33	1.06 (0.92-1.23)
Model 2	1	0.93 (0.57-1.52)	1.20 (0.74-1.95)	0.17	1.10 (0.95-1.27)
Model 3	1	0.91 (0.56-1.48)	1.21 (0.74-1.97)	0.07	1.12 (0.96-1.30)

Model 1: adjusted for sex and energy intake, stratified for age; Model 2: further adjusted for lifestyle (smoking, education, physical activity); Model 3: further adjusted for anthropometry (BMI and waist circumference) and prevalent comorbidities (diabetes, CHD, hypertension and hyperlipidemia); *based on the score by Trichopoulou et al.[66], modified by Sofi et al.[67]

Appendix XII: Extract from the Questionnaire of the Fourth Follow-up including the Question about Heart Failure



Appendix XIII: Validation Form for Heart Failure in EPIC



Anfrage der Brandenburger Ernährungs- und Krebsstudie vom 12.12.2006 zu Herzinsuffizienz

Betr.: Herrn Max Mustermann

hier abtrennen und diesen Teil bitte ausgefüllt zurücksenden

geboren am: **11.11.1911**

42123456

Deutsches Institut für Ernährungsforschung
Brandenburger Ernährungs- und Krebsstudie
Leitung der Nachbeobachtung
Dr. M. Bergmann
Arthur-Scheunert-Allee 114-116

14558 Nuthetal

_____
Datum

Bitte unbedingt zutreffendes ankreuzen oder ausfüllen!

Ist oder war die o. g. Person Ihr Patient bzw. Ihre Patientin?

- ◯ ja, gegenwärtig
- ◯ ja, früher, aber jetzt nicht mehr
- ◯ nein

Ist bei dieser Person eine Herzinsuffizienz festgestellt worden?

- ◯ nein
- ◯ ja

Datum der Erstdiagnose: T T M M J J J J

Die Erstdiagnose wurde von mir gestellt. ◯ ja ◯ nein

_____
Bei nein: falls bekannt, bitte diagnosestellenden Arzt/Krankenhaus angeben

Wurden bei der Person **sonstige kardiale Diagnosen** gestellt?

- ◯ nein
- ◯ ja (bitte angeben)

	Datum der Erstdiagnose
_____	T T M M J J J J
_____	T T M M J J J J
_____	T T M M J J J J

Betr.: Herrn Max Mustermann

hier abtrennen und diesen Teil bitte ausgefüllt zurücksenden

geboren am: **11.11.1911**

42123456

Hier bitte bei Herzinsuffizienz ausfüllen!

Die **Erstdiagnose Herzinsuffizienz** basiert auf:

	Diagnostik durchgeführt pass. pathol. Befund	Diagnostik durchgeführt unauffälliger Befund	Diagnostik nicht durchgeführt	Diagnostik unbekannt
Echokardiographie	◯	◯	◯	◯
Klinische Symptome	◯	◯	◯	◯
Herzkatheteruntersuchung	◯	◯	◯	◯
Röntgen-Thorax	◯	◯	◯	◯
EKG	◯	◯	◯	◯
Brain natriuretic peptide (BNP)	_____pg/ml		◯	◯

Wie wurde die **Erstdiagnose Herzinsuffizienz klassifiziert**?

NYHA-Klasse ◯ I ◯ II ◯ III ◯ IV ◯ unbekannt

nach Lokalisation
- ◯ Rechtsherzinsuffizienz
- ◯ Linksherzinsuffizienz
- ◯ Globalinsuffizienz
- ◯ unbekannt

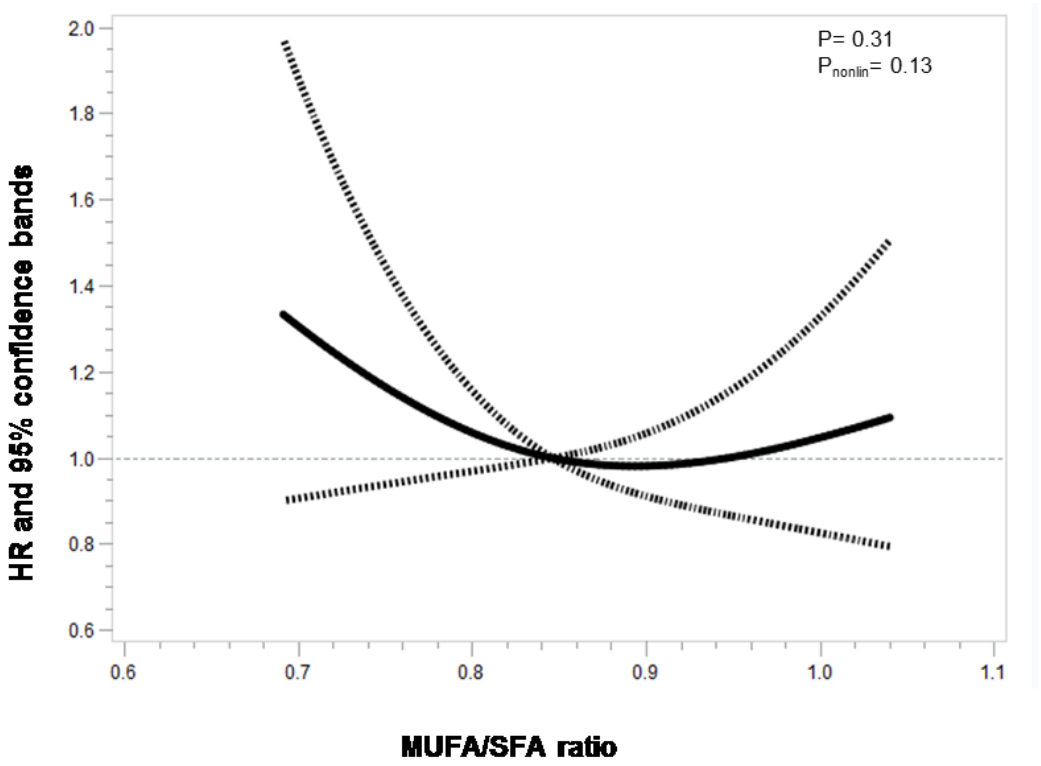
nach Funktion
- ◯ diastolisch
- ◯ systolisch
- ◯ diastolisch und systolisch
- ◯ unbekannt

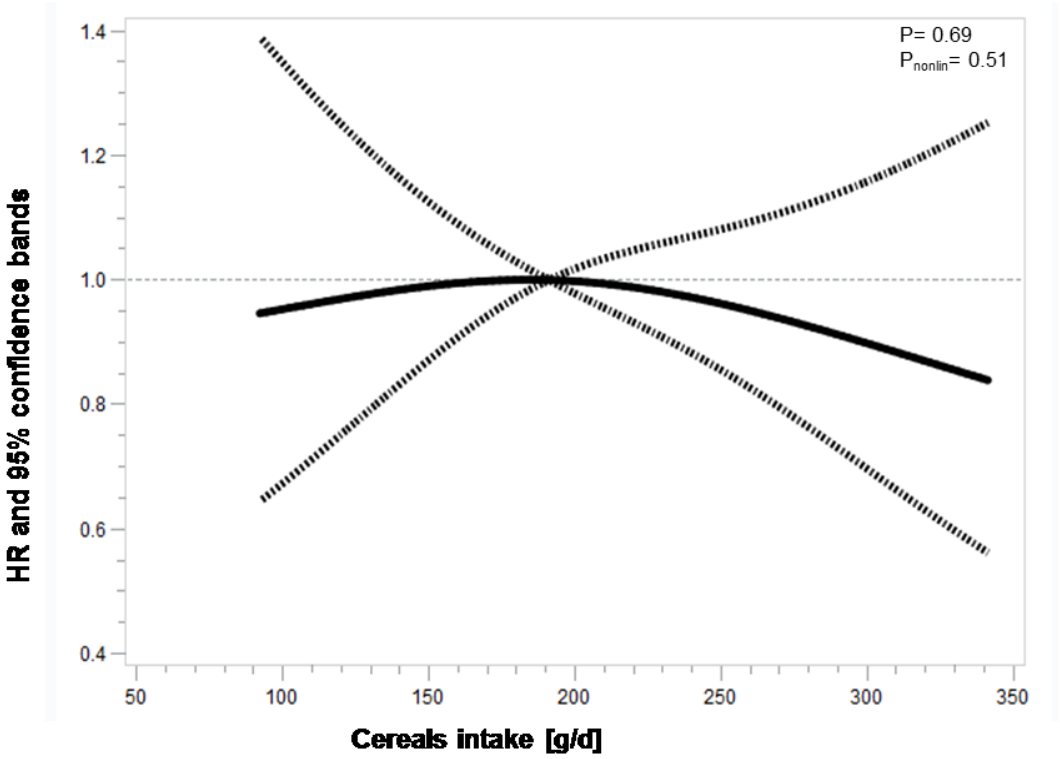
Als **Hauptursache der Herzinsuffizienz** wird angesehen:

- ◯ Koronare Herzkrankheit
- ◯ Hypertonie
- ◯ primäre Herzklappenerkrankung
- ◯ angeborener Herzfehler
- ◯ Kardiomyopathie
- ◯ nicht eindeutig bestimmbar
- ◯ Zustand nach Myokardinfarkt
- ◯ andere Ursache _____

Wir danken für Ihre freundliche Unterstützung!

Appendix XIV: Results from Restricted Cubic Spline Cox Regression Analyses Regarding Individual Mediterranean Diet Score Components and the Risk of Heart Failure

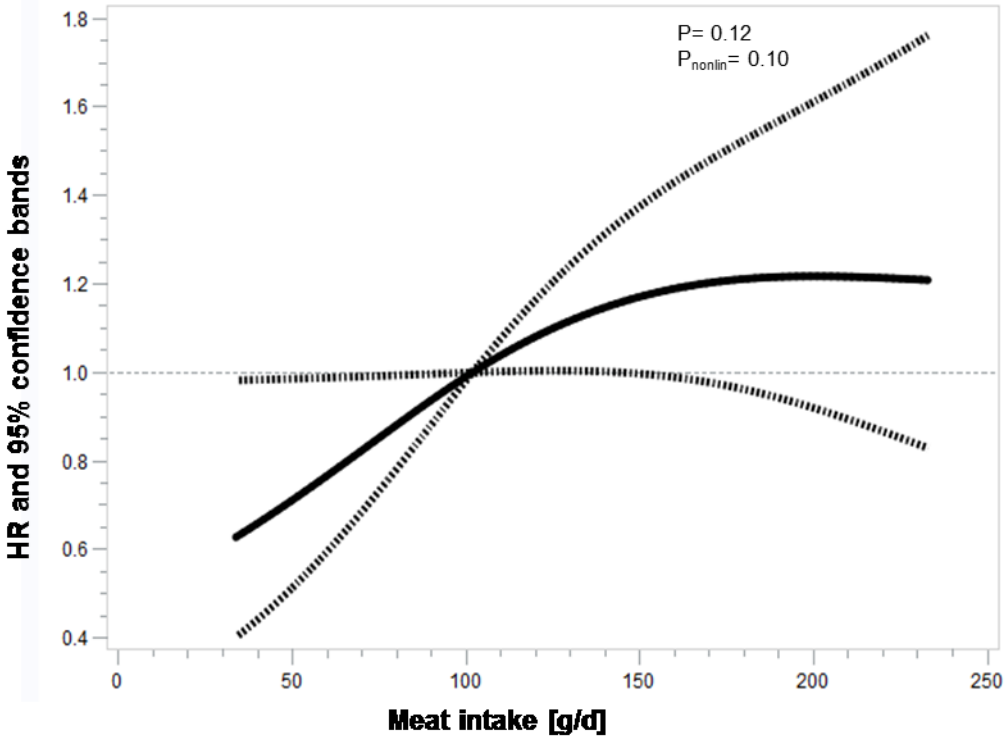


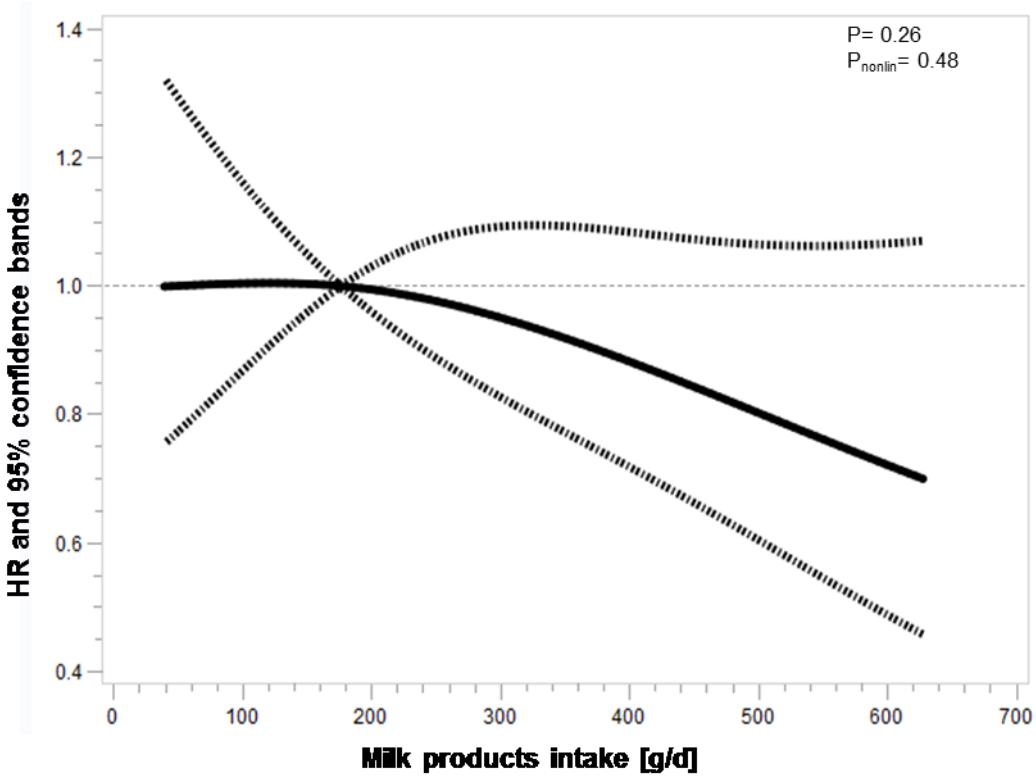


Restricted cubic spline regression analysis was performed using knots at the 5th, 50th (reference) and 95th percentile. Hazard ratios and 95% confidence bands (dotted lines) are stratified by age and adjusted for sex, total energy intake, education, smoking, physical activity, BMI, waist circumference, prevalent comorbidities (diabetes, hypertension, hyperlipidemia) and all remaining tMED score components (continuously). P for nonlinearity was computed by Wald chi-square test.

Abbreviations: BMI, body mass index; HR, hazard ratio; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; tMED, traditional Mediterranean diet

Appendix XIV continued

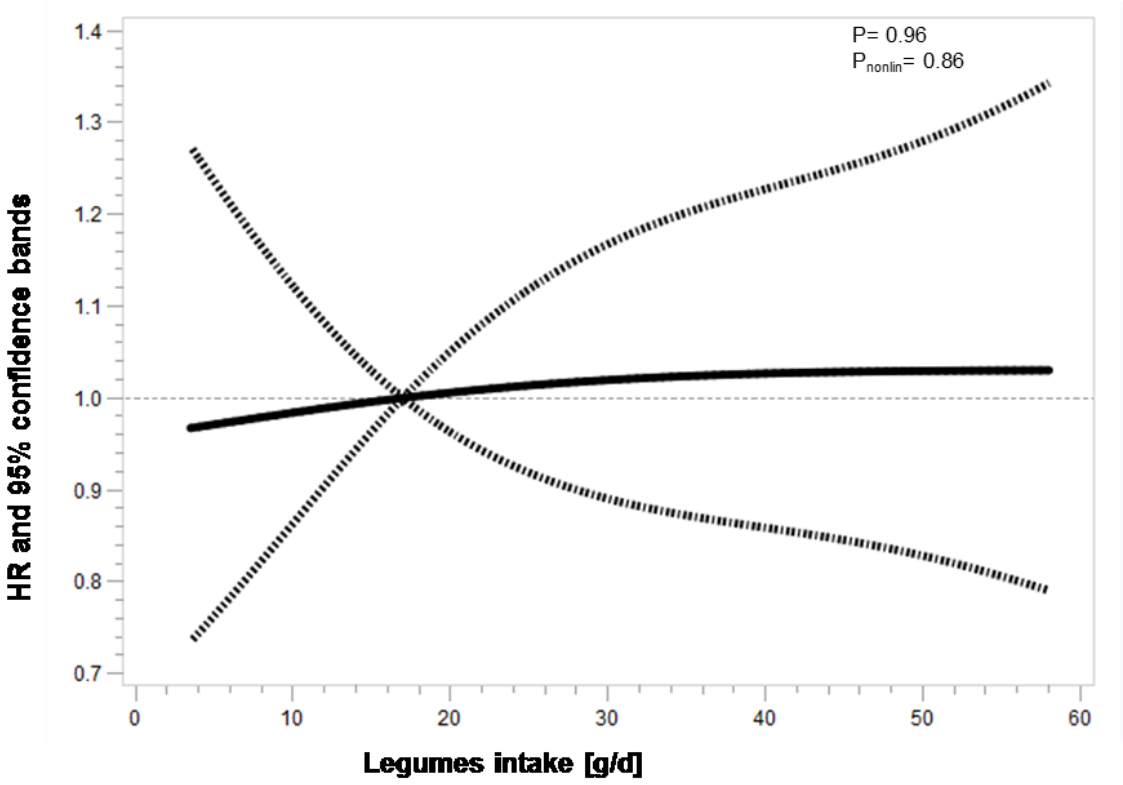


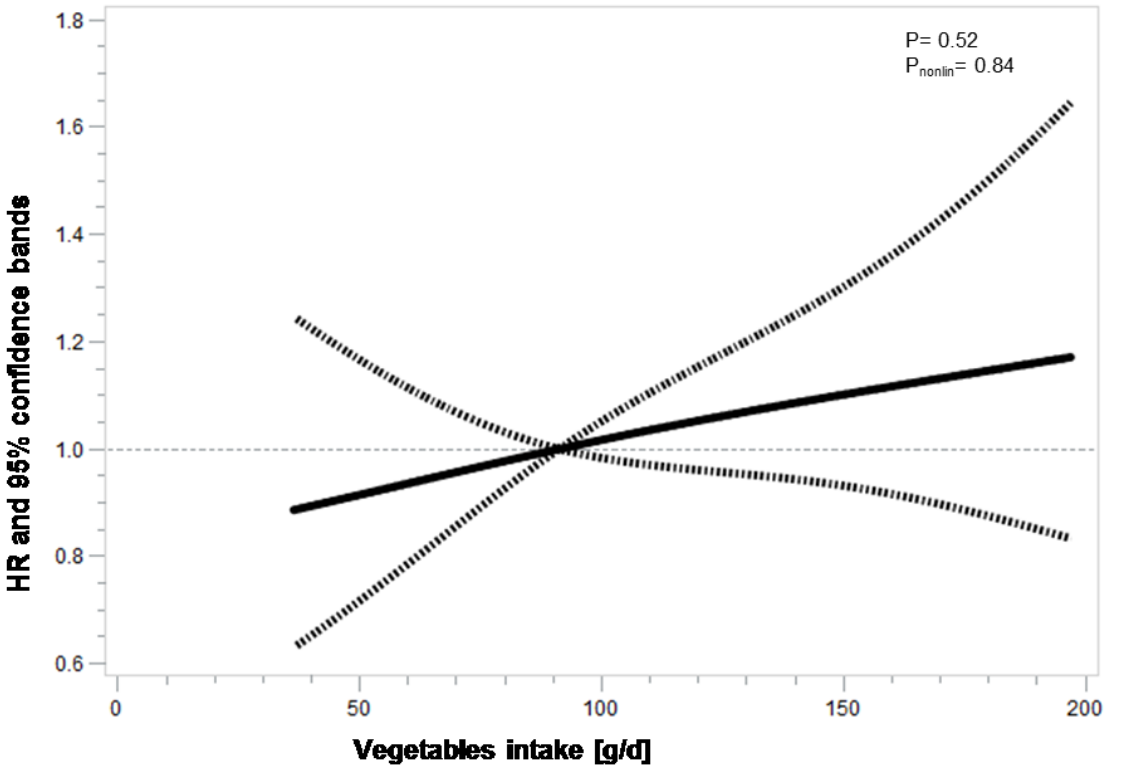


Restricted cubic spline regression analysis was performed using knots at the 5th, 50th (reference) and 95th percentile. Hazard ratios and 95% confidence bands (dotted lines) are stratified by age and adjusted for sex, total energy intake, education, smoking, physical activity, BMI, waist circumference, prevalent comorbidities (diabetes, hypertension, hyperlipidemia) and all remaining tMED score components (continuously). P for nonlinearity was computed by Wald chi-square test.

Abbreviations: BMI, body mass index; HR, hazard ratio; tMED, traditional Mediterranean die

Appendix XIV continued

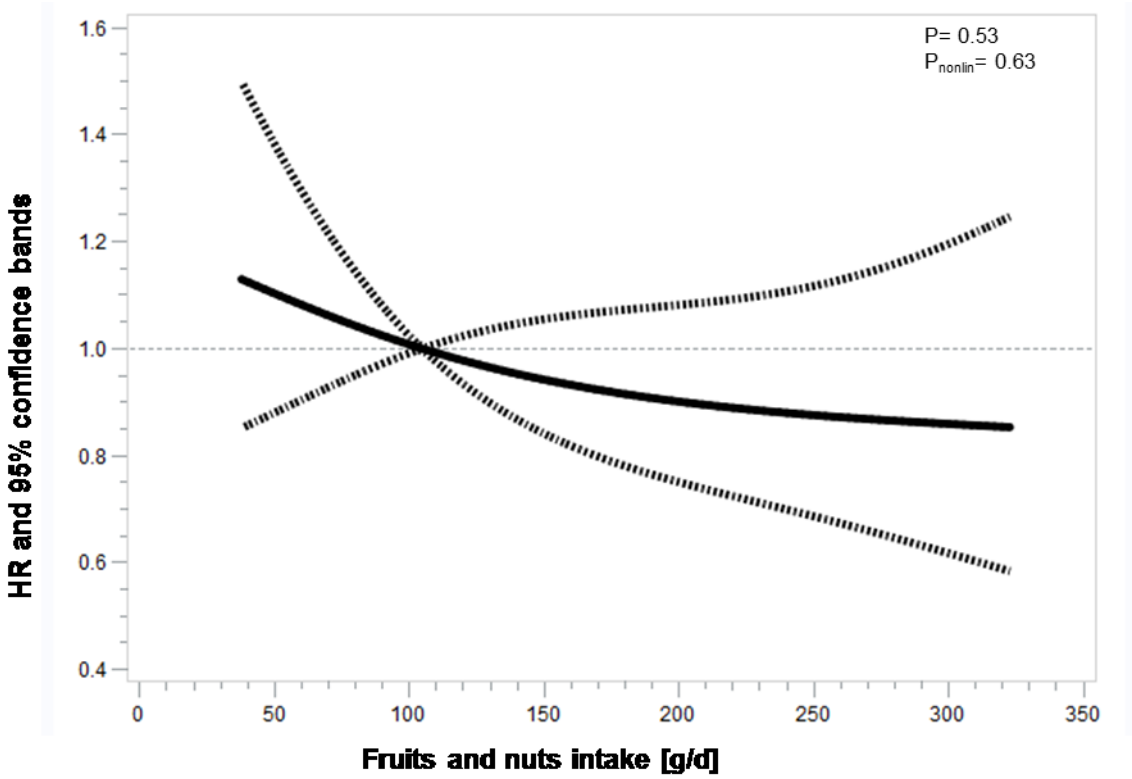




Restricted cubic spline regression analysis was performed using knots at the 5th, 50th (reference) and 95th percentile. Hazard ratios and 95% confidence bands (dotted lines) are stratified by age and adjusted for sex, total energy intake, education, smoking, physical activity, BMI, waist circumference, prevalent comorbidities (diabetes, hypertension, hyperlipidemia) and all remaining tMED score components (continuously). P for nonlinearity was computed by Wald chi-square test.

Abbreviations: BMI, body mass index; HR, hazard ratio; tMED, traditional Mediterranean diet

Appendix XIV continued



Restricted cubic spline regression analysis was performed using knots at the 5th, 50th (reference) and 95th percentile. Hazard ratios and 95% confidence bands (dotted lines) are stratified by age and adjusted for sex, total energy intake, education, smoking, physical activity, BMI, waist circumference, prevalent comorbidities (diabetes, hypertension, hyperlipidemia) and all remaining tMED score components (continuously). P for nonlinearity was computed by Wald chi-square test.

Abbreviations: BMI, body mass index; HR, hazard ratio; tMED, traditional Mediterranean diet

Appendix XV: Baseline Characteristics According to Wine Consumption in Men

Characteristics	Categories of Wine Consumption*				
	1	2	3	4	5
Intake, ml	0	1-<35.7	35.7-<125	125-<250	≥ 250
n (cases)	1,511 (40)	4,491 (69)	2,243 (13)	542 (2)	398 (6)
Age, mean, years	52.9 (8.1)	51.8 (7.9)	51.9 (7.8)	50.9 (7.7)	51.0 (7.8)
Body mass index, kg/m^2	27.3 (0.1)	26.8 (0.1)	26.9 (0.1)	26.6 (0.2)	26.7 (0.2)
Waist circumference, cm	95.9 (0.3)	94.4 (0.1)	94.3 (0.2)	93.7 (0.4)	93.6 (0.5)
University Degree, %	26.8	49.6	59.4	70.4	68.3
Current smoking, %	40.6	23.8	18.9	16.8	24.4
Physical activity, hours/week	2.65 (0.09)	2.62 (0.05)	2.84 (0.08)	3.23 (0.15)	3.53 (0.18)
Medical History, %					
Prevalent hypertension	60.4	53.0	52.9	53.2	52.4
Prevalent diabetes	10.3	5.1	4.7	3.6	5.2
Prevalent hyperlipidemia	35.1	31.2	33.2	34.1	33.2
Scored Components					
Total energy intake, MJ/d	**10,156 (67)**	**10,066 (39)**	**10,375 (55)**	**10,318 (113)**	**10,680 (132)**
Total alcohol intake, g/d	20.0 (0.5)	19.3 (0.3)	23.5 (0.4)	31.1 (0.9)	52.9 (1.0)
Fruits and nuts intake, g/d	121 (1.3)	122 (1.3)	130 (1.9)	137 (3.8)	137 (4.5)
Vegetable intake, g/d	87 (1.3)	88 (0.7)	93 (1.0)	100 (2.1)	98 (2.5)
Cereals intake, g/d	227 (2.2)	236 (1.3)	234 (1.8)	229 (3.7)	212 (4.3)
Fish intake, g/d	25.9 (0.7)	26.3 (0.4)	29.5 (0.6)	31.3 (1.2)	35.1 (1.4)
Legumes intake, g/d	31.2 (0.6)	28.4 (0.3)	28.3 (0.5)	28.0 (1.0)	28.5 (1.2)
Fat-ratio	0.87 (0.0)	0.87 (0.0)	0.87 (0.0)	0.88 (0.0)	0.89 (0.0)
Milk products intake, g/d	206 (5.5)	213 (3.3)	219 (4.6)	215 (9.4)	218 (10.9)
Meat intake, g/d	156 (1.8)	146 (1.1)	147 (1.5)	137 (3.0)	142 (3.6)

Baseline characteristics are expressed as age- and sex-adjusted mean (standard error) or percentages, age is shown as unadjusted means (standard deviation).
* Categories of intakes based on standard portion sizes in Germany (wine=250ml), 35.7ml of wine reflect an intake of one glass per week

Appendix XVI: Baseline Characteristics According to Wine Consumption in Women

Characteristics	Categories of Wine Consumption*				
	1	2	3	4	5
Intake, ml	0	1-<35.7	35.7-<125	125-<250	≥ 250
n (cases)	1,244 (13)	7,624 (44)	4,325 (18)	966 (2)	624 (2)
Age, mean, years	51.1 (9.5)	49.2 (9.2)	48.2 (8.9)	46.5 (8.6)	47.6 (8.7)
Body mass index, kg/m^2	26.4 (0.1)	25.7 (0.1)	25.7 (0.1)	25.0 (0.1)	25.0 (0.2)
Waist circumference, cm	82.8 (0.3)	80.3 (0.1)	80.2 (0.2)	78.8 (0.3)	79.1 (0.4)
University Degree, %	18.8	27.1	32.0	41.4	42.8
Current smoking, %	28.8	15.9	16.6	18.0	27.6
Physical activity, hours/week	2.68 (0.10)	2.68 (0.04)	2.90 (0.05)	3.27 (0.11)	3.02 (0.13)
Medical History, %					
Prevalent hypertension	43.8	39.5	39.7	34.7	38.7
Prevalent diabetes	8.4	3.6	2.4	2.4	2.9
Prevalent hyperlipidemia	29.7	22.4	20.8	23.1	22.7
Scored Components					
Total energy intake, MJ/d	7,746 (60)	7,801 (24)	8,037 (32)	8,269 (68)	8,546 (85)
Total alcohol intake, g/d	2.9 (0.2)	4.1 (0.1)	10.1 (0.1)	21.1 (0.2)	39.9 (0.3)
Fruits and nuts intake, g/d	149 (2.8)	155 (1.1)	160 (1.5)	164 (3.1)	150 (3.9)
Vegetable intake, g/d	104 (1.6)	107 (0.6)	109 (0.9)	114 (1.8)	116 (2.2)
Cereals intake, g/d	178 (1.8)	180 (0.7)	177 (1.0)	179 (2.1)	169 (2.6)
Fish intake, g/d	18.7 (0.6)	19.9 (0.2)	22.2 (0.3)	24.3 (0.7)	23.9 (0.8)
Legumes intake, g/d	20.2 (0.4)	19.0 (0.2)	19.2 (0.2)	18.7 (0.5)	20.2 (0.6)
Fat-ratio	0.83 (0.0)	0.84 (0.0)	0.85 (0.0)	0.85 (0.0)	0.87 (0.0)
Milk products intake, g/d	260 (6.0)	244 (2.4)	236 (3.2)	230 (6.8)	216 (8.5)
Meat intake, g/d	92.7 (1.4)	93.3 (0.6)	95.4 (0.7)	91.7 (1.6)	92.3 (1.9)

Baseline characteristics are expressed as age- and sex-adjusted mean (standard error) or percentages, age is shown as unadjusted means (standard deviation).

* Categories of intakes based on standard portion sizes in Germany (wine=250ml), 35.7ml of wine reflect an intake of one glass per week

Appendix XVII: Baseline Characteristics According to Beer Consumption in Men

Characteristics	Categories of Beer Consumption*				
	1	2	3	4	5
Intake, ml	0	1-<250	250-<500	500-<1000	≥1000
n (cases)	686 (13)	4,155 (62)	1,270 (19)	1,643 (23)	1,471 (13)
Age, mean, years	52.5 (8.0)	52.3 (8.0)	51.1 (7.7)	51.9 (7.7)	51.1 (7.7)
Body mass index, kg/m^2	26.8 (0.1)	26.8 (0.1)	27.0 (0.1)	27.0 (0.1)	27.1 (0.1)
Waist circumference, cm	93.8 (0.4)	93.9 (0.2)	94.6 (0.3)	94.9 (0.2)	96.2 (0.3)
University Degree, %	36.6	54.0	53.1	52.9	40.4
Current smoking, %	36.7	20.7	21.4	25.8	34.3
Physical activity, hours/week	3.2 (0.1)	2.8 (0.1)	2.7 (0.1)	2.7 (0.1)	2.4 (0.1)
Medical History, %					
Prevalent hypertension	54.2	51.5	53.1	53.8	63.1
Prevalent diabetes	9.9	5.8	4.3	4.6	6.4
Prevalent hyperlipidemia	32.6	31.2	32.1	32.9	36.7
Scored Components					
Total energy intake, MJ/d	10,214 (99)	9,836 (40)	10,001 (73)	10,384 (64)	11,173 (68)
Total alcohol intake, g/d	5.0 (0.5)	11.2 (0.2)	21.4 (0.4)	29.1 (0.3)	56.9 (0.4)
Fruits and nuts intake, g/d	140 (3.4)	133 (1.4)	125 (2.5)	116 (2.2)	108 (2.3)
Vegetable intake, g/d	94 (1.9)	91 (0.8)	91 (1.4)	89 (1.2)	87 (1.3)
Cereals intake, g/d	233 (3.3)	236 (1.3)	232 (2.4)	236 (2.1)	218 (2.2)
Fish intake, g/d	27.7 (1.1)	26.8 (0.4)	27.8 (0.8)	29.0 (0.7)	28.5 (0.8)
Legumes intake, g/d	27.9 (0.9)	28.0 (0.4)	28.6 (0.6)	29.1 (0.6)	31.6 (0.6)
Fat-ratio	0.86 (0.0)	0.86 (0.0)	0.88 (0.0)	0.88 (0.0)	0.89 (0.0)
Milk products intake, g/d	269 (8.2)	244 (3.3)	196 (6.0)	181 (5.3)	153 (5.6)
Meat intake, g/d	148 (2.7)	138 (1.1)	149 (2.0)	154 (1.7)	164 (1.8)

Baseline characteristics are expressed as age- and sex-adjusted mean (standard error) or percentages, age is shown as unadjusted means (standard deviation).
* Categories of intakes based on standard portion sizes in Germany (beer=500ml)

Appendix XVIII: Baseline Characteristics According to Beer Consumption in Women

Characteristics	Categories of Beer Consumption			
	1	2	3	4
Intake, ml	0	1-<125	125-<250	≥250
n (cases)	5,801 (40)	7,469 (34)	845 (3)	668 (2)
Age, mean, years	49.1 (9.5)	48.7 (8.9)	47.9 (8.7)	48.3 (8.4)
Body mass index, kg/m^2	26.1 (0.1)	25.5 (0.1)	25.3 (0.2)	24.9 (0.2)
Waist circumference, cm	81.0 (0.1)	80.0 (0.1)	79.9 (0.4)	79.6 (0.4)
University Degree, %	25.3	31.4	36.7	33.4
Current smoking, %	20.0	14.9	22.0	26.1
Physical activity, hours/week	2.74 (0.04)	2.82 (0.04)	3.09 (0.12)	2.67 (0.13)
Medical History, %				
Prevalent hypertension	40.4	38.8	38.9	41.5
Prevalent diabetes	4.5	3.0	1.5	3.9
Prevalent hyperlipidemia	24.1	21.9	20.2	20.6
Scored Components				
Total energy intake, MJ/d	7,758 (28)	7,951 (24)	8,305 (73)	8,647 (82)
Total alcohol intake, g/d	5.1 (0.1)	8.0 (0.1)	16.4 (0.3)	30.0 (0.4)
Fruits and nuts intake, g/d	161 (1.3)	157 (1.1)	145 (3.3)	126 (3.7)
Vegetable intake, g/d	108 (0.7)	108 (0.7)	106 (1.9)	102 (2.2)
Cereals intake, g/d	176 (0.9)	181 (0.8)	183 (2.2)	174 (2.5)
Fish intake, g/d	20.2 (0.3)	21.0 (0.2)	23.0 (0.7)	23.0 (0.8)
Legumes intake, g/d	18.6 (0.2)	19.2 (0.2)	20.7 (0.5)	21.6 (0.6)
Fat-ratio	0.84 (0.0)	0.84 (0.0)	0.84 (0.0)	0.85 (0.0)
Milk products intake, g/d	251 (2.8)	238 (2.4)	226 (7.3)	202 (8.2)
Meat intake, g/d	90.0 (0.6)	94.3 (0.6)	102 (1.7)	109 (1.9)

Baseline characteristics are expressed as age- and sex-adjusted mean (standard error) or percentages, age is shown as unadjusted means (standard deviation).
* Categories of intakes based on standard portion sizes in Germany (beer=500ml)

EIDESSTATTLICHE ERKLÄRUNG

Hiermit versichere ich an Eides statt, dass ich die am Fachbereich Gesundheitswissenschaften der Technischen Universität Berlin eingereichte Dissertation mit dem Titel „The Mediterranean Diet and its Components and the Risk of Heart Failure in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study – A Top-Down Approach“ selbstständig angefertigt und verfasst habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt wurden. Die Dissertation wurde noch nicht veröffentlicht oder einer anderen Prüfungsbehörde vorgelegt.

Berlin, den 29.09.2014 .....

(Unterschrift)