Aus dem Institut für Versorgungsforschung und Gesundheitsökonomie,
Deutsches Diabetes-Zentrum, Leibniz-Zentrum für Diabetes-Forschung
an der Heinrich-Heine-Universität Düsseldorf
Direktorin: Frau Univ.-Prof. Dr. Dr. Andrea Icks, MBA

Anreize für körperliche Aktivität bei Herzpatient:innen in Deutschland: Gesundheitsökonomische Modellierung vor Studienbeginn

zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von
Damon Mohebbi, MSc
2025

Angabe der Gutachter:innen

Als Inauguraldissertation gedruckt mit Genehmigung der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:

Dekan:	Prof. Dr. Nikolaj Klöcker
Erstgutachterin:	Prof. Dr. Dr. Andrea Icks, MBA
Zweitgutachter:	Prof. Dr. Dr. Christian Jung
Drittgutachterin:	Prof. Dr. Jolene Skordis

Widmung

Für meine Eltern

Auflistung der Publikationen

Teile dieser Arbeit wurden veröffentlicht:

Mohebbi, D., Ogurtsova, K., Dyczmons, J., Dintsios, C. M., Kairies-Schwarz, N., & Icks, A. (2023). Incentives for physical activity in cardiac patients in Germany: pre-trial health economic modelling. European Journal of Preventive Cardiology, 30 (Suppl). DOI: 10.1093/eurjpc/zwad125.298

Mohebbi, D., Ogurtsova, K., Dyczmons, J., Dintsios, M., Kairies-Schwarz, N., Jung, C. & Icks, A. (2024). Cost-effectiveness of incentives for physical activity in coronary heart disease in Germany: pre-trial health economic model of a complex intervention following the new MRC framework. BMJ Open Sport Exerc Med. DOI: 10.1136/bmjsem-2024-001896

Tagungen:

Herbsttagung der Deutschen Gesellschaft für Epidemiologie und der Deutschen Gesellschaft für Sozialmedizin und Prävention, 2022, Berlin, Deutschland

15. Jahrestagung der Deutschen Gesellschaft für Gesundheitsökonomie, 2023, Hannover, Deutschland

ESC Preventive Cardiology Congress, 2023, Malaga, Spanien

UK Health Economics Study Group Conference, 2023, Oxford, Vereinigtes Königreich

3rd World Non-Communicable Diseases Congress, 2023, Toronto, Kanada

15th International Health Economics Association World Congress, 2023, Kapstadt, Südafrika

Zusammenfassung

Herz-Kreislauf-Erkrankungen sind die weltweit häufigste Todesursache. Bisherige Forschungserkenntnisse deuten darauf hin, dass bewegungsbasierte Interventionen der Sekundärprävention, Gesundheitsschäden abmildern können. Die Einführung von Anreizsystemen zur Bewegungsförderung von Patient:innen könnte ein vielversprechender Ansatz für eine verbesserte Adhärenz sein. Die derzeit am Universitätsklinikum Düsseldorf entwickelte INPHY-Studie zielt darauf ab, körperliche Aktivität bei Menschen mit koronarer Herzkrankheit (KHK) durch monetäre und soziale Anreize zu verbessern. Das Rahmenwerk des britischen Medical Research Council für die Entwicklung und Evaluierung komplexer Interventionen empfiehlt gesundheitsökonomische Modellierung im Vorfeld der Studie.

Es wurde ein entscheidungsanalytisches Markov-Modell entwickelt, um die Kosten und die Effekte von bewegungsbasierten, incentivierten Sekundärpräventionsmaßnahmen aus der Kostenträger-Perspektive zu bewerten. Eine Kohorte von 65-jährigen Personen mit einem Zustand nach Myokardinfarkt wurde in dem Modell über insgesamt 25 1-Jahres-Markov-Zyklen verfolgt. Zu den Ergebnissen gehörten die Kosten, gewonnene qualitätsadjustierte Lebensjahre (QALY) und inkrementelle Kosten-Effektivitäts-Relationen (IKER). Sensitivitäts- und Szenarioanalysen wurden durchgeführt, um Parameter- und Modellunsicherheiten zu berücksichtigen.

Im Basisfall wurden die durch monetäre und soziale Anreize gewonnenen inkrementellen QALYs im Vergleich zur Kontrolle auf 0,01 [95% KI 0,00-0,01] bzw. 0,03 [95% KI 0,02-0,05] geschätzt. Im Vergleich zur Kontrollgruppe erhöhte die Durchführung der monetären und sozialen Anreize die Kosten um 795€ [95% KI 697-884] bzw. 831€ [95% KI 593-1.191]. Die IKER betrugen 24.473€ [95 % KI 15.871-38.868] bzw. 112.015€ [95 % KI 81.140-169.888] pro gewonnenem QALY für die sozialen und monetären Anreize. Bei einem Schwellenwert des deutschen Pro-Kopf-Bruttoinlandsprodukts von 43.000€/QALY lag die Wahrscheinlichkeit für Kosten-Effektivität der sozialen und monetären Anreize bei 100% bzw. 0%.

Bewegungsbasierte Sekundärprävention unter Nutzung von Anreizsystemen könnte zukünftig eine kosteneffektive Strategie zur Reduktion gesundheits-ökonomischer Belastungen verursacht durch KHK darstellen. Die Umsetzung dieser Erkenntnisse in Politik und Praxis sowie strenges Studienmonitoring und -evaluation sind wichtig. Weitere epidemiologische Untersuchungen aus Deutschland können verbleibende Modell-Unsicherheiten verringern.

Abstract

Cardiovascular disease is the most-prevalent non-communicable disease and leading cause of death globally. Evidence suggests that exercise-based interventions in secondary prevention can mitigate adverse health events. Implementing incentive schemes for patients to engage in physical activity might be a promising approach to improve adherence. The INPHY trial, a complex intervention which is currently being developed at the University Hospital Düsseldorf, aims at improving physical activity (PA) in people with coronary heart disease (CHD) using monetary and social incentives. The UK Medical Research Council framework for the development and evaluation of complex interventions recommends pre-trial health economic modelling to inform the design of the trial.

A decision-analytic Markov model was developed to evaluate costs and effects of exercise-based, incentivised secondary prevention interventions from a health services provider perspective. A cohort of individuals with a previous myocardial infarction was followed in the model from age 65 years through 25 1-year Markov cycles. Primary outcomes included the costs, quality-adjusted life-years (QALY) gained and incremental cost-effectiveness ratios (ICERs). Sensitivity and scenario analyses were performed to reflect parameter and model uncertainty.

In the base-case, the incremental QALYs gained from the monetary and social incentives, relative to control, were respectively estimated at 0.01 [95% CI 0.00-0.01] and 0.03 [95% CI 0.02-0.05]. In comparison to control, implementation of the monetary and social incentive interventions increased the costs by 795€ [95% CI 697-884] and 831€ [95% CI 593-1,191], respectively. ICERs were 24,473€ [95% CI 15,871-38,868] and 112,015€ [95% CI 81,140-169,888] per QALY gained for the social and monetary incentive intervention, respectively. At a per-capita gross domestic product threshold of 43,000€/QALY for Germany, the probability that the social and monetary incentive intervention would be seen as cost effective was 100% and 0%, respectively.

Exercise-based secondary prevention using incentivised reinforcement schemes might offer a cost-effective strategy to reduce the burden of CHD, offering good value for money in preventing a significant non-communicable disease. Translation of these findings into policy and practice alongside rigorous monitoring and evaluation is important. More epidemiological research from Germany is recommended to reduce remaining model uncertainty surrounding this decision.

List of Abbreviations

AHA	American Heart Association
AUD	Australian Dollar; AU$
C0	cost of control group
C1	cost of intervention group
CEAC	cost-effectiveness acceptability curve
CG	control group
CHD	coronary heart disease
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CVD	cardiovascular disease
DALY	disability-adjusted life year
DEGS	German Health Interview and Examination Survey; Deutsches Erwachsenen Gesundheitssurvey
DESTATIS	German Federal Statistical Office; Statistisches Bundesamt
E0	effect of control group
E1	effect of intervention group
e.g.	exempli gratia; for example
EQ-5D	European Quality of Life 5 Dimensions
ESC	European Society of Cardiology
EUR	Euro; €
GBP	Great Britain Pound; £
GDP	gross domestic product
G-DRG	German Diagnosis Related Group
GEDA	German Health Update; Gesundheit in Deutschland aktuell
h	hour
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
i.e.	id est; that is
IG 1	intervention group 1
IG 2	intervention group 2
IGFBP2	insulin-like growth factor binding protein-2
INPHY	Incentives for Physical Activity in Cardiac Patients with or without Diabetes

kg	kilogram
MET	metabolic equivalent of task
MET.h	metabolic equivalent of task-hour
MI	myocardial infarction
min	minute
ml	millilitre
mmHg	millimetre of mercury
mmol/L	millimoles per litre
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
PA	physical activity
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RR	relative risk
SMR	standardised mortality rate
ST2	suppression of tumorigenicity-2
T2DM	type 2 diabetes mellitus
UK	United Kingdom
US	United States
USD	United States Dollar; US$
WHO	World Health Organisation

Table of Contents

1 Introduction

This first chapter describes the public health relevance of cardiovascular diseases (CVDs), by presenting the burden of disease and the costs associated with CVDs and coronary heart disease (CHD), in particular. In addition, the role of exercise-based programmes in secondary prevention and incentive-based interventions for health behaviour change in the context of CHD is illustrated. Furthermore, the theoretical background of designing complex behavioural interventions is highlighted, before the current state of evidence regarding health economic CHD models is examined.

1.1 Background and current state of knowledge

1.1.1 The burden of cardiovascular diseases (CVDs)

CVDs are a diverse group of non-communicable disorders that involve the heart or blood vessels (Mendis et al., 2011). Epidemiologically, CVDs continue to be the leading cause of disease burden in the world. According to the Global Burden of Disease Study, prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019 (Roth et al., 2020). Coronary heart disease (CHD) is the predominant type of CVD which affected 197 million people in 2019 (Roth et al., 2020). Acute CVD events, notably myocardial infarction (MI) and stroke, affect around 35 million people each year, and 20% to 40% of these events happen to people with established CVD. The five year recurrence rate of cardiovascular events in CVD patients is about 30%, which is five times higher than for people without a history of CVD (Govender et al., 2019; Perel et al., 2015). In 2019 CHD accounted for 182 million disability-adjusted life-years (DALYs) globally, an aggregate indicator of years lost due to premature death and years of healthy life lost due to disability. An estimated 17.9 million died from CVDs in 2019 accounting for almost one third of all global deaths. Projections for 2030 show that almost 23.6 million people will die of CVDs (World Health Organisation, 2020).

In addition to morbidity and mortality, CVDs cause substantial economic burden for individuals, households, and health systems. Estimates of the global

economic burden of CVDs were developed in a report by the World Economic Forum and the Harvard School of Public Health (Bloom et al., 2011). For 2020, the global cost of CVD was estimated at 957 billion United States Dollars (USD, US$), meaning more than 11% of the global expenditures on health were CVD-related. Global expenditure for CVD is estimated to rise to 1,044 billion US$ in 2030. More than half of the total cost comes from direct healthcare costs and the remainder from indirect costs such as productivity loss from disability or premature death.

In Germany, following global trends, CVDs remain the most common cause of death among women and men. Although a steady decline in mortality rates has been observed in the past decade, high prevalence persists. Pooled data from the German Health Update (GEDA) revealed that the overall lifetime prevalence of major cardiovascular disease (MI, CHD, heart failure and stroke) in Germany was 12.0% (Dornquast et al., 2016). The rate was 2.6% higher in men (13.3%) than in women (10.7%). The prevalence of more specific conditions was analysed in the German Health Interview and Examination Survey for Adults (DEGS1). The lifetime prevalence of MI in adults aged 40–79 years in DEGS1 was 4.7% (men 7.0%; women 2.5%) and of CHD (excluding MI) was 8.0% (men 10.4%; women 5.7%) (Gößwald et al., 2013). CHD caused the largest number of DALYs lost while back pain followed closely after with 2.5 million and 2.1 million DALYs, respectively (Plass et al., 2014). In addition, CVDs cause the highest costs to the German healthcare system compared to all other disease groups: in 2015, 13.7% of the direct costs of illness, i.e. more than 46 billion Euro (EUR, €), were caused by cardiovascular diseases. Costs include expenses directly related to the medical treatment, prevention, rehabilitation or care measures (DESTATIS, 2017).

1.1.2 Risk factors of coronary heart disease (CHD)

The development of CHD is multifactorial and dependent on numerous cardiovascular risk factors consistently identified in large long-term studies such as the Framingham Heart Study, the INTERHEART Study or the British-Regional Heart Study (Lennon et al., 2015; Mahmood et al., 2014; Yusuf et al., 2004). A distinction is made between risk factors that are non-modifiable such as age, sex, ethnicity, hereditary factors and familial occurrence. Individual modifiable risk factors include physical inactivity, tobacco use, harmful use of alcohol, dyslipidaemia, obesity,

hyperglycaemia and hypertension (Eriksen et al., 2021). For instance, the INTERHEART Study conducted in 52 countries showed that modifiable risk factors were responsible for about 90% of new MIs worldwide and independent of age and sex (Yusuf et al., 2005, 2004). For Germany, the population-representative MONICA-Augsburg study showed that smoking, hypercholesterolaemia and hypertension were responsible for about 65% of new MIs in the population (Liese et al., 2000). Simultaneously, health-promoting lifestyles such as healthy nutrition and physical exercise are recognised as protective factors reducing the risk of CHD by 60 to 80% (Chiuve et al., 2006; Stampfer et al., 2000). Many preventive measures and treatment recommendations aim to minimise the risk factors and strengthen the protective factors. In this context, secondary prevention is an important component of comprehensive long-term management of patients with CHD.

1.1.3 The role of CHD prevention

Traditionally, prevention is divided into three levels: primary, secondary, and tertiary prevention. Primary prevention intends to reduce the incidence of a condition in the wider population by eliminating or treating particular risk factors and increasing protective factors. In secondary prevention, the focus is on reducing the impact of a disease for an affected population through early detection and management. Tertiary prevention involves the impact reduction of complications and disability that result from a long-term disease in the population afflicted (Goldsteen et al., 2015; Gullotta et al., 2003).

Secondary prevention of CHD can be defined as all measures designed to reduce morbidity and mortality among individuals with diagnosed CHD (Pencheon, 2006). Secondary prevention of CHD can ameliorate symptoms, improve quality of life, reduce subsequent cardiovascular events, and prevent death. In addition to the well-established pharmacological and/or interventional therapy of patients with CHD, the modification of lifestyle factors through behavioural changes forms the basis of secondary prevention strategies. Lifestyle modification including physical activity (PA), smoking cessation, dietary modification and weight management have significant and clinically important beneficial effects on cardiovascular morbidity and mortality (Chow et al., 2010; Iestra et al., 2005).

Despite this fact, non-pharmacological secondary prevention strategies are often limited by inadequate implementation and low participation. It has been demonstrated that many CHD patients do not accomplish the suggested treatment goals, and that necessary and effective lifestyle adjustments are rarely implemented. The results of the Euroaspire IV and V studies, which are European Society of Cardiology (ESC) surveys on the lifestyle, risk factor and therapeutic management of coronary patients from 24 and 27 European countries, recently verified this (De Backer et al., 2019; Kotseva et al., 2016). While the frequency of recommended medical management has improved since the first Euroaspire survey in 1995, lifestyle modifications have not. The studies concluded that a large majority of coronary patients does not achieve the guideline standards for secondary prevention with high prevalence of persistent smoking, unhealthy diets, physical inactivity and consequently most patients are overweight or obese with a high prevalence of diabetes. For instance, little or no physical activity was still reported by 59.9% of the 7998 interviewed patients in the Euroaspire IV survey. This emphasises the relevance of participatory, nonpharmacological secondary preventive interventions for people with CHD.

1.1.4 Physical activity as an integral part of CHD prevention

Regular PA is a well-known and important component of leading a lifestyle modification in secondary prevention patients. PA is defined as any body movements through muscle contractions beyond the basal metabolic rate (Bianchini and Vainio, 2002). In some cases, activities are categorised according to their energy expenditure as “light”, “moderate” and “heavy” physical activities. The measurement of absolute exercise intensity in physical activity can be done using metabolic equivalents of task (MET). 1 MET corresponds to oxygen uptake at rest at approximately 3.5 millilitre (ml) per kilogram (kg) body weight per minute (min), while 3 to 6 MET correspond to moderate-intensity exercise (Jetté et al., 1990).

PA improves both the cardiovascular risk profile and patients’ clinical outcomes. In their scientific statement, the American Heart Association (AHA) substantiates the beneficial effects of exercise on blood pressure, lipid levels, glycaemic control and body weight (Franklin et al., 2020). In addition, PA has anti-atherogenic and anti-inflammatory effects, improves coronary endothelial function

and may lead to an increase in fibrinolytic activity (Gao et al., 2022; Palmefors et al., 2014). The impact of exercise on novel cardiovascular biomarkers such as soluble suppression of tumorigenicity-2 (ST2) or insulin-like growth factor binding protein-2 (IGFBP2) is also being investigated (Martins da Costa et al., 2021; Mirna et al., 2020). Likewise, PA is associated with lower risk of many adverse health outcomes. According to the 2021 ESC guidelines, there is an inverse relationship between moderate-to-vigorous PA and all-cause mortality, CV morbidity and mortality, as well as incidence of type 2 diabetes mellitus (T2DM) (Visseren et al., 2021).

Following national and international recommendations, people with pre-existing CVD should undergo moderate-to-vigorous intensity aerobic exercise training ≥3 times a week and for 30 min per session (Montalescot et al., 2013; Piepoli et al., 2014; Rütten et al., 2016). The World Health Organisation (WHO) and ESC recommended in their guidelines on PA and CVD prevention for adults of all ages to strive for at least 150 to 300 min a week of moderate intensity, or 75 to 150 min a week of vigorous intensity aerobic PA, or an equivalent combination thereof, to reduce all-cause mortality, cardiovascular mortality, and morbidity (Bull et al., 2020; Visseren et al., 2021). Recommendations for exercise training in the management of cardiovascular health in individuals with cardiovascular risk factors were published several years ago but challenges in their implementation remain (Bull et al., 2020; Guthold et al., 2018; Piepoli et al., 2016; Rütten et al., 2018).

1.1.5 Incentives as a way to increase physical activity

Insights from behavioural economics could be used in the promotion of physical activity. Behavioural economics combines insights from economics and psychology to understand how individuals make decisions (Thaler, 2016). It has been used to develop several strategies for increasing physical activity, including the use of incentives (Hare et al., 2021). Incentives are rewards that are given to individuals for engaging in a desired behaviour (Skinner, 1953). They align with the principles of operant conditioning, a type of learning in which behaviours are influenced by their consequences. When a behaviour is followed by a positive reinforcement, such as a reward, it is more likely to be repeated in the future (Ferster and Skinner, 1957; Kazdin, 2013).

With the aim of fostering engagement in PA programmes, several reviews have shown that incentives can act as external stimuli and alter behaviour (Carrera et al., 2018; Charness and Gneezy, 2009; Dellavigna and Malmendier, 2006; Mitchell et al., 2020, 2013). Incentives can be both financial, i.e. payment of a monetary amount as a reward for achieving a certain goal, and non-financial such as support groups or social feedback. Incentive design has the potential to influence the effectiveness, costs, and cost-effectiveness of prevention interventions. However, reviews show partly mixed results on the effectiveness of incentivised reinforcement strategies to increase physical activity (Barte and Wendel-Vos, 2017; Giles et al., 2014; Mantzari et al., 2015; Mitchell et al., 2013; Molema et al., 2016). Positive trends can be observed mostly for short intervention periods. Individual study results indicate a tendency toward better results among previously inactive persons and persons with lower incomes. Therefore, the suitability and sustainability of incentives in physical activity promotion needs to be further studied.

1.1.6 MRC frame: Conceptual foundations of complex interventions

Incentivised reinforcement interventions for behaviour change are typically complex (Higgins et al., 2020; Michaelsen and Esch, 2022; Petticrew, 2011; Vlaev et al., 2019). The United Kingdom's (UK) Medical Research Council (MRC) published a widely accepted research framework on developing and evaluating complex interventions in 2000 and revised it in 2008 (Campbell et al., 2000; Craig et al., 2008). To depict the important conceptual, methodological and theoretical developments since 2008, a new framework was introduced in 2021, broadening the notion of complexity (Skivington et al., 2021). "*An intervention might be considered complex because of properties of the intervention itself, such as the number of components involved; the range of behaviours targeted; expertise and skills required by those delivering and receiving the intervention; the number of groups, settings, or levels targeted; or the permitted level of flexibility of the intervention or its components*" (Skivington et al., 2021). The framework divides complex intervention research into four phases (Figure 1): development or identification of the intervention, feasibility, evaluation, and implementation. Each phase has a common set of core elements, which include consideration of context, development and refinement of programme theory, engagement with stakeholders, identification of key uncertainties, intervention refinement, and economic considerations.

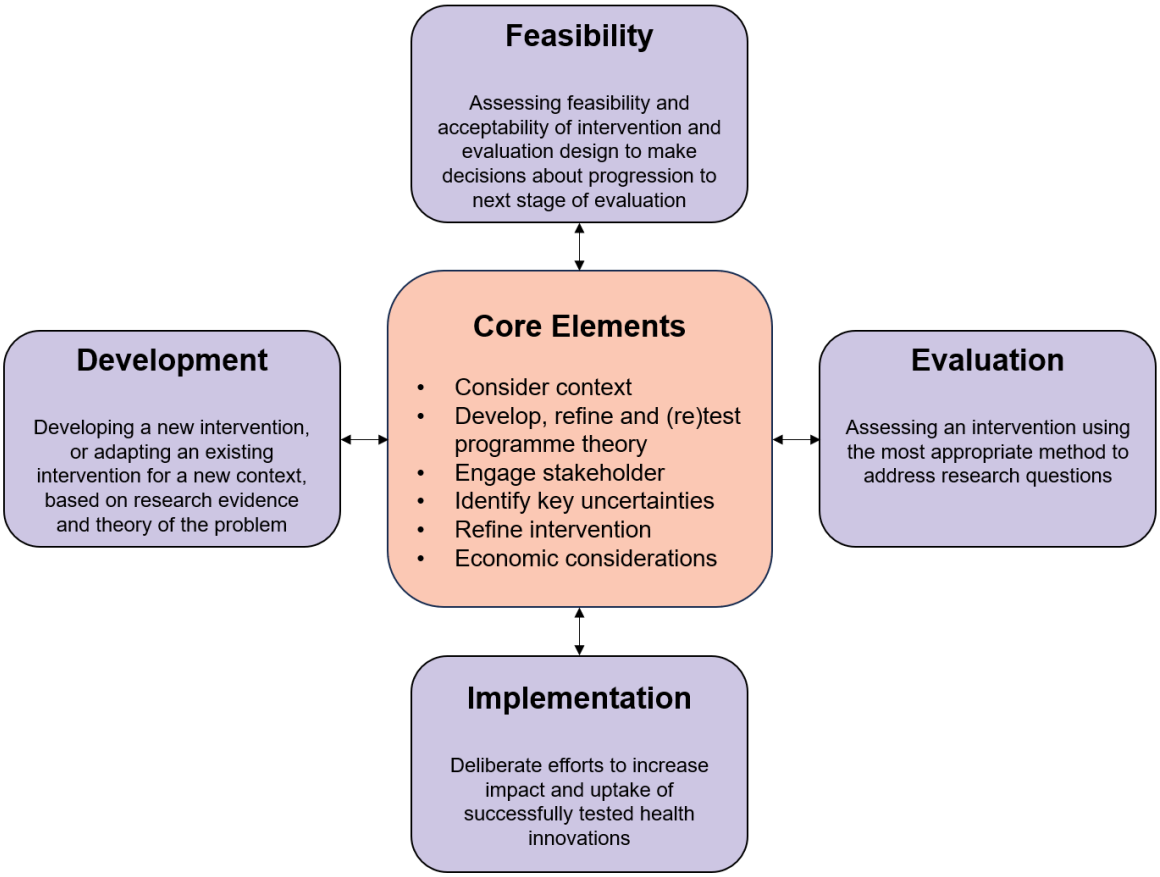

Figure 1: Framework for developing and evaluating complex interventions proposed by the UK Medical Research Council (adapted from Skivington *et al.*, 2021). Complex intervention research can be considered in terms of phases and at each phase six core elements should be considered.

Currently, the Institute for Health Services Research and Health Economics of the University Hospital Düsseldorf is developing a complex intervention intended to improve physical activity by monetary or social incentives, following the Medical Research Council (MRC) framework (Icks and Dyczmons, 2020). The INPHY trial, an acronym for Incentives for Physical Activity in Cardiac Patients with or without Diabetes, will be a prospective, three-arm, randomised-controlled trial in patients who are treated for suspected or known CHD in Düsseldorf, Germany. Patients of the day-unit of the University Hospital's Department for Cardiology, Pneumology & Angiology and of the Cardio Centrum Düsseldorf will be eligible to participate in the study. Further details on the trial are described in the Methods section.

1.1.7 Economic evaluation and pre-trial modelling as part of intervention research

Economic considerations should be a core component of all phases of intervention research (Eisman et al., 2019; Ramsey et al., 2005; Skivington et al., 2021). Economic evaluations are defined as the comparison of alternative options regarding both costs in terms of resource use and consequences in terms of outcomes or effects (Drummond et al., 2005). Early involvement of economic expertise will assist in determining the range of costs and benefits involved in order to provide an evidence-based foundation for researchers, decision makers and funders (Skivington et al., 2021). Given the constraints on health budgets, healthcare systems increasingly focus on the adoption of not only effective, but also cost-effective interventions (Hutubessy et al., 2003).

In the scope of economic evaluations, a decision-analytic model uses mathematical techniques that enable the comparative analysis of factual and hypothetical intervention strategies over a determined time period (Petrou and Gray, 2011). Based on the inputs into the model, "*models synthesize evidence on health consequences and costs from many different sources, including data from clinical trials, observational studies, insurance claim databases, case registries, public health statistics, and preference surveys*" (Weinstein et al., 2003). The model can link the data to outcomes of interest in the decision analysis. For decisions about resource allocation, the end result of a model is often a measure of value-for-money, such as the incremental cost per quality-adjusted life year (QALY) gained (Briggs et al., 2018). For the development of such a decision-analytic model, it initially needs to be conceptualised and relevant evidence for the model's input parameters should be identified and systematised. Characterizing potential bias and sources of uncertainty such as parameter or model uncertainty are hallmarks of good modelling practice. Extensive sensitivity or scenario analysis is essential to assess the robustness of the model (Briggs et al., 2018, 2012).

Pre-trial health economic modelling, one form of health economic analysis, is a useful and MRC-recommended approach to study intervention components and underlying mechanisms by which they influence outcomes (Claxton et al., 2002; Torgerson and Byford, 2002). Modelling a complex intervention prior to a full-scale

clinical trial can provide valuable insights to refine the intervention design, to determine suitable evaluation measures, and to project long-term outcomes (Craig, 2019; Craig et al., 2008). In contrast to post-trial assessments, where relevant data is already collected, pre-trial health economic models are developed to estimate the likelihood of cost-effectiveness on the basis of the anticipated intervention effect (Kim et al., 2020).

Health economic modelling has been conducted previously in the context of CVDs, however critical knowledge gaps in the existing literature prevail. Economic analyses have predominantly focused on simulating risk factor levels as part of primary prevention models (Lewsey et al., 2015; Unal et al., 2006). They have usually been used to estimate population costs for policy purposes. One traditional example is the CHD Policy Model developed by Weinstein *et al.* (1987) which was used to establish target levels of mortality and morbidity as a result of different policy initiatives in the United States (US). A more contemporary example is the Harvard CVD PREDICT Model, a comprehensive micro-simulation model for analysing cost-effectiveness of CVD policies, whose principal investigator was consulted for technical expertise of this dissertation (Pandya et al., 2017). Medical decision models along clinical CVD trials, which simulate disease progression or treatment comparisons, are less common. But those available have reported rather on (pharmacological) treatment and management programmes for CVD patients than on prevention and control interventions (Cooper et al., 2008; National Institute for Health and Care Excellence, 2014; Wisløff et al., 2012). Also, existing evaluations tend to be based on post-trial analyses, while pre-trial modelling studies with extrapolation to longer time horizons are yet to emerge (Asaria et al., 2016; Barton et al., 2011). These analyses are lacking in Germany, with the vast majority of CVD models being developed in the US and UK setting (Crossan et al., 2018).

1.2 Research aim and work packages

This dissertation aims to estimate the cost-effectiveness of the complex INPHY trial for the secondary prevention of CHD by performing pre-trial health economic modelling. This study aims to fill the gap in the literature on German CVD models and to inform the intervention design of the INPHY trial. The dissertation has the following work packages to achieve this aim:

- to design a conceptual model of the complex INPHY trial considering key components including incentives, adherence, and physical activity;
- to develop and to parameterise a decision-analytic Markov model for CHD to estimate the cost-effectiveness of exercise-based programmes and to evaluate the impact of monetary and social incentives;
- to perform sensitivity and scenario analyses to inform the design and feasibility of the INPHY study as well as the analysis of the best set of parameters/conditions of cost-effectiveness in this trial;
- to derive implications and recommendations for the INPHY trial's settings and outcomes.

2 Methods

This second chapter describes first the characteristics of the study population, the setting and the interventions being compared within the INPHY trial. Then, it outlines the methodology applied for the development and design of the preceding conceptual, logic model and the subsequent health-economic, decision-analytic model. Lastly, to reflect the uncertainty around model parameters, techniques of sensitivity and scenario analyses are delineated. On principle, this cost-effectiveness analysis follows the methodological framework proposed by the Gates/International Decisions Support Initiative Reference Case for Economic Evaluation (Wilkinson et al., 2016) as well as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement to ensure structure, quality and transparency in its reporting (Husereau et al., 2022) (Appendix 1).

2.1 Population, setting and comparators

The INPHY trial will be conducted as a prospective, three-arm, randomised-controlled trial in patients who are treated for suspected or known CHD in Düsseldorf, Germany. Patients of the day-unit of the University Hospital's Department for Cardiology, Pneumology and Angiology and of the Cardio Centrum Düsseldorf will be eligible to participate in the study.

Overarching aim will be to develop, conduct, and evaluate a complex intervention that aims at improving physical activity in terms of daily walking steps in patients with a history of CHD. It should be noted that the following descriptions of the interventions reflect the current state of their conceptualisation. Some elements might change throughout the development of the clinical trial. Two interventions will be tested in two groups, i.e. monetary incentive (IG 1) and social incentive (IG 2) compared to a control group (CG) that receives no incentives. Randomisation will be performed at the individual level with equal randomisation (1:1:1). The intervention will last for 24 weeks, followed by a 24-week follow-up period. Figures 2 and 3 provide an overview of the study characteristics and it phases.

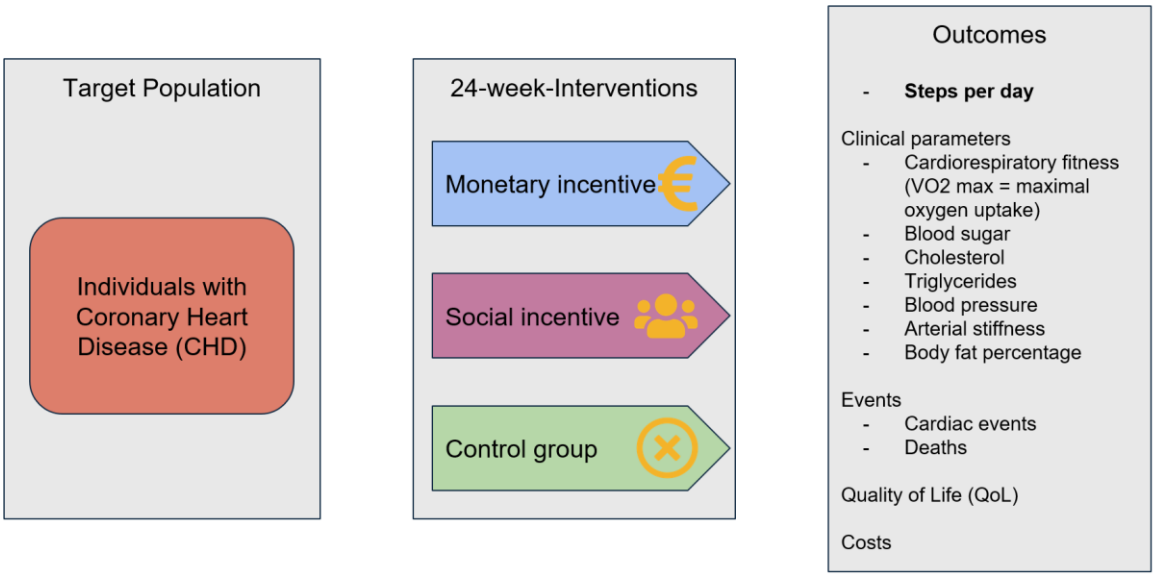

Figure 2: Design of the three-arm randomised controlled INPHY trial. Individuals with coronary heart disease receiving monetary and social incentives are compared with a control group with the primary physical activity outcome being steps per day.

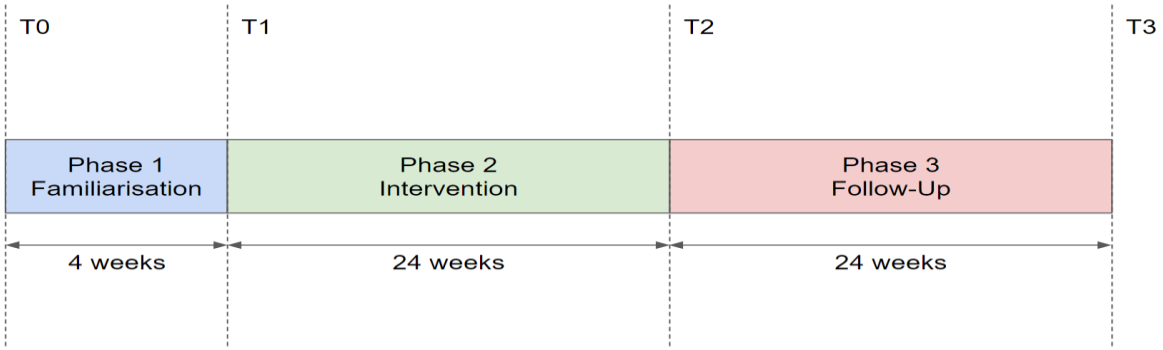

Figure 3: Phases of the planned INPHY trial. After a 4-week familiarisation phase, participants will undergo 24 weeks of intervention with a 24-week follow-up period.

To design the 24-week plan, an adaptive goal design will be chosen. While participants' baseline step count will mark their individual starting point, everyone will have a daily goal of 8,500 steps in the last week (week 24) (Ayabe et al., 2008). To prevent physical overload, step goals will gradually increase weekly from the individual base level step count. The weekly physical activity goal will be defined as achieving the predetermined daily goal of walked steps on at least 5 days of a week. To provide participants with aims, which are perceived accessible, participants will be asked to achieve the daily physical activity goal on only 5 of 7 days in a week. If participants fall short to meet the physical activity goal, the current and all subsequent physical activity goals according to the 24-week plan will be postponed by one week and the former step goal of the past week will be carried over as the step goal of the following week.

Incentives will be provided on a weekly basis if the weekly physical activity goal will be accomplished. Participants in the first arm will receive a monetary incentive, which will be framed in terms of loss reduction. In particular, incentives will refer to costs incurred by physical activity, e.g. sportswear, sport courses or equipment. Incentives will be framed to repay these costs which we assumed to sum up to 420€ over 6 months. Every participant in this arm will receive the same monetary incentive of 17.50€ for reaching the weekly physical activity goal, corresponding to 420€ in total. Feedback about successively achieving the physical activity goal will be provided by text message to a mobile phone at the end of each week during the intervention phase.

Participants in the second arm will receive a social incentive in the form of a social pre-commitment where they will designate two persons of their social environment (e.g. friends, family members). During the intervention period, these persons will be notified via text message at the end of each week if the participant has reached the weekly physical activity goal. If the participant has failed to reach the weekly goal, no message will be sent to the contact persons. This will ensure a focus on receiving positive gratification for participants. Participants will receive weekly feedback about the number of steps walked and whether the weekly goal will have been reached. Participants in the third arm, the control group, will receive no form of incentives.

2.2 Conceptual model

The appropriate development of a health economic model in medical decision analysis starts with "*understanding the problem that is being represented*" (Roberts et al., 2012). Current guidance in economic evaluations suggests first conceptualising the decision problem into a graphic abstraction as a foundation for the subsequent structures of the decision-analytic model (Squires et al., 2016; Tappenden et al., 2012). This so-called conceptual or logic model is a top-level visual representation of a real-world system in a simplified form. It illustrates causal relationships using simplifying assumptions by linking the key elements in a process and explaining how these interconnect and interact (Brassington and Younger, 2010; Gray and Sockolow, 2016). Epidemiologic evidence helps clarify possible causal mechanisms and serves as an essential basis for logically sequencing intervention strategies to expected outcomes with intended intervention steps. The theory of change

developed from the conceptual framework should guide the practical implementation of the intervention and its comprehensive programme evaluation.

In the case of INPHY's pre-trial modelling exercise, this theory-based approach was applied and is explained in the following. First, the context of the conceptual model was considered by immersing into the decision problem of incentivised, exercise-based secondary prevention interventions for CHD. Assembling a core project team of seven interdisciplinary members, an understanding of the problem system and the available evidence was gained, and the research aims and objectives were set. Second, we decided on the scope of the model, its components as well as their dynamics and interlinkage. For the conceptual model to be as relevant as possible, we aimed to accurately depict the trial logics and characteristics of INPHY. Therefore, study population, setting and comparators were analysed. Lastly, various external experts with a background in medicine, public health, health economics and modelling were consulted to discuss the feasibility and rigor of the theoretical framework. The conceptual model diagram was finalised in an iterative process of review, revision, and refinement.

Figure 4 depicts the conceptual model, illustrating the hypothesised causal pathway of the INPHY trial and its interlinkage to the health economic Markov model. Participants of this complex intervention will be randomised into three intervention arms, namely the monetary incentive group, the social incentive group, and the control group. It was expected that participation in the incentivised interventions will have a direct effect on the PA levels of CHD patients. The primary outcome of the INPHY trial will be mean steps per day objectively measured by a sealed pedometer worn on the waistband, for which reliability and validity has been established (Chan et al., 2022; Germini et al., 2022). Due to the lack of data regarding the dose-response relationship of PA measured in steps/day to clinical health outcomes, it was necessary to transform the measure "steps/day" to "MET.h/week", a more standardised physical activity measure. To incorporate the concomitant intervention effect of increased PA levels on health outcomes, relative risks parameters were used in the model. By applying relative risks (as multiplicatives) to model transitions, the CHD progression of participants with different PA levels could be projected. This allowed the estimation of health economic outcomes relevant to the three intervention arms, including a cross-comparison of costs and effects.

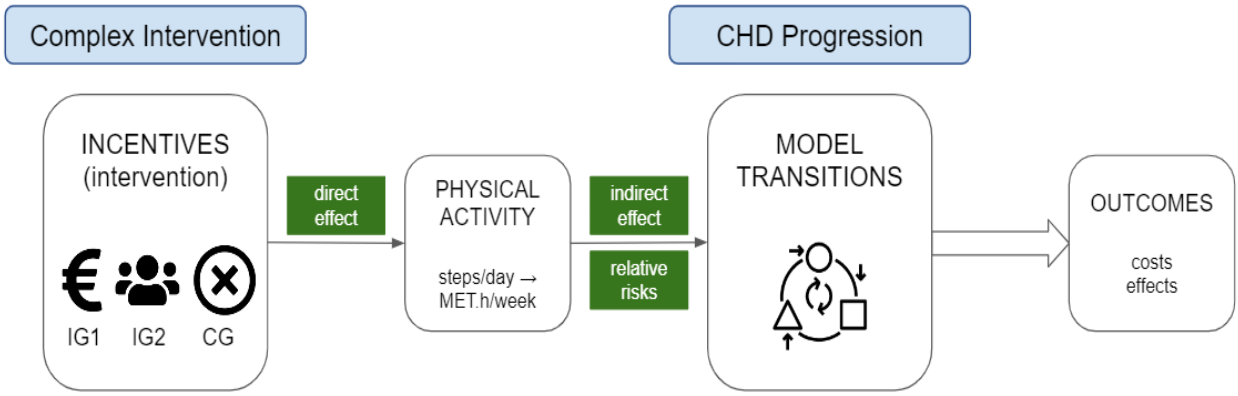

Figure 4: Conceptual, logic model. Participation in the incentivised interventions has effects on physical activity, which in turn influences model transitions through relative risks being applied to transition probabilities. IG = intervention group, CG = control group, MET.h = metabolic equivalent of task-hour, CHD = coronary heart disease.

2.3 Decision-analytic model

As described earlier, decision-analytic models may synthesise evidence from various sources. Against this background, input parameters were informed by comprehensive literature searches using a snowball approach. Covering databases including MEDLINE, Embase and Google Scholar, studies published in English and German were thoroughly screened regarding their applicability for the modelling exercise of this dissertation. The literature searches started with identification of keywords (related to the input parameters) and formulation of search strings. Then a tentative “start set” of published articles was used to begin backward and forwards snowballing. Backwards snowballing involved using the reference list to identify new papers to include. Through forward snowballing new papers were identified by looking at the citations of the original article after its publication. Final consideration of an article as a potential source was done after sequentially screening title, abstract and the full paper. After backward and forward snowballing, new articles identified in the iteration were put into a pile to go into the next iteration. Where available, evidence specific to the German setting was selected. However, due to lack of data, many model inputs had to be drawn from other high-income countries such as the US or the UK.

2.3.1 Model structure

A de novo economic decision-analytic model was developed by applying a Markovian approach (Briggs and Sculpher, 1998). As depicted in Figure 5, the Markov model comprised four mutually exclusive health states:

1. History of first MI
2. Reinfarction
3. Post-reinfarction
4. Death

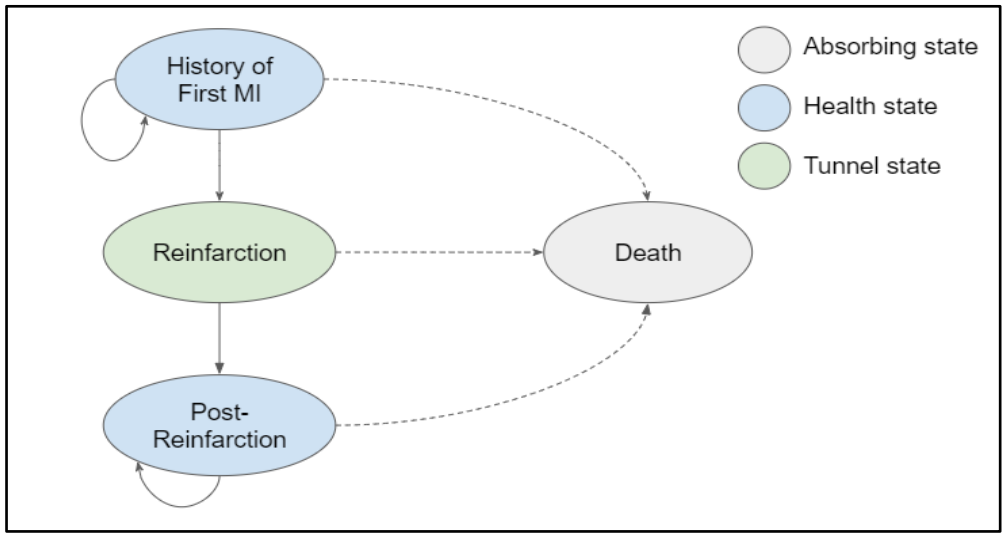

Figure 5: The four-state Markov model. This simulation considers a hypothetical cohort of patients who enter the model with a "history of first MI". The cohort follows their transition among the states from cycle to cycle based on transition probabilities. The arrows show transitions that can happen with each Markov cycle (1 year). The “reinfarction” state is built into the model as a unidirectional/transient tunnel state. This implies that, if entered, the cohort suffering a reinfarction has a 100% probability of exiting towards the “post-reinfarction” state after one cycle. The dead state is called an absorbing state, i.e. once a patient enters that state, the probability of exiting from the state is zero. MI = myocardial infarction.

For the base-case analysis, it was assumed that a cohort of 100 individuals aged 65 years with a male to female distribution of 1:1 entered the model with a “history of MI”. They could stay in their state or suffer a reinfarction. The transitional tunnel state “reinfarction” was added in order to more accurately capture the increased costs and morbidity associated with an acute infarction. Individuals with a reinfarction spend only one cycle in this tunnel state, before they move to the “post-reinfarction” state. At any time, participants with a history of first MI, reinfarction or post-reinfarction could die and, consequently, move to the absorbing state “death”.

Participants moved across the health states at the end of each discrete time interval, also known as a Markov cycle (Phillips, 2008). Along with the frequency of events in the disease progression of CHD, a cycle length of one year was applied to reflect the nature of this chronic disease. To account for all relevant differences in costs and effects between the alternative strategies being compared, the analytical time horizon of economic evaluations should be sufficiently long (O'Mahony et al., 2015). Especially with interventions for prevention or treatment of chronic diseases, as is the case for CHD, this requires a time horizon that captures the lifetime of the cohorts (Crossan et al., 2018; Lomas et al., 2018). Therefore, the model simulated until the age of 90 was reached in the cohort. Further, a health services provider (health system) perspective was taken.

2.3.2 Transition probabilities

Transition probabilities describe the likelihood of moving from one state to another, thereby "*governing the direction and speed of transitions*" (Briggs et al., 2018). They can be derived from epidemiological estimates, which must be annualised, given that one-year cycles were taken in this model.

For someone transitioning from the "history of first MI" to the "reinfarction" state, the cumulative incidence of reinfarction at one year in a cohort with a history of CHD/MI was estimated to be 0.04. This was based on a follow-up study of the HORIZON-AMI trial (Stone et al., 2014). Since "reinfarction" is a tunnel state, individuals only remain in that state for one cycle, after which they must transition to the "post-reinfarction" or "death" state. The probability of transition to post-reinfarction is therefore: $1 - probability\ of\ dying * RR\ of\ dying\ in\ the\ first\ year\ after\ reinfarction$. Within this model, once individuals are in the post-reinfarction state, they cannot experience another event. Therefore, they remain in that state or move to the death state.

The probability of dying was obtained from the national life table of Germany that, among others, describes the general population's all-cause probability of dying for different age and sex groups (DESTATIS, 2020). The age and gender distribution of the people entering the model, as well as how these changed over time, were

considered when calculating cycle-specific general population mortality. Previous studies found that individuals with CHD have an increased disease-specific probability of dying in contrast to healthy individuals (Johansson et al., 2017; Mozaffarian et al., 2003). To account for this, standardised mortality ratios (SMRs) in terms of relative risks (RR) were applied to cycle-specific general population mortality rates for the “history of MI”, “reinfarction” and ”post-reinfarction” states. They were estimated at 2.0 [95% Confidence Interval (CI) 1.99-2.01], 4.5 [95% CI 4.43-4.57] and 3.0 [95% CI 2.95-3.05], respectively. The SMRs were obtained from Smolina *et al.* (2012) and the UK’s guidance by the National Institute for Health and Care Excellence (NICE) (2020), reporting long-term survival after a first and second MI in England in 387,452 individuals.

2.3.3 Intervention effect

Individuals with CHD who participate in exercise-based prevention programmes such as the INPHY trial are assumed to transition differently across health states. To account for this concomitant intervention effect, it is common to apply RRs to estimate adjusted transition probabilities for intervention cohorts (Olariu et al., 2017). This requires data to be available regarding the dose-response relationship between walking steps, the primary endpoint variable of INPHY, and clinical health outcomes. However, pedometers are a relatively new technique to monitor walking steps as a surrogate of physical activity. Evidence on the effectiveness concerning the role of *steps* on long-term morbidity and mortality is yet to emerge for the specific population of CHD patients in Germany and around the world (Bjarnason-Wehrens et al., 2009; Bull et al., 2020; Department of Health & Human Services, 2018). To still account for intervention effects, walking steps were transformed into metabolic equivalents (MET), a more standardised measure to assess energy expenditure in physical activity studies. A MET is defined as the ratio of the rate of energy expended during an activity to the rate of energy expended at rest (Lee, 2009). For example, 1 MET is the rate of energy expenditure while at rest. A 6 MET activity expends 6 times the energy used by the body at rest. If a person does a 6 MET activity for 1 hour, he or she has done 6 x 1 = 6.0 MET-hours (MET.h) of physical activity. Against this background, walking steps were transformed into absolutely defined intensities (metabolic equivalents) by applying average walking cadence estimates (steps/min). In the following the methodology is explained.

The number of step goal in week *w* is:

$$S_w = S_0 + (\frac{S_{24}-S_0}{L}) * w,$$

where $w \in [1, \dots, 24]$, is a week of intervention, S_0 is the mean number of daily steps at baseline, S_{24} is a final goal, namely 8.500 steps/day, *L* is a length of the intervention in weeks. If a participant's baseline level is equal to or more than 8,500 steps/day, then the daily step goal is fixed at 8,500 steps/day. The pedometer-cut point for the maximum of the light intensity walking was roughly 100 steps/min or 6000 steps/hour (h) for both genders that corresponds to approximately 3 metabolic equivalents per hour (MET.h) (Tudor-Locke et al., 2019, 2005). The PA per week was categorised into "least active" (<24 MET.h/week), "intermediate" (24-56 MET.h/week) and "most active" (>58 MET.h/week). The categorisation was based on Stewart *et al.* (2017), analysing the relationships between the amount of mild, moderate, and vigorous physical activity and subsequent MI, stroke, and mortality in a large cohort of patients (n = 15,486) with stable CHD who participated in the global STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial. Total MET.h/week is calculated as

$$MET_w = \frac{(S_w * D_a + S_0 * (7 - D_a))}{v} * MET_0 ,$$

where MET_w is a total METs per week, MET_0 is an intensity of activity equal 3 MET.h, S_w is a daily step goal, S_0 is a baseline step level, D_a is a number of day when a person adheres, v is a light walking intensity equal to 6,000 steps/h. A baseline step level of 3000 steps per day was assumed in the model. According to these calculations, the maximum level of physical activity possible in INPHY will correspond to 29.75 MET.h/week, if a participant walks 8,500 steps every day with a cadence of 100 steps/min. Therefore, in this model, participants could maximally reach the "intermediate" PA category at the end of the intervention, if they keep their pace.

Depending on the different PA categories ("least active", "intermediate", "most active"), respective exercise-related intervention effects in terms of adjusted RRs for morbidity and mortality were applied. They are shown in Table 2. In the conservative base-case analysis, the intervention effect was applied only in the intervention year. The model presumed that after the end of the first year, potential intervention-related benefits of PA on health outcomes lapsed. Figure 6 depicts the probability equations associated with the different transitions and how the intervention effect was taken into account.

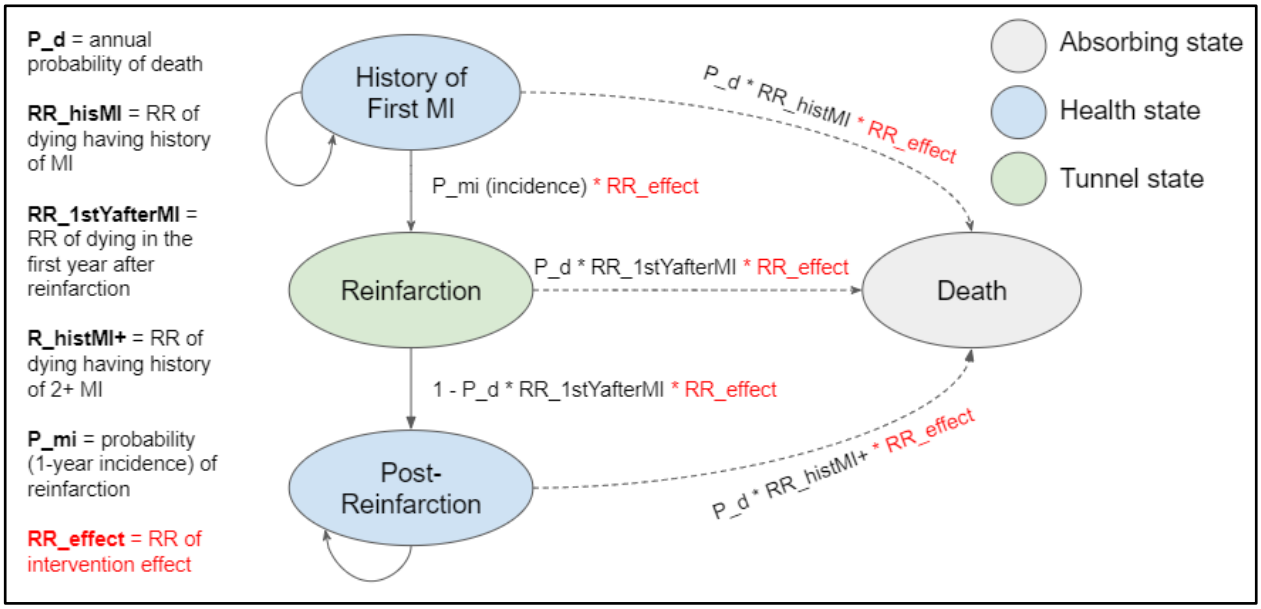

Figure 6: Four-state Markov model with probability equations between transitions. Transitions among Markov states are associated with a transition probability. The transition probabilities differ for intervention arms.

2.3.4 Adherence

The effect of PA on clinical outcomes depends on adherence to the prevention intervention, which was integrated in the model as follows. Along the participants' intervention life cycle, different key adherence variables were identified (Figure 7). First, the actual number of days per week on which the participant will adhere to the predetermined daily goal of walking steps. In order to receive the incentive, participants will be required to achieve the step goal on 5 out of 7 days. Second, the level of PA on non-adhering days. On days where the step goal was not reached, participants were modelled to walk as much as at baseline, as at the previous week or as the mean of all last weeks. Third, the level of PA in the remaining 28 weeks of the intervention year. In the post-intervention period participants could return with their PA level to baseline, to the mean of previous weeks or to the maximum PA level of the previous weeks. Fourth, the effect of PA on health outcomes in the post-intervention year. For the time period after the intervention year, no effect, the same effect or a twice lower effect, relative to the intervention year, was modelled. As described in the previous subchapter, potential exercise-related intervention effects on health outcomes are restricted to the intervention year in the base-case analysis, i.e. no effect in the post-intervention years.

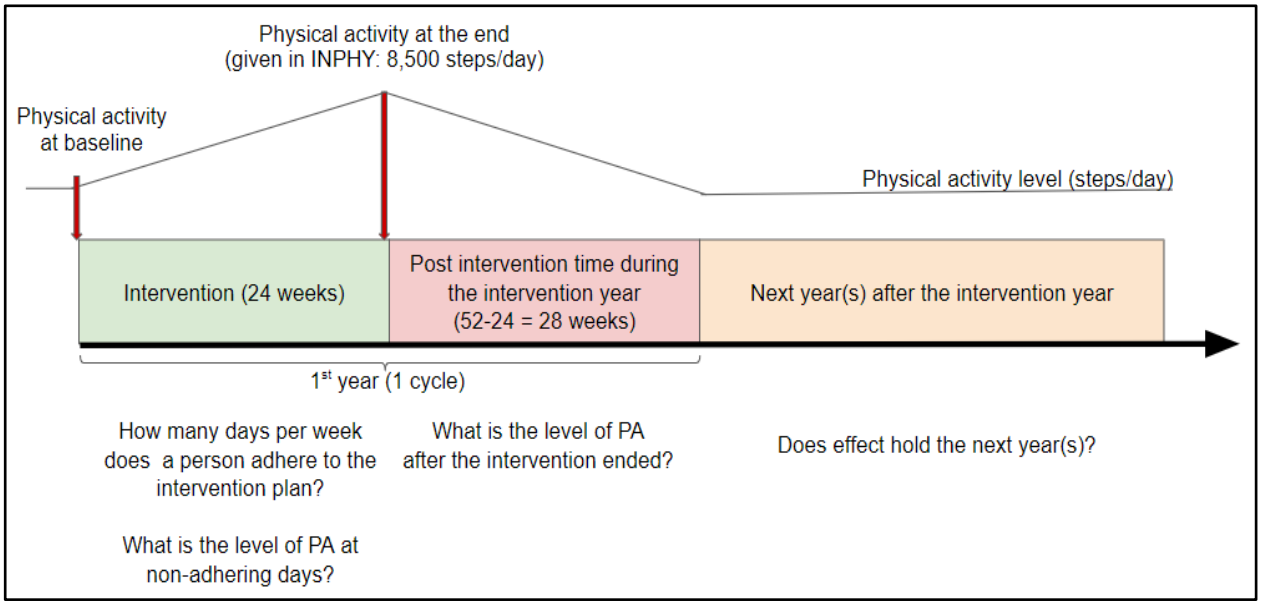

Figure 7: Key adherence variables along the participants' intervention life cycle. Assumed changes in physical activity levels throughout the intervention life cycle are displayed (top), with guiding questions to elucidate relevant adherence variables (bottom). PA = physical activity.

2.3.5 Costs

Cost estimates can be applied to both health states and interventions. Corresponding to the healthcare services provider perspective, only direct medical costs from the primary and secondary care level were considered (Appendix 2). The annual direct medical cost of care for individuals with a history of MI was 1873€ in Germany (Lutter et al., 2019). This estimate was drawn from the German population-based KORA FF4 study (Cooperative Health Research in the Region of Augsburg). The instant costs of myocardial infarction for the tunnel state "reinfarction" was estimated at 14,315€ based on the systematic review by Schmid (2015), analysing individual-level medical costs of the cardiovascular events in Germany after the German Diagnosis Related Groups (G-DRG) reform. The annual direct cost for the post-reinfarction state was 2482.2€, adding an increase in costs following recurrent MI to account for the assumed additional development of heart failure in 20% of patients after MI (Sehested et al., 2019). The instant cost of death was estimated at 2247.6€ (Bonafede et al., 2015).

The total costs of the monetary incentive and social incentive intervention per year (excluding direct incentive costs) was estimated at 549.46€ per person and

510.7€ per person, respectively. The costs of the monetary and social incentive interventions were primarily developed on an activity-based costing basis. Firstly, different cost components of the intervention were identified. Secondly, contact frequency and duration of these cost components were ascertained. Thirdly, staff cost estimates were applied and an additional cost was allocated to overheads as well as materials and supplies. We assumed that the intervention was implemented, disregarding additional RCT costs (Appendix 3).

2.3.6 Health effects

Health outcomes can be measured in health-related quality of life weights (HRQoL) ranging from the value of 0 (equivalent to death) to 1 (perfect health). These utility scores are used to calculate quality-adjusted life-years (QALYs) through multiplication with the time duration spent in different health states (Drummond et al., 2005). HRQoL values can be applied to both health states and interventions. The utility value was lower in the acute reinfarction state than in the chronic “history of first MI” and “post-reinfarction” state. Utility scores for “history of first MI”, “reinfarction” and “post-reinfarction” were 0.842, 0.779 and 0.821, respectively (NICE, 2011; NICE, 2020). In post-trial economic evaluations, it is common to measure incremental utilities gained from the interventions and apply them to the intervention cohorts in the model (Briggs et al., 2018). However, because of a conservative modelling approach and because trial data regarding the impact of INPHY’s intervention arms on HRQoL is not collected yet, incremental utilities associated with participating in an incentivised reinforcement scheme were not applied.

It is widely accepted in economic evaluations that both costs and effects need to be adjusted for differential timing. This includes discounting of costs and effects that occur in the future to their present value (Severens and Milne, 2004). The common practice of discounting is done to reflect the fact that individuals and society have a positive rate of time preference for money or health in the present over money or health in the future (Attema et al., 2018). The present model applied an annual discount rate of 3% in accordance with recommendations by the WHO (Edejer and World Health Organization, 2003). Tables 1 and 2 summarise key parameter values.

Table 1: Costs and utilities associated with each health state.

Health state	Cost of care (€)	Utility (QALYs)
History of first MI	1,873 *	0.842 §
Acute reinfarction	14,315 †	0.779 §
Post-reinfarction	2,482.2 ††	0.821 §
Death	2,247.6 ¶	0 #

* Lutter et al., 2019. † Schmid, 2015. †† Lutter et al., 2019; Sehested et al., 2019. ¶ Bonafede et al., 2015; § NICE, 2011; NICE, 2020. # by definition.

Table 2: Markov model parameters and physical activity effects on outcomes.

Input	Data
Markov model parameters	
Standardised mortality ratio (SMR) in the "history of first MI" state	2.00 [1.99-2.01] *
Standardised mortality ratio (SMR) in the "reinfarction" state	4.50 [4.43-4.57] *
Standardised mortality ratio (SMR) of death in the "post-reinfarction" state	3.00 [2.95-3.05] *
Annual probability of a reinfarction	0.04 †
Annual probability of dying	life-tables ††
Physical activity effects on outcomes	
Relative risk (RR) of a new MI in an intermediately active group comparing with a least active group	1.02 [0.86-1.22] ¶
Relative risk (RR) of a new MI in an active group comparing with a least active group	0.90 [0.74-1.08] ¶
Relative risk (RR) of death in an intermediately active group comparing with a least active group	0.75 [0.65-0.87] ¶
Relative risk (RR) of death in an active group comparing with a least active group	0.70 [0.60-0.82] ¶
The threshold between a least active and intermediately active group, MET.h/week	24 ¶

* Smolina et al., 2012; NICE, 2020. † Stone et al., 2014. †† DESTATIS, 2020. ¶ Stewart et al., 2017.

2.3.7 Base-case analysis

The base-case consisted of a 65-year-old cohort (n=100) with a female-to-male ratio of 1:1, which was followed for 25 1-year cycles, i.e. up to the age of 90. A baseline step count of 3,000 steps/day was assumed with a cadence of 100 steps/h. The following adherence parameters were applied. First, participants adhered to the predetermined daily goal of walking steps on 5 out of 7 days. Second, the level of PA on non-adhering days was as much as at the mean of all last weeks. Third, the level of PA in the remaining 28 weeks of the intervention year was assumed to be different for the intervention arms based on behaviour research (Mitchell et al., 2020). While the monetary incentive group returned to baseline PA after the 24-week intervention (as the financial contributions were not paid any longer), the social incentive group was assumed to achieve the mean PA of the previous intervention weeks. Fourth, no effect of PA was assumed on health outcomes in the years after the intervention year.

Outcomes over a lifetime-period were calculated for each intervention and included the (1) discounted cumulative healthcare costs and (2) the number of discounted QALYs gained associated with each intervention arm. (3) Incremental cost- effectiveness ratios (ICERs) were determined for the interventions, using the following formula:

$$ICER\ (€\ per\ QALY)\ =\ (C1\ -\ C0)\ \div\ (E1\ -\ E0),$$

where C1 is the cost of an intervention in Euros, E1 the corresponding effect of the intervention in QALYs gained, and C0 and E0 respectively the costs and effects of control.

2.3.8 Sensitivity and scenario analyses

As input parameters can contribute to uncertainty, additional sensitivity analyses were used to explore how the direction and magnitude of model outputs change upon variation in inputs. Accordingly, inferences can be drawn about the extent to which the model's results are affected by the underlying assumptions (Briggs et al., 2012). Probabilistic sensitivity analysis (PSA) and scenario analysis were conducted which are described in the following.

Probabilistic sensitivity analysis (PSA) was conducted, which does not focus on single parameter uncertainties as in the classical deterministic sensitivity analysis. Instead, PSA explores interactions between different sources of uncertainty and overall model uncertainty (Briggs et al., 2012). The process starts by assigning specified probability distributions to input parameters as specified by good research practice (Appendix 4) (Briggs et al., 2012). Then, random draws are taken from these distributions in a process called Monte Carlo simulation. This leads to the generation of a large number of cost and utility estimates, which finally enables the plotting and analysis of the average range of cost-effectiveness results (Health Information and Quality Authority, 2014; O'Mahony and Coughlan, 2016). Against this backdrop, in this Markov model, PSA was performed with simultaneous random variation of input parameters using a second-order Monte Carlo simulation with 50 iterations. To judge their stability, the results are presented as scatter plots on the cost-effectiveness plane, where each point represents one simulation. Moreover, cost-effectiveness acceptability curves (CEAC) were calculated to delineate the probability that each intervention is cost-effective compared to control.

Eight scenario analyses were undertaken to explore the impact of varying some of the base-case assumptions. Scenario 1 explores the impact of adherence to PA in the post-intervention period in year one. In the scenarios 2 and 3, different effect durations of 2 years and 5 years were simulated, respectively. A fourth and fifth scenario varied the baseline PA of participants, simulating 2000 steps per day and 4000 steps per day. Scenario 6 ascertains the role of PA intensity, assuming moderate/brisk walking at 4 MET instead of light walking at 3 MET in the base-case. In the final two scenarios, patient heterogeneity in the model was explored by re-running the model for a mean patient age of 55 and 75 years, respectively.

The Markov model and its analyses and simulations were conducted using software programme R and the library "hesim 0.5.1" (health economic simulation modelling).

3 Results

This third chapter presents the results of the health-economic, decision-analytic model. In the base-case analysis, outcomes obtained by running the Markov model with the most probable assumptions and input parameters are displayed. Thereafter, the findings of the sensitivity and scenario analyses, where model assumptions and input parameters were altered, are delineated.

3.1 Base-case analysis

Given the model assumptions used for the base-case, which were described in the Methods section, the incremental QALYs gained of the monetary and social incentive, relative to control, were respectively estimated at 0.01 [95% CI 0.00-0.01] and 0.03 [95% CI 0.02-0.05]. In comparison to control, implementation of the monetary and social incentive interventions increased the costs by 795€ [95% CI 697-884] and 831€ [95% CI 593-1,191], respectively. Calculations of ICERs, relative to control, reveal that the social incentive intervention was cost-effective with an ICER of 24,473€/QALY [95% CI 15,871-38,868], while the monetary incentive was cost-effective with an ICER of 112,015€/QALY [95% CI 81,140-169,888].

Table 3: Incremental quality-adjusted life years (QALY), incremental costs and incremental cost-effectiveness ratios (ICER) for the intervention arms, relative to control.

Outcome	Monetary Incentive	Social Incentive
Incremental QALY (relative to control)	0.01 [0.00-0.01]	0.03 [0.02-0.05]
Incremental costs (relative to control), Euro	795 [697-884]	831 [593-1,191]
ICER, Euro/QALY	112,015 [81,140-169,888]	24,473 [15,871-38,868]

3.2 Sensitivity and scenario analyses

In the multivariate sensitivity analysis, the model was simulated 50 times with input parameters being simultaneously varied according to their distribution of uncertainty (Appendix 4). After each iteration, the incremental differences in costs and effects were recorded. The results of the simulations were projected in a cost-effectiveness plane (Figure 8), consisting of a diagram with four quadrants, classically represented by compass points. Dots representing the simulations in the north-east quadrant indicate that both the monetary and social incentive interventions were more costly but also more effective in terms of QALYs gained, relative to control. None of the incentive interventions dominated the control arm, i.e. were more effective and less costly (south-east quadrant). Likewise, none of the incentive interventions were dominated by the control arm, i.e. were less effective and more costly (north-west quadrant).

To ascertain whether the additional QALY benefit justifies the additional costs, the willingness-to-pay (WtP) threshold of Germany was applied as a diagonal line. Although Germany does not apply a specific willingness-to-pay threshold for the introduction of new interventions, this model followed the WHO's practice recommendations to use thresholds of one to three times (1-3x) Gross Domestic Product (GDP) per capita (Edejer and World Health Organization, 2003). Therefore, a conservative willingness-to-pay threshold of 43,000€ per QALY gained was assumed, corresponding to one time (1x) the 2021 per-capita GDP in Germany. The vast majority of scenarios from the social incentive intervention fell in the area below this threshold and may be deemed cost-effective. In contrast, the simulations from the monetary incentive intervention laid above the threshold, suggesting it may not be cost-effective for the German setting.

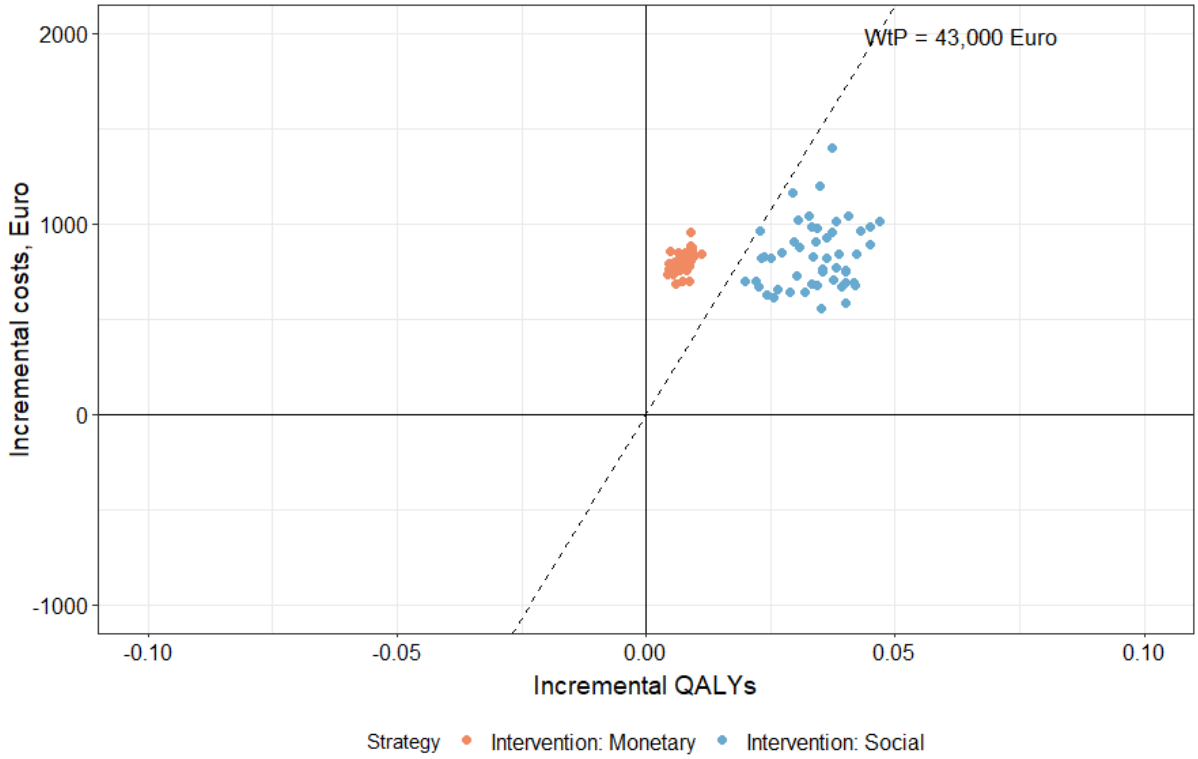

Figure 8: Cost-effectiveness plane. Incremental costs (ΔC) and effects (ΔE) of the intervention arms over a hypothesised maximum acceptable incremental cost–effectiveness ratio, i.e. willingness-to-pay (WtP) threshold of 43,000€/QALY gained (dotted line). QALYs = quality-adjusted life years.

Figure 9 presents the results as a cost-effectiveness acceptability curve (CAEC), a way to display the uncertainty around the value of the willingness-to-pay threshold. The CEAC shows the relationship between the probability of the incentive interventions' cost-effectiveness and a range of hypothesised willingness-to-pay thresholds per additional QALY gained. At the threshold of 43,000€ per QALY gained, the probability that the social and monetary incentive intervention would be seen as cost effective was 100% and 0%, respectively. A cost-effectiveness probability of 100% was already reached for the social incentive intervention at a willingness-to-pay threshold of 42,000€/QALY gained. For the monetary incentive intervention, the probability of cost-effectiveness was at 4% and 68% at double and triple the threshold, i.e. 86,000€/QALY gained and 129,000€/QALY gained, respectively. A cost-effectiveness probability of 100% was reached for the monetary incentive intervention at a threshold of 174,500€/QALY gained.

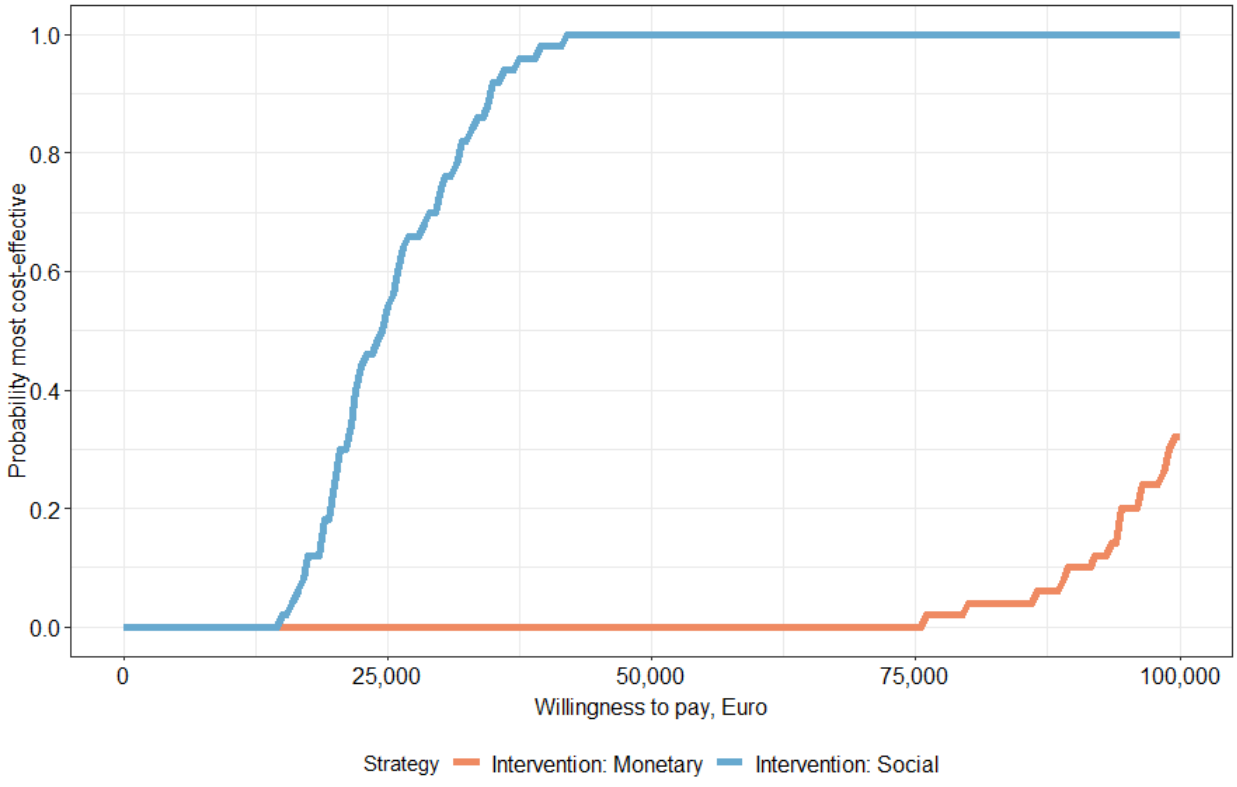

Figure 9: Cost-effectiveness acceptability curve (CEAC). The CEAC represents the probability that each intervention arm is cost-effective (y-axis, ranging from 0 to 1) for given willingness-to-pay thresholds (x-axis).

Table 4 displays the results for the eight different scenarios simulated, which explored the impact of variation in the base-case assumptions.

Table 4: Results of the scenario analyses.

Scenario	ICER monetary incentive	ICER social incentive
Post-intervention PA during the first year: maximum of previous weeks	31,555	24,473
2-year effect period with the same (continuing) effect as in year 1	103,328	24,224
5-year effect period with the same (continuing) effect as in year 1	84,241	23,515
65 years, 2000 steps at baseline	129,509	24,933
65 years, 4000 steps at baseline	94,421	23,831
65 years at 4 MET (moderate/brisk walking)	69,225	22,650
55 years, 3000 steps at baseline	201,271	36,801
75 years, 3000 steps at baseline	78,497	19,829

4 Discussion

In this fourth chapter, the results are summarised, critically discussed and interpreted in light of the current research context. After acknowledging the strengths and weaknesses of the dissertation from different angles, implications of this pre-trial health economic modelling are deduced for the INPHY trial and for future research, practice, and policy.

4.1 Main findings

Addressing the lack of health economic research concerning secondary prevention programmes for CHD, this dissertation is the first to model the long-term cost-effectiveness of incentivised reinforcement interventions for physical activity promotion, relative to control, both internationally and in Germany. In line with the recommendations of the UK MRC for complex interventions, economic and clinical consequences of a socially incentivised and monetarily incentivised intervention were estimated using a decision-analytical Markov model, before implementation as part of the INPHY trial. This pre-trial health economic modelling suggested that health effects are observed for both intervention arms, compared to control. The social incentive intervention was more cost-effective at an ICER of 24,473€/QALY gained [95% CI 15,871-38,868], than the monetary incentive intervention with an ICER of 112,015€/QALY gained [95% CI 81,140-169,888], relative to control (Table 3).

To identify whether the interventions are good value for money, ICERs should be compared with cost-effectiveness thresholds specific to the local healthcare system. Unlike in England or Ireland, for example, no explicit threshold value for the cost-effectiveness of interventions or medical technologies has yet been defined for Germany. Ireland's cost-effectiveness threshold is currently 45,000€/QALY gained (Health Information and Quality Authority, 2014; O'Mahony and Coughlan, 2016). In the UK, for example, a range of 20,000 to 30,000 Great Britain Pounds (GBP, £)/QALY gained has been defined as a cost-effective technology by the National Institute for Health and Care Excellence (NICE) (National Institute for Health and Clinical Excellence, 2013). Against this background, it is consequently difficult to clearly categorise the ICERs listed above as cost-effective or not. However, one to three times a country's annual GDP per capita has been a widely used threshold for

cost-effectiveness studies within public health, which was initially proposed by the WHO (Edejer and World Health Organization, 2003). Given Germany's 2021 per-capita GDP of approximately 43,000€ (DESTATIS, 2022), a probability of cost-effectiveness of 100% for the social incentive intervention was reached. When three times per-capita GDP was applied, a 68% probability of cost-effectiveness was reached for the monetary incentive intervention. Integration of cost-effectiveness assessments into recommended interventions or services is also proposed by physician specialist societies, such as the AHA (Anderson et al., 2014). Comparing INPHY's cost-effectiveness results to the proposed level of value categories by the AHA, the social and monetary incentive interventions would be of high value (ICER <50,000 US$/QALY gained) or intermediate value (ICER 50,000-150,000 US$/QALY gained), respectively.

4.2 Comparison with other studies

Drawing direct head-to-head comparisons of the main findings with previous studies is limited. This is because no other studies were found which cover the same combinations of characteristics as this dissertation, namely

(a) CHD as patient population,
(b) physical activity as lifestyle modification technique,
(c) monetary and/or social incentives as intervention strategy,
(d) cost-effectiveness measures as outcome parameters and
(e) pre-trial modelling as study type.

Only few international studies have estimated cost-effectiveness measures of incentive-based prevention programmes for increasing physical activity using modelling techniques, although not specific to the CHD population. For instance, Verhoef et al. (2016) investigated the cost-effectiveness of the Give-it-a-Go programme, which offers free leisure centre memberships to physically inactive members of the public in a single London Borough receiving state benefits. To analyse the costs and QALYs a lifetime Markov model was developed. Compared with control, the PA incentive scheme increased costs by 67.25£ and QALYs by 0.0033. The incremental costs per QALY gained were 20,347£ [95% 513-35,119]. While the Give-it-a-Go programme was associated with comparable cost-effectiveness estimates as the INPHY's social incentive arm, important differences in

model assumptions remain. Participants of the Give-it-a-Go programme were physically inactive, some of whom had comorbidities such as CHD, diabetes, or stroke. However, in the model, all participants were assumed to be healthy at the start. Further, Verhoef et al. (2016) added mental health gains for time spent on physical activity to the utility values. Due the conservative modelling approach for INPHY and its uncertain effects on HRQoL, incremental utilities such as mental health gains were not applied. Interestingly, when the mental health gain was omitted from the analysis for the Give-it-a-Go programme, the incremental costs per QALY gained increased to almost 1.5 million GBP.

Another example is the Australian ACHIEVE study, where participants received incentives in the form of material goods such as clothing, supermarket vouchers and cookbooks, when physical activity targets were reached (Maple et al., 2022). The study included adults aged 40 to 65 years with membership in an Australian health insurance fund. In the post-trial analysis where the intervention effect was assumed to be maintained for one year, the ICER was estimated at 74,683 Australian Dollars (AUD, AU$) [95% CI 12,054-520,362] per QALY gained. The cost-effectiveness acceptability curve revealed that 24% of the iterations modelled were predicted to be cost-effective at a willingness-to-pay threshold of 50,000 AU$ per QALY gained. Despite the differences in terms of study population, incentive design and study type, the resulting cost-effectiveness estimates can be seen on a similar scale to that of INPHY's pre-trial model. INPHY's social incentive arm achieved higher probability of cost-effectiveness at a willingness-to-pay threshold equivalent to 50,000 AU$ (approximately 32,000€), while the monetary incentive arm was comparatively less cost-effective (Figure 9).

In conclusion, both studies showed promise for cost-effectiveness from their health sector (provider) perspective, but the results were constrained by uncertainty over the sustainability of the benefits. The incremental costs per QALY gained were 20,347£ and 74,683 AU$ in the base-case with wide confidence intervals in sensitivity analyses, frequently crossing the respective thresholds of cost-effectiveness.

The cost-effectiveness of preventive care *in general* (i.e. not specific for CHD secondary prevention interventions and not based on modelling techniques), has been extensively studied (Cohen et al., 2008; Maciosek et al., 2009; van Baal et al., 2008). Different reviews suggest that adult counselling regarding the use of low-dose aspirin and childhood immunisation are two preventive measures that could reduce costs. Against a common misconception, however, the vast majority of preventive treatment does not result in cost savings in the given analytical time horizons. Numerous preventive strategies appear to be rather cost-effective than cost-saving, providing good value for the limited resources in the healthcare system. In order to compare with the case of INPHY, the sensitivity analysis with its cost-effectiveness plane should be taken into consideration (Figure 8). It suggested that the scenarios would almost entirely fall in the north-east quadrant suggesting cost-effectiveness, and not in the south-east quadrant suggesting cost-savings. The cost-effectiveness estimates of INPHY support evidence from previous observations in preventive care.

4.3 Rationale for adherence model assumptions

It remains unclear to which degree INPHY impacts participants' physical activity adherence towards its interventions and beyond. Therefore, the model employed assumptions regarding the adherence variables, which might be considered conservative. It was assumed that after the 24-week intervention, exercise levels in the remaining 28-weeks of the intervention year differed between the monetary and social incentive interventions. On one hand, the monetary incentive group returned to their baseline physical activity after the intervention period since the financial contributions were not paid any longer. On the other, participants in the social incentive group achieved to walk the average step count of the previous intervention weeks, assuming the medium-term formation of physical exercise habits as a result of broader social environment integration. In the following it is explained how this assumption framework for INPHY was informed by previous research around incentivised reinforcement schemes. Nevertheless, it is important to highlight that prior evidence primarily emanates from studies of the general population and of overweight/obese populations, not cardiac populations specifically.

For monetary incentives, several systematic reviews and meta-analyses have concluded that financial rewards boost physical activity in the short term (3 months or

less) and while in place. The evidence for persistent improvements in physical activity over the long run (six months or more) and after monetary incentives have been removed is inconclusive (Barte and Wendel-Vos, 2017; Giles et al., 2014; Mitchell et al., 2013; Strohacker et al., 2014). Because of the inconclusive effects of financial incentives in the follow-up, we used the assumption of returning to baseline physical activity in the model. For the assumption on social incentives, the findings of the STEP UP trial (Social Incentives to Encourage Physical Activity and Understand Predictors) were considered. The randomised controlled STEP UP trial assessed the role of a 24-week long behaviourally designed intervention to increase physical activity among overweight and obese adults in the US (Harrison et al., 2019; Patel et al., 2019). In the “supportive social incentive arm”, which was relatively comparable to INPHY’s social incentive design, participants were asked to identify a family member or friend who would be a support sponsor and be emailed a weekly report on the participant’s step performance. In the adjusted model, compared with controls, participants had a significantly greater increase in mean daily steps from baseline in the support arm (adjusted difference from control, 689; 95% CI 267-977). During the 3-month follow-up, physical activity in the supportive social incentive arm remained greater in the support arm (adjusted difference from control, 428; 95% CI 19-837) than the control arm. Support from and accountability to family and friends are seen as common facilitators to physical activity (Wahlich et al., 2017).

Overall, these insights into incentives for physical activity led to the differing model assumptions for INPHY’s intervention. It is crucial to consider the potential bias of these findings, given that studies involving behavioural economic incentives have predominantly taken place within the general and overweight/obese population. For patients with CHD, research is currently underway to establish the effectiveness of incentives in promoting physical activity, but early results seem promising (Chokshi et al., 2018; Fanaroff et al., 2023).

4.4 Strengths and limitations

This dissertation exhibits several strengths and limitations attributable to multiple overarching categories, including model type, structure, scope, and evidence.

Conducting pre-trial health economic modelling is recommended to inform the design and development of behavioural interventions. It is considered best practice according to health economic and intervention development guidelines, including the latest MRC framework for complex interventions (Caro et al., 2012; Husereau et al., 2022; Skivington et al., 2021). Modelling can provide valuable insights before trials are implemented, but seems to be underused, potentially due to its complexity and the preference for feasibility and efficacy studies (Gray et al., 2011; Komorowski and Raffa, 2016).

State-transition models, such as Markov models, are well adapted to simulate the progression of chronic diseases in the context of public health. Their usefulness to appropriately guide medical decision-making has been shown in research and policy alike (Carta and Conversano, 2020; Sonnenberg and Beck, 1993; Sox et al., 2013). Nonetheless, this model type might not adequately account for the population's variation in CHD. The use of average values restricts the scope of inferences that may be formed because physiological changes in CHD are continuous variables, and costs and benefits may differ correspondingly. One could argue that individual-level simulation modelling with unique risk equations might be more suitable for economic analyses of CHD prevention strategies, but seems too ambitious for the purpose of pre-trial modelling due to its need of extensive data (Dakin et al., 2020; Marshall et al., 2020).

This dissertation uses a comprehensive four-state model of CHD that incorporates both chronic states and an acute tunnel state of reinfarction. Simultaneously, as all models are approximations of clinical reality, this dissertation concentrated on MI while the role of other entities of CHD such as angina were not explored. Moreover, this model was only able to capture one episode of recurrent infarction, although in clinical reality patients can suffer multiple reinfarctions. These limitations could be addressed by adding additional states and incorporating time dependency into transitions, if more disaggregated, long-term data on CHD in Germany and the world was available.

Real-world evidence has been praised for its potency in providing data-driven answers and thereby in its ability to decisively inform health decision-making (Bowrin et al., 2019; Lu et al., 2021; Sonnenberg and Beck, 1993; Trerayapiwat et al., 2022). For instance, Trerayapiwat *et al.* (2022) used data retrieved from Thailand's national database, covering 75% of the whole population, to generate a cost-effectiveness analysis of fibrinolytic therapy in patients with ST-segment elevation myocardial infarction. Asaria *et al.* (2016) used electronic health records from the UK to inform their input parameters when modelling the costs and outcomes in stable CHD for individuals with different risk profiles. In their health economic analysis, Thokala *et al.* (2020) even used real-world data to define the health states of their Markov Model and to model transitions between them, specific to the UK setting, to estimate the cost-effectiveness of telemonitoring for heart failure. Appropriately designed and methodologically sound real-world evidence from Germany's claims data could be used to address the challenge of generating local data for model inputs (Gansen, 2018; Jaksa, 2019).

The model focused mainly on CHD-related costs and QALYs. Benefits of INPHY's lifestyle programmes on other disease entities such as hypertension, dyslipidaemia or diabetes were not captured, but would likely optimise cost-effectiveness. For example, an exercise-based cardiac rehabilitation programme for cardiovascular patients in Australia showed significant reductions in systolic and diastolic blood pressure with an average participant's blood pressure diminishing from 130.2/71.3 millimetre of mercury (mmHg) to 126/68.8 mmHg. Total cholesterol decreased from 4.0 to 3.7 mmol/L, with significant decreases in LDL cholesterol from 2.56 to 2.09 millimoles per litre (mmol/L), and non-significant increases in HDL cholesterol from 1.08 to 1.14 mmol/L (Gardiner et al., 2017). Moreover, vigorous physical activity levels led to improved endothelial function and improved arterial stiffness measured by ultrasonographic flow mediated dilation and pulse wave velocity in patients after myocardial infarction (Tršan et al., 2021).

No additional quality of life estimates were added to the exercise-based intervention arms, because of the conservative approach taken in this model. Although strong evidence has demonstrated that in the general population even mild PA improves quality of life (Gill et al., 2013; Marquez et al., 2020). In the specific population of older adults, meta-analytic results reported that, collectively, exercise

programmes improved life quality (overall and health-related combined) of older adult participants relative to inactive control groups (Z=2.23, p=0.03), with a pooled standardised mean difference of 0.86 [95% CI 0.11-1.62] (Park et al., 2014). Among CHD patients, physical activity improves QoL and well-being when compared with sedentary controls (Bailly et al., 2018; Gutama et al., 2022; Wang et al., 2020). In the French randomised “As du Cœur” (Ace of Heart) study, the EQ-5D utility score mean was 0.828 for the “progressively autonomous physical activity” arm at baseline and 0.891 after the 5-month-intervention and 0.882 at year 1, corresponding to a gain of 0.054 (Bailly et al., 2018). Given the modest gains in QALYs associated with INPHY’s interventions in the conservative base-case (Table 3), the inclusion of incremental utilities for the PA arms would further improve its cost-effectiveness. One could even argue that benefits in the quality-of-life estimates would be reasonable to assume as they are likely to occur in a real-life implementation of INPHY.

Very limited evidence regarding the dose-response relationship between steps and clinical endpoints, including morbidity and mortality, in the special population of CHD patients restricted the application of exercise-based intervention effects. According to randomised clinical trials of exercise training after MI, increased exercise appears to reduce cardiovascular risk (Anderson and Taylor, 2014). These trials, however, offer scant data about the significance of exercise intervention intensity and duration for prognosis on major clinical outcomes. Most trials were small, and reporting on exercise interventions was frequently inadequate (Abell et al., 2015). The assessment of the observational STABILITY study by Stewart *et al.* (2017) is the largest analysis evaluating the relationship between the amount of mild, moderate, and vigorous physical activity and subsequent mortality, MI, and stroke in a cohort of patients with CHD. The study population was categorised into physical activity tertiles in terms of MET.h/week assessed by self-reported questionnaires (“least active”, “intermediate active”, “most active”). As seen in the conceptual model in Figure 4, this resulted in the necessity to transform INPHY’s endpoint “steps/day” to the measure “MET.h/week” in order to incorporate the concomitant intervention effect of increased PA levels on health outcomes. It is important to bear in mind the possible limitations in this method. For one, causality cannot be established from observational studies, even less when using subjective self-reported exercise questionnaires rather than formal physical activity testing. RCTs are needed to reliably determine the independent benefit from increasing habitual exercise. For

another, the categorical classification of physical activity disregards the (curve-)linear association between exercise or step volume as well as morbidity and mortality (Jayedi et al., 2022; Kraus et al., 2019a, 2019b; Paluch et al., 2022). Moreover, concentration on adverse clinical outcomes neglects the role of exercise on the variety of physical fitness components, including morphology (e.g. subcutaneous fat distribution), muscle activity (e.g. muscular endurance), motor function (e.g. speed of movement), cardiorespiration (e.g. maximal oxygen consumption) and metabolism (e.g. insulin sensitivity). Lastly, the STABILITY study suggested that physical activity volume was associated with mortality, but myocardial infarction was not associated with exercise volume (Table 2). The risk of MI was lower at higher physical activity before but not after adjusting for covariates. This highlights the need for more stratified evidence to evaluate the dose-response relationship between steps or exercise and clinical endpoints.

In general, this modelling exercise is meant to be an ongoing process that considers the growing body of research rather than offering final cost-effectiveness results of the prevention interventions. Because model structures and inputs may be easily changed, this pre-trial model's framework offers transferability, which is one of its strengths. For future modification and update of the pre-trial model, it is crucial to include the results of the current feasibility study of INPHY's interventions. Rigorous follow-up evaluation of the INPHY trial, examining aspects including adherence and effect size parameters, will be important for its health economic evaluation. Once these measures are collected, post-trial economic modelling could be used to assess the cost-effectiveness of INPHY's interventions at scale.

4.5 Implications for INPHY

The INPHY trial at University Hospital Düsseldorf, a complex intervention, is currently being developed and aims at improving physical activity in people with CHD using monetary and social incentives. One of the main aims of this dissertation was to provide recommendations for designing and conducting the INPHY trial. On one hand, the implications are drawn from the pre-trial model itself. Modelling process and outcomes prior to a full-scale implementation and evaluation of a clinical trial are important contributions to the establishment of a successful intervention in clinical practice. The scenario analyses offered varied insights into the best-case scenario

for the interventions' cost-effectiveness, from which important inferences for developing the INPHY trial can be derived. On the other hand, implications for INPHY are drawn from the extensive reviews of the literature, which were conducted as part of this dissertation. Identification of evidence-based best practices from previous research and their thoughtful implementation in the trial concepts of INPHY are important.

In the following implications for INPHY from the pre-trial model are discussed. The first scenario indicates that ICER improved considerably, especially for the monetary incentive group, when the maximum physical activity during the 24-week-programme was preserved throughout the whole intervention year. This applied especially for the monetary incentive group, which overall reached its best ICER value with this scenario (31,555€/QALY gained). Maintaining post-intervention activity plays a significant role in improving cost-effectiveness outcomes, even in year 1. Therefore, it is recommended to counsel participants to regard the incentive interventions as a way to establish a lifestyle habit that will extend the trial period. One could also think of prolonging the intervention period with the goal of more long-term increases in physical activity. This would likely improve health outcomes and cost-effectiveness parameters with intervention costs being offset by health gains.

Because the weekly step count goal increases gradually over the intervention duration, participants with low baseline step counts spend, in total, less weeks walking 8500 steps/day. This limits their ability to reach the relevant "threshold" to intermediate physical activity in order to benefit from the exercise-based intervention effects in a sustained manner (scenario 4). Conversely, when participants started the interventions with a higher baseline step count of 4000 steps/day in the fifth scenario, ICERs improved to 94,421€/QALY gained and 23,831€/QALY gained for the monetary and social incentive arms, respectively. This highlights the relevance of thorough baseline assessments of participants both as part of a rigorous feasibility study as well as in the familiarisation phase of the RCT (Figure 3).

Cost-effectiveness ratios improved even further when participants walked at a brisk pace of 4 MET, instead of light walking at 3 MET in the base-case. The intensity of physical activity plays an important role on ICERs. INPHY's participants, if able, are recommended to engage in brisk walking at moderate-to-vigorous speed rather

than light speed. The final two scenarios simulated patient heterogeneity in terms of entry age to the model. Re-running the model for a mean patient age of 55 years decreased cost-effectiveness for both interventions. This contrasts with a significant increase of cost-effectiveness for both interventions when modelling a mean patient age of 75 years. The improved ICER was notably true for the group receiving social incentives, whose best ICER value was attained in these modelling conditions (19,829€/QALY gained). This may be explained by the fact that the older the participants, the more mortality benefits weigh in from their physical activity. With the relative risk of death in an intermediately active group of 0.75 [0.65-0.87] (Table 4), the majority of exercise-based intervention effects resulted from prolonged survival. According to life tables, the 75-years-old cohort has a higher probability of dying than the 55-years-old (scenario 7) or 65-years-old (base-case) cohort. It hence benefited greater from the risk reductions in mortality than the younger cohorts. These aspects might be of interest if inclusion ages are defined for INPHY participants.

In the following implications for INPHY from best practice examples are discussed. Participants in the social incentive arm might be advised to designate a contact person of their choice thoughtfully. Improved physical activity is associated with appointing individuals who live nearby, are interested in exercise themselves, or to whom the participants maintain a professional relationship with, such as a coworker (Sarkar et al., 2016; Yan et al., 2015). Use of gamification techniques or teaming might be an innovative way to improve adherence. Integrating experiences from cardiac rehabilitation by adding joint training sessions among the participants and supervised guidance sessions with facilitators could be considered (Dalal et al., 2015). Supervision might notably increase costs, but also effectiveness. Validated questionnaires including the Exercise Self-Efficacy Scale (McAuley, 1993) or the Social Support Score (Sallis et al., 1987) could be used in the INPHY trial. It is advised to extend the post-trial observation or follow-up as much as possible to collect important, long-term data of increased daily steps on various outcomes, including major adverse events, but also clinical fitness parameters. Scale-up of INPHY should be assessed as part of the full health economic evaluation of the trial.

4.6 Directions for research, practice, and policy

This dissertation has affirmed various domains within CHD prevention that would benefit from additional research, practice, and policy attention. First, investigating the long-term effects of physical activity programmes, using RCT designs rather than prospective observational studies. Second, evaluating the suitability of pedometers and their physical activity metric “steps”, which are not designed for measuring more vigorous forms of exercise (e.g. swimming, cycling). Third, determining the optimal type, amount, and delivery method of incentives, including the exploration of combined approaches for physical activity. Fourth, undertaking longer range follow-up of incentive-based physical activity interventions to assess sustainability and adherence profiles of participants. Fifth, integration of pre-trial modelling studies in the design and evaluation of complex interventions for behaviour change.

5 Conclusions

In Germany and other high-income countries, an urgent need prevails to address the growing burden of CHD with cost-effective lifestyle interventions. Given the lack of pre-trial health economic models on exercise-based prevention programmes in Germany, this dissertation is the first to model the long-term cost-effectiveness of a monetarily and socially incentivised reinforcement intervention, relative to control. On balance, this analysis indicates that both incentive strategies were associated with more costs, but also more effectiveness than control. In comparison, evidence for cost-effectiveness favoured the social incentive strategy at an ICER of 24,473€/QALY gained [95% CI 15,871-38,868], rather than the monetary incentive strategy at an ICER of 112,015€/QALY gained [95% CI 81,140-169,888]. With the very conservative approach adopted for this model, the long-term cost-effectiveness of INPHY's intervention is likely to be underestimated. This study is preparing the economic evaluation and the development of the INPHY trial on one hand, on the other it also highlights what implications can be drawn for future prevention research. Research funders, policymakers and other decision-makers can use this evidence while additional research is needed to fill evidence gaps on unknown effects and uncertainty.

6 References

Abell, B., Glasziou, P., Hoffmann, T., 2015. Reporting and replicating trials of exercise-based cardiac rehabilitation: do we know what the researchers actually did? Circ Cardiovasc Qual Outcomes 8, 187–194. https://doi.org/10.1161/CIRCOUTCOMES.114.001381

Anderson, J.L., Heidenreich, P.A., Barnett, P.G., Creager, M.A., Fonarow, G.C., Gibbons, R.J., Halperin, J.L., Hlatky, M.A., Jacobs, A.K., Mark, D.B., Masoudi, F.A., Peterson, E.D., Shaw, L.J., 2014. ACC/AHA Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures. Circulation 129, 2329–2345. https://doi.org/10.1161/CIR.0000000000000042

Anderson, L., Taylor, R.S., 2014. Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev CD011273. https://doi.org/10.1002/14651858.CD011273.pub2

Asaria, M., Walker, S., Palmer, S., Gale, C.P., Shah, A.D., Abrams, K.R., Crowther, M., Manca, A., Timmis, A., Hemingway, H., Sculpher, M., 2016. Using electronic health records to predict costs and outcomes in stable coronary artery disease. Heart 102, 755–762. https://doi.org/10.1136/heartjnl-2015-308850

Attema, A.E., Brouwer, W.B.F., Claxton, K., 2018. Discounting in Economic Evaluations. Pharmacoeconomics 36, 745–758. https://doi.org/10.1007/s40273-018-0672-z

Ayabe, M., Brubaker, P.H., Dobrosielski, D., Miller, H.S., Kiyonaga, A., Shindo, M., Tanaka, H., 2008. Target step count for the secondary prevention of cardiovascular disease. Circ J 72, 299–303. https://doi.org/10.1253/circj.72.299

Bailly, L., Mossé, P., Diagana, S., Fournier, M., d'Arripe-Longueville, F., Diagana, O., Gal, J., Grebet, J., Moncada, M., Domerego, J.-J., Radel, R., Fabre, R., Fuch, A., Pradier, C., 2018. "As du Coeur" study: a randomized controlled trial on quality of life impact and cost effectiveness of a physical activity program in patients with cardiovascular disease. BMC Cardiovasc Disord 18, 225. https://doi.org/10.1186/s12872-018-0973-3

Barte, J.C.M., Wendel-Vos, G.C.W., 2017. A Systematic Review of Financial Incentives for Physical Activity: The Effects on Physical Activity and Related

Outcomes. Behavioral Medicine 43, 79–90. https://doi.org/10.1080/08964289.2015.1074880

Barton, P., Andronis, L., Briggs, A., McPherson, K., Capewell, S., 2011. Effectiveness and cost effectiveness of cardiovascular disease prevention in whole populations: modelling study. BMJ 343, d4044. https://doi.org/10.1136/bmj.d4044

Bianchini, Vainio, 2002. Weight control and physical activity, IARC handbooks of cancer prevention. IARC, Lyon.

Bjarnason-Wehrens, B., Schulz, O., Gielen, S., Halle, M., Dürsch, M., Hambrecht, R., Lowis, H., Kindermann, W., Schulze, R., Rauch, B., 2009. Leitlinie körperliche Aktivität zur Sekundärprävention und Therapie kardiovaskulärer Erkrankungen. Clin Res Cardiol Suppl 4, 1–44. https://doi.org/10.1007/s11789-009-0078-8

Bloom, D.E., Cafiero, Jané-Llopis, Abrahams-Gessel, 2011. The Global Economic Burden of Noncommunicable Diseases.

Bonafede, M.M., Johnson, B.H., Richhariya, A., Gandra, S.R., 2015. Medical costs associated with cardiovascular events among high-risk patients with hyperlipidemia. ClinicoEconomics and Outcomes Research 7, 337–345. https://doi.org/10.2147/CEOR.S76972

Bowrin, K., Briere, J.-B., Levy, P., Millier, A., Clay, E., Toumi, M., 2019. Cost-effectiveness analyses using real-world data: an overview of the literature. Journal of Medical Economics 22, 545–553. https://doi.org/10.1080/13696998.2019.1588737

Brassington, F.C., Younger, P.L., 2010. A proposed framework for hydrogeological conceptual modelling. Water and Environment Journal 24, 261–273. https://doi.org/10.1111/j.1747-6593.2009.00173.x

Briggs, A., Claxton, K., Sculpher, M., 2018. Decision modelling for health economic evaluation. Oxford University Press, New Delhi.

Briggs, A., Sculpher, M., 1998. An introduction to Markov modelling for economic evaluation. Pharmacoeconomics 13, 397–409. https://doi.org/10.2165/00019053-199813040-00003

Briggs, A.H., Weinstein, M.C., Fenwick, E.A.L., Karnon, J., Sculpher, M.J., Paltiel, A.D., ISPOR-SMDM Modeling Good Research Practices Task Force, 2012. Model parameter estimation and uncertainty analysis: a report of the ISPOR-

SMDM Modeling Good Research Practices Task Force Working Group-6. Med Decis Making 32, 722–732. https://doi.org/10.1177/0272989X12458348

Bull, F.C., Al-Ansari, S.S., Biddle, S., Borodulin, K., Buman, M.P., Cardon, G., Carty, C., Chaput, J.-P., Chastin, S., Chou, R., Dempsey, P.C., DiPietro, L., Ekelund, U., Firth, J., Friedenreich, C.M., Garcia, L., Gichu, M., Jago, R., Katzmarzyk, P.T., Lambert, E., Leitzmann, M., Milton, K., Ortega, F.B., Ranasinghe, C., Stamatakis, E., Tiedemann, A., Troiano, R.P., van der Ploeg, H.P., Wari, V., Willumsen, J.F., 2020. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 54, 1451–1462. https://doi.org/10.1136/bjsports-2020-102955

Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A.L., Sandercock, P., Spiegelhalter, D., Tyrer, P., 2000. Framework for design and evaluation of complex interventions to improve health. British Medical Journal. https://doi.org/10.1136/bmj.321.7262.694

Caro, J.J., Briggs, A.H., Siebert, U., Kuntz, K.M., ISPOR-SMDM Modeling Good Research Practices Task Force, 2012. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. Value Health 15, 796–803. https://doi.org/10.1016/j.jval.2012.06.012

Carrera, M., Royer, H., Stehr, M., Sydnor, J., 2018. Can financial incentives help people trying to establish new habits? Experimental evidence with new gym members. Journal of Health Economics 58, 202–214. https://doi.org/10.1016/j.jhealeco.2018.02.010

Carta, A., Conversano, C., 2020. On the Use of Markov Models in Pharmacoeconomics: Pros and Cons and Implications for Policy Makers. Front Public Health 8, 569500. https://doi.org/10.3389/fpubh.2020.569500

Chan, A., Chan, D., Lee, H., Ng, C.C., Yeo, A.H.L., 2022. Reporting adherence, validity and physical activity measures of wearable activity trackers in medical research: A systematic review. International Journal of Medical Informatics 160, 104696. https://doi.org/10.1016/j.ijmedinf.2022.104696

Charness, G., Gneezy, U., 2009. Incentives to Exercise. Econometrica 77, 909–931.

Chiuve, S.E., McCullough, M.L., Sacks, F.M., Rimm, E.B., 2006. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive

medications. Circulation 114, 160–167. https://doi.org/10.1161/CIRCULATIONAHA.106.621417

Chokshi, N.P., Adusumalli, S., Small, D.S., Morris, A., Feingold, J., Ha, Y.P., Lynch, M.D., Rareshide, C.A.L., Hilbert, V., Patel, M.S., 2018. Loss-Framed Financial Incentives and Personalized Goal-Setting to Increase Physical Activity Among Ischemic Heart Disease Patients Using Wearable Devices: The ACTIVE REWARD Randomized Trial. Journal of the American Heart Association 7. https://doi.org/10.1161/JAHA.118.009173

Chow, C.K., Jolly, S., Rao-Melacini, P., Fox, K.A.A., Anand, S.S., Yusuf, S., 2010. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation 121, 750–758. https://doi.org/10.1161/CIRCULATIONAHA.109.891523

Claxton, K., Sculpher, M., Drummond, M., 2002. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). Lancet 360, 711–715. https://doi.org/10.1016/S0140-6736(02)09832-X

Cohen, J.T., Neumann, P.J., Weinstein, M.C., 2008. Does preventive care save money? Health economics and the presidential candidates. N Engl J Med 358, 661–663. https://doi.org/10.1056/NEJMp0708558

Cooper, K., Davies, R., Raftery, J., Roderick, P., 2008. Use of a coronary heart disease simulation model to evaluate the costs and effectiveness of drugs for the prevention of heart disease. Journal of the Operational Research Society 59, 1173–1181. https://doi.org/10.1057/palgrave.jors.2602468

Craig, P., 2019. Developing and evaluating complex interventions. Maternal and Child Nutrition.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M., 2008. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 337, a1655. https://doi.org/10.1136/bmj.a1655

Crossan, C., Dehbi, H.M., Williams, H., Poulter, N., Rodgers, A., Jan, S., Thom, S., Lord, J., 2018. A protocol for an economic evaluation of a polypill in patients with established or at high risk of cardiovascular disease in a UK NHS setting: RUPEE (NHS) study. BMJ Open 8, 1–11. https://doi.org/10.1136/bmjopen-2016-013063

Dakin, H.A., Leal, J., Briggs, A., Clarke, P., Holman, R.R., Gray, A., 2020. Accurately Reflecting Uncertainty When Using Patient-Level Simulation Models to

Extrapolate Clinical Trial Data. Med Decis Making 40, 460–473. https://doi.org/10.1177/0272989X20916442

Dalal, H.M., Doherty, P., Taylor, R.S., 2015. Cardiac rehabilitation. BMJ 351, h5000. https://doi.org/10.1136/bmj.h5000

De Backer, G., Jankowski, P., Kotseva, K., Mirrakhimov, E., Reiner, Ž., Rydén, L., Tokgözoğlu, L., Wood, D., De Bacquer, D., EUROASPIRE V collaborators, Writing Committee, Scientific Steering/ Executive Committee, Coordinating centre, Diabetes centre, Data management centre, Statistical analysis centre, Central laboratory, Study centres, organisations, investigators and other research personnel (National Co-ordinators in each country are indicated by asterisk, 2019. Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. Atherosclerosis 285, 135–146. https://doi.org/10.1016/j.atherosclerosis.2019.03.014

Dellavigna, S., Malmendier, U., 2006. Paying Not to Go to the Gym.

Department of Health & Human Services, 2018. 2018 Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Scientific Report 779.

DESTATIS, 2022. Bruttoinlandsprodukt (BIP) [WWW Document]. Statistisches Bundesamt. URL https://www.destatis.de/DE/Themen/Wirtschaft/Volkswirtschaftliche-Gesamtrechnungen-Inlandsprodukt/Tabellen/bip-bubbles.html (accessed 9.28.22).

DESTATIS, 2020. Deaths, life expectancy [WWW Document]. Federal Statistical Office. URL https://www.destatis.de/EN/Themes/Society-Environment/Population/Deaths-Life-Expectancy/Tables/_tables.html (accessed 7.24.22).

DESTATIS, 2017. Herz-Kreislauf-Erkrankungen verursachen die höchsten Kosten.

Dornquast, C., Kroll, L.E., Neuhauser, H.K., Willich, S.N., Reinhold, T., Busch, M.A., 2016. Regional Differences in the Prevalence of Cardiovascular Disease. Deutsches Ärzteblatt international. https://doi.org/10.3238/arztebl.2016.0704

Drummond, M.F., Sculpher, M.J., Torrance, G.W., O'Brien, B.J., Stoddart, G.L., 2005. Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press.

Edejer, T.T.-T., World Health Organization (Eds.), 2003. Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization, Geneva.

Eisman, A., Kilbourne, A., Dopp, A., Saldana, L., Eisenberg, D., 2019. Economic evaluation in implementation science: Making the business case for implementation strategies. Psychiatry research 283. https://doi.org/10.1016/j.psychres.2019.06.008

Eriksen, C.U., Rotar, O., Toft, U., J??rgensen, T., Health Evidence Network, 2021. What is the effectiveness of systematic population-level screening programmes for reducing the burden of cardiovascular diseases?

Fanaroff, A.C., Patel, M.S., Chokshi, N., Coratti, S., Farraday, D., Norton, L., Rareshide, C., Zhu, J., Szymczak, J.E., Russell, L.B., Small, D.S., Volpp, K.G.M., 2023. A randomized controlled trial of gamification, financial incentives, or both to increase physical activity among patients with elevated risk for cardiovascular disease: rationale and design of the be active study. American Heart Journal 260, 82–89. https://doi.org/10.1016/j.ahj.2023.02.014

Ferster, C.B., Skinner, B.F., 1957. Schedules of reinforcement, Schedules of reinforcement. Appleton-Century-Crofts, East Norwalk, CT, US. https://doi.org/10.1037/10627-000

Franklin, B.A., Thompson, P.D., Al-Zaiti, S.S., Albert, C.M., Hivert, M.-F., Levine, B.D., Lobelo, F., Madan, K., Sharrief, A.Z., Eijsvogels, T.M.H., 2020. Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective–An Update: A Scientific Statement From the American Heart Association. Circulation 141, e705–e736. https://doi.org/10.1161/CIR.0000000000000749

Gansen, F.M., 2018. Health economic evaluations based on routine data in Germany: a systematic review. BMC Health Services Research 18, 268. https://doi.org/10.1186/s12913-018-3080-3

Gao, J., Pan, X., Li, G., Chatterjee, E., Xiao, J., 2022. Physical Exercise Protects Against Endothelial Dysfunction in Cardiovascular and Metabolic Diseases. J. of Cardiovasc. Trans. Res. 15, 604–620. https://doi.org/10.1007/s12265-021-10171-3

Gardiner, F.W., Regan, E., Nwose, E.U., Bwititi, P.T., Crockett, J., Wang, L., 2017. Outpatient cardiac rehabilitation: Effects on patient improvement outcomes.

Diabetes Metab Syndr 11 Suppl 2, S1025–S1030. https://doi.org/10.1016/j.dsx.2017.07.034

Germini, F., Noronha, N., Borg Debono, V., Abraham Philip, B., Pete, D., Navarro, T., Keepanasseril, A., Parpia, S., de Wit, K., Iorio, A., 2022. Accuracy and Acceptability of Wrist-Wearable Activity-Tracking Devices: Systematic Review of the Literature. J Med Internet Res 24, e30791. https://doi.org/10.2196/30791

Giles, E.L., Robalino, S., McColl, E., Sniehotta, F.F., Adams, J., 2014. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis. PLoS One 9, e90347. https://doi.org/10.1371/journal.pone.0090347

Gill, D.L., Hammond, C.C., Reifsteck, E.J., Jehu, C.M., Williams, R.A., Adams, M.M., Lange, E.H., Becofsky, K., Rodriguez, E., Shang, Y.-T., 2013. Physical Activity and Quality of Life. J Prev Med Public Health 46, S28–S34. https://doi.org/10.3961/jpmph.2013.46.S.S28

Goldsteen, R.L., Goldsteen, K., Dwelle, T., 2015. Introduction to public health: promises and practices, Second edition. ed. Springer Publishing Company, LLC, New York, NY.

Gößwald, A., Schienkiewitz, A., Nowossadeck, E., Busch, M.A., 2013. Prävalenz von Herzinfarkt und koronarer Herzkrankheit bei Erwachsenen im Alter von 40 bis 79 Jahren in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsbl. 56, 650–655. https://doi.org/10.1007/s00103-013-1666-9

Govender, R.D., Al-Shamsi, S., Soteriades, E.S., Regmi, D., 2019. Incidence and risk factors for recurrent cardiovascular disease in middle-eastern adults: a retrospective study. BMC Cardiovasc Disord 19, 253. https://doi.org/10.1186/s12872-019-1231-z

Gray, A.M., Clarke, P.M., Wolstenholme, J.L., Wordsworth, S., 2011. Applied Methods of Cost-effectiveness Analysis in Healthcare. OUP Oxford.

Gray, K., Sockolow, P., 2016. Conceptual Models in Health Informatics Research: A Literature Review and Suggestions for Development. JMIR Medical Informatics 4, e5021. https://doi.org/10.2196/medinform.5021

Gullotta, T., Bloom, M., Child and Family Agency of Southeastern Connecticut (Eds.), 2003. Encyclopedia of primary prevention and health promotion. Kluwer Academic/Plenum, New York.

Gutama, F., Barliana, M.I., Puspitasari, I.M., 2022. Factors associated with health-related quality of life in patients with coronary heart disease. Pharmacia 69, 771–777. https://doi.org/10.3897/pharmacia.69.e87279

Guthold, R., Stevens, G.A., Riley, L.M., Bull, F.C., 2018. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. The Lancet Global Health 6, e1077–e1086. https://doi.org/10.1016/S2214-109X(18)30357-7

Hare, A.J., Patel, M.S., Volpp, K., Adusumalli, S., 2021. The Role of Behavioral Economics in Improving Cardiovascular Health Behaviors and Outcomes. Curr Cardiol Rep 23, 153. https://doi.org/10.1007/s11886-021-01584-2

Harrison, J.D., Jones, J.M., Small, D.S., Rareshide, C.A.L., Szwartz, G., Steier, D., Guszcza, J., Kalra, P., Torio, B., Reh, G., Hilbert, V., Patel, M.S., 2019. Social incentives to encourage physical activity and understand predictors (STEP UP): Design and rationale of a randomized trial among overweight and obese adults across the United States. Contemp Clin Trials 80, 55–60. https://doi.org/10.1016/j.cct.2019.04.001

Health Information and Quality Authority, 2014. Guidelines for the Economic Evaluation of Health Technologies in Ireland [WWW Document]. URL https://www.hiqa.ie/sites/default/files/2017-01/Revised_Economic_Guidelines_posted_100714.pdf (accessed 9.26.22).

Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A., Cochrane Collaboration, 2020. Cochrane handbook for systematic reviews of interventions.

Husereau, D., Drummond, M., Augustovski, F., Briggs, A., Carswell, C., Caulley, L., Chaiyakunapruk, N., de Bekker-Grob, E., Greenberg, D., Loder, E., Mauskopf, J., Mullins, C., Petrou, S., Pwu, R.-F., Staniszewska, S., Force, C. 2022 I.G.R.P.T., 2022. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BJOG: An International Journal of Obstetrics & Gynaecology 129, 336–344. https://doi.org/10.1111/1471-0528.17012

Hutubessy, R., Chisholm, D., Edejer, T.T.-T., 2003. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. Cost Eff Resour Alloc 1, 8. https://doi.org/10.1186/1478-7547-1-8

Icks, A., Dyczmons, J., 2020. Entwicklung und Evaluation der komplexen Intervention: Incentives for Physical Activity in Cardiac Patients with or without Diabetes (INPHY).

Iestra, J.A., Kromhout, D., van der Schouw, Y.T., Grobbee, D.E., Boshuizen, H.C., van Staveren, W.A., 2005. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review. Circulation 112, 924–934. https://doi.org/10.1161/CIRCULATIONAHA.104.503995

Jaksa, A., 2019. The case for real-world evidence in Germany [WWW Document]. Aetion. URL https://aetion.com/evidence-hub/the-case-for-real-world-evidence-in-germany/ (accessed 9.27.22).

Jayedi, A., Gohari, A., Shab-Bidar, S., 2022. Daily Step Count and All-Cause Mortality: A Dose-Response Meta-analysis of Prospective Cohort Studies. Sports Med 52, 89–99. https://doi.org/10.1007/s40279-021-01536-4

Jetté, M., Sidney, K., Blümchen, G., 1990. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol 13, 555–565. https://doi.org/10.1002/clc.4960130809

Johansson, S., Rosengren, A., Young, K., Jennings, E., 2017. Mortality and morbidity trends after the first year in survivors of acute myocardial infarction: a systematic review. BMC Cardiovascular Disorders 17, 53. https://doi.org/10.1186/s12872-017-0482-9

Kazdin, A.E., 2013. Behavior modification in applied settings, 7. ed. ed. Waveland Press, Long Grave, Ill.

Kim, H., Goodall, S., Liew, D., 2020. The Potential for Early Health Economic Modelling in Health Technology Assessment and Reimbursement Decision-Making Comment on “Problems and Promises of Health Technologies: The Role of Early Health Economic Modeling.” Int J Health Policy Manag 10, 98–101. https://doi.org/10.15171/ijhpm.2020.17

Komorowski, M., Raffa, J., 2016. Markov Models and Cost Effectiveness Analysis: Applications in Medical Research, in: Secondary Analysis of Electronic Health Records. Springer International Publishing, Cham, pp. 351–367. https://doi.org/10.1007/978-3-319-43742-2_24

Kotseva, K., Wood, D., De Bacquer, D., De Backer, G., Rydén, L., Jennings, C., Gyberg, V., Amouyel, P., Bruthans, J., Castro Conde, A., Cífková, R., Deckers, J.W., De Sutter, J., Dilic, M., Dolzhenko, M., Erglis, A., Fras, Z.,

Gaita, D., Gotcheva, N., Goudevenos, J., Heuschmann, P., Laucevicius, A., Lehto, S., Lovic, D., Miličić, D., Moore, D., Nicolaides, E., Oganov, R., Pajak, A., Pogosova, N., Reiner, Z., Stagmo, M., Störk, S., Tokgözoğlu, L., Vulic, D., EUROASPIRE Investigators, 2016. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 23, 636–648. https://doi.org/10.1177/2047487315569401

Kraus, W.E., Janz, K.F., Powell, K.E., Campbell, W.W., Jakicic, J.M., Troiano, R.P., Sprow, K., Torres, A., Piercy, K.L., 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE*, 2019a. Daily Step Counts for Measuring Physical Activity Exposure and Its Relation to Health. Med Sci Sports Exerc 51, 1206–1212. https://doi.org/10.1249/MSS.0000000000001932

Kraus, W.E., Powell, K.E., Haskell, W.L., Janz, K.F., Campbell, W.W., Jakicic, J.M., Troiano, R.P., Sprow, K., Torres, A., Piercy, K.L., 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE*, 2019b. Physical Activity, All-Cause and Cardiovascular Mortality, and Cardiovascular Disease. Med Sci Sports Exerc 51, 1270–1281. https://doi.org/10.1249/MSS.0000000000001939

Lee, I.-M., 2009. Epidemiologic Methods in Physical Activity Studies. Oxford University Press.

Lennon, L.T., Ramsay, S.E., Papacosta, O., Shaper, A.G., Wannamethee, S.G., Whincup, P.H., 2015. Cohort Profile Update: The British Regional Heart Study 1978–2014: 35 years follow-up of cardiovascular disease and ageing. Int J Epidemiol 44, 826–826g. https://doi.org/10.1093/ije/dyv141

Lewsey, J.D., Lawson, K.D., Ford, I., Fox, K.A.A., Ritchie, L.D., Tunstall-Pedoe, H., Watt, G.C.M., Woodward, M., Kent, S., Neilson, M., Briggs, A.H., 2015. A cardiovascular disease policy model that predicts life expectancy taking into account socioeconomic deprivation. Heart 101, 201–208. https://doi.org/10.1136/heartjnl-2014-305637

Liese, A.D., Hense, H.W., Brenner, H., Löwel, H., Keil, U., 2000. Assessing the impact of classical risk factors on myocardial infarction by rate advancement periods. Am J Epidemiol 152, 884–888. https://doi.org/10.1093/aje/152.9.884

Lomas, J., Asaria, M., Bojke, L., Gale, C.P., Richardson, G., Walker, S., 2018. Which Costs Matter? Costs Included in Economic Evaluation and their Impact on Decision Uncertainty for Stable Coronary Artery Disease.

PharmacoEconomics Open 2, 403–413. https://doi.org/10.1007/s41669-018-0068-1

Lu, Z.K., Xiong, X., Lee, T., Wu, J., Yuan, J., Jiang, B., 2021. Big Data and Real-World Data based Cost-Effectiveness Studies and Decision-making Models: A Systematic Review and Analysis. Frontiers in Pharmacology 12.

Lutter, J.I., Szentes, B., Wacker, M.E., Winter, J., Wichert, S., Peters, A., Holle, R., Leidl, R., 2019. Are health risk attitude and general risk attitude associated with healthcare utilization, costs and working ability? Results from the German KORA FF4 cohort study. Health Econ Rev 9, 26. https://doi.org/10.1186/s13561-019-0243-9

Maciosek, M.V., Coffield, A.B., Edwards, N.M., Flottemesch, T.J., Solberg, L.I., 2009. Prioritizing Clinical Preventive Services: A Review and Framework with Implications for Community Preventive Services. Annu. Rev. Public Health 30, 341–355. https://doi.org/10.1146/annurev.publhealth.031308.100253

Mahmood, S.S., Levy, D., Vasan, R.S., Wang, T.J., 2014. The Framingham Heart Study and the Epidemiology of Cardiovascular Diseases: A Historical Perspective. Lancet 383, 999–1008. https://doi.org/10.1016/S0140-6736(13)61752-3

Mantzari, E., Vogt, F., Shemilt, I., Wei, Y., Higgins, J.P.T., Marteau, T.M., 2015. Personal financial incentives for changing habitual health-related behaviors: A systematic review and meta-analysis. Prev Med 75, 75–85. https://doi.org/10.1016/j.ypmed.2015.03.001

Maple, J.-L., Ananthapavan, J., Ball, K., Teychenne, M., Moodie, M., 2022. Economic evaluation of an incentive-based program to increase physical activity and reduce sedentary behaviour in middle-aged adults. BMC Health Services Research 22, 932. https://doi.org/10.1186/s12913-022-08294-7

Marquez, D.X., Aguiñaga, S., Vásquez, P.M., Conroy, D.E., Erickson, K.I., Hillman, C., Stillman, C.M., Ballard, R.M., Sheppard, B.B., Petruzzello, S.J., King, A.C., Powell, K.E., 2020. A systematic review of physical activity and quality of life and well-being. Transl Behav Med 10, 1098–1109. https://doi.org/10.1093/tbm/ibz198

Marshall, D.A., Grazziotin, L.R., Regier, D.A., Wordsworth, S., Buchanan, J., Phillips, K., Ijzerman, M., 2020. Addressing Challenges of Economic Evaluation in Precision Medicine Using Dynamic Simulation Modeling. Value in Health 23, 566–573. https://doi.org/10.1016/j.jval.2020.01.016

Martins da Costa, A., Teixeira, R., Vilela, E.M., Tavares, A., Torres, S., Sampaio, F., Teixeira, M., Fontes-Carvalho, R., Pedro Nunes, J., 2021. Suppression of tumorigenicity 2 after exercise: a systematic review. Monaldi Arch Chest Dis 92. https://doi.org/10.4081/monaldi.2021.1839

McAuley, E., 1993. Self-efficacy and the maintenance of exercise participation in older adults. J Behav Med 16, 103–113. https://doi.org/10.1007/BF00844757

Mendis, S., Puska, P., Norrving, B., Organization, W.H., Federation, W.H., Organization, W.S., 2011. Global atlas on cardiovascular disease prevention and control. World Health Organization.

Michaelsen, M.M., Esch, T., 2022. Functional Mechanisms of Health Behavior Change Techniques: A Conceptual Review. Frontiers in Psychology 13.

Mirna, M., Lichtenauer, M., Wernly, B., Paar, V., Jung, C., Kretzschmar, D., Uhlemann, M., Franz, M., Hoppe, U.C., Schulze, P.C., Hilberg, T., Adams, V., Sponder, M., Möbius-Winkler, S., 2020. Novel cardiovascular biomarkers in patients with cardiovascular diseases undergoing intensive physical exercise. Panminerva Med 62, 135–142. https://doi.org/10.23736/S0031-0808.20.03838-0

Mitchell, M.S., Goodman, J.M., Alter, D.A., John, L.K., Oh, P.I., Pakosh, M.T., Faulkner, G.E., 2013. Financial incentives for exercise adherence in adults: Systematic review and meta-analysis. American Journal of Preventive Medicine 45, 658–667. https://doi.org/10.1016/j.amepre.2013.06.017

Mitchell, M.S., Orstad, S.L., Biswas, A., Oh, P.I., Jay, M., Pakosh, M.T., Faulkner, G., 2020. Financial incentives for physical activity in adults: systematic review and meta-analysis. Br J Sports Med 54, 1259–1268. https://doi.org/10.1136/bjsports-2019-100633

Molema, C., Wendel-Vos, W., Puijk, L., Jensen, J., Schuit, A., De wit, G.A., 2016. A systematic review of financial incentives given in the healthcare setting; do they effectively improve physical activity levels? BMC Sports Science, Medicine and Rehabilitation 8. https://doi.org/10.1186/s13102-016-0041-1

Montalescot, G., Sechtem, U., Achenbach, S., Andreotti, F., Arden, C., Budaj, A., Bugiardini, R., Crea, F., Cuisset, T., Di Mario, C., Ferreira, J.R., Gersh, B.J., Gitt, A.K., Hulot, J.S., Marx, N., Opie, L.H., Pfisterer, M., Prescott, E., Ruschitzka, F., Sabaté, M., Senior, R., Taggart, D.P., Van Der Wall, E.E., Vrints, C.J.M., Zamorano, J.L., Baumgartner, H., Bax, J.J., Bueno, H., Dean, V., Deaton, C., Erol, C., Fagard, R., Ferrari, R., Hasdai, D., Hoes, A.W.,

Kirchhof, P., Knuuti, J., Kolh, P., Lancellotti, P., Linhart, A., Nihoyannopoulos, P., Piepoli, M.F., Ponikowski, P., Sirnes, P.A., Tamargo, J.L., Tendera, M., Torbicki, A., Wijns, W., Windecker, S., Valgimigli, M., Claeys, M.J., Donner-Banzhoff, N., Frank, H., Funck-Brentano, C., Gaemperli, O., Gonzalez-Juanatey, J.R., Hamilos, M., Husted, S., James, S.K., Kervinen, K., Kristensen, S.D., Maggioni, A.P., Romeo, F., Rydén, L., Simoons, M.L., Steg, P.G., Timmis, A., Yildirir, A., 2013. 2013 ESC guidelines on the management of stable coronary artery disease. European Heart Journal 34, 2949–3003. https://doi.org/10.1093/eurheartj/eht296

Mozaffarian, D., Bryson, C.L., Spertus, J.A., McDonell, M.B., Fihn, S.D., 2003. Anginal symptoms consistently predict total mortality among outpatients with coronary artery disease. Am Heart J 146, 1015–1022. https://doi.org/10.1016/S0002-8703(03)00436-8

National Institute for Health and Care Excellence, 2014. Lipid Modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (No. July). National Institute for Health and Care Excellence.

National Institute for Health and Care Excellence, 2011. Overview | Ticagrelor for the treatment of acute coronary syndromes | Guidance | NICE [WWW Document]. URL https://www.nice.org.uk/guidance/ta236 (accessed 10.19.22).

National Institute for Health and Care Excellence (NICE), 2020. Acute coronary syndromes. Acute coronary syndromes 54.

National Institute for Health and Clinical Excellence, 2013. Guide to the methods of technology appraisal 2013.

Olariu, E., Cadwell, K.K., Hancock, E., Trueman, D., Chevrou-Severac, H., 2017. Current recommendations on the estimation of transition probabilities in Markov cohort models for use in health care decision-making: a targeted literature review. Clinicoecon Outcomes Res 9, 537–546. https://doi.org/10.2147/CEOR.S135445

O'Mahony, J.F., Coughlan, D., 2016. The Irish Cost-Effectiveness Threshold: Does it Support Rational Rationing or Might it Lead to Unintended Harm to Ireland's Health System? PharmacoEconomics 34, 5–11. https://doi.org/10.1007/s40273-015-0336-1

O'Mahony, J.F., Newall, A.T., van Rosmalen, J., 2015. Dealing with Time in Health Economic Evaluation: Methodological Issues and Recommendations for

Practice. PharmacoEconomics 33, 1255–1268. https://doi.org/10.1007/s40273-015-0309-4

Palmefors, H., DuttaRoy, S., Rundqvist, B., Börjesson, M., 2014. The effect of physical activity or exercise on key biomarkers in atherosclerosis--a systematic review. Atherosclerosis 235, 150–161. https://doi.org/10.1016/j.atherosclerosis.2014.04.026

Paluch, A.E., Bajpai, S., Bassett, D.R., Carnethon, M.R., Ekelund, U., Evenson, K.R., Galuska, D.A., Jefferis, B.J., Kraus, W.E., Lee, I.-M., Matthews, C.E., Omura, J.D., Patel, A.V., Pieper, C.F., Rees-Punia, E., Dallmeier, D., Klenk, J., Whincup, P.H., Dooley, E.E., Pettee Gabriel, K., Palta, P., Pompeii, L.A., Chernofsky, A., Larson, M.G., Vasan, R.S., Spartano, N., Ballin, M., Nordström, P., Nordström, A., Anderssen, S.A., Hansen, B.H., Cochrane, J.A., Dwyer, T., Wang, J., Ferrucci, L., Liu, F., Schrack, J., Urbanek, J., Saint-Maurice, P.F., Yamamoto, N., Yoshitake, Y., Newton, R.L., Yang, S., Shiroma, E.J., Fulton, J.E., Steps for Health Collaborative, 2022. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. Lancet Public Health 7, e219–e228. https://doi.org/10.1016/S2468-2667(21)00302-9

Pandya, A., Sy, S., Cho, S., Alam, S., Weinstein, M.C., Gaziano, T.A., 2017. Validation of a Cardiovascular Disease Policy Microsimulation Model Using Both Survival and Receiver Operating Characteristic Curves. Medical Decision Making 37, 802–814. https://doi.org/10.1177/0272989X17706081

Park, S.-H., Han, K.S., Kang, C.-B., 2014. Effects of exercise programs on depressive symptoms, quality of life, and self-esteem in older people: a systematic review of randomized controlled trials. Appl Nurs Res 27, 219–226. https://doi.org/10.1016/j.apnr.2014.01.004

Patel, M.S., Small, D.S., Harrison, J.D., Fortunato, M.P., Oon, A.L., Rareshide, C.A.L., Reh, G., Szwartz, G., Guszcza, J., Steier, D., Kalra, P., Hilbert, V., 2019. Effectiveness of Behaviorally Designed Gamification Interventions With Social Incentives for Increasing Physical Activity Among Overweight and Obese Adults Across the United States. JAMA Intern Med 179, 1624–1632. https://doi.org/10.1001/jamainternmed.2019.3505

Pencheon, D., 2006. Oxford Handbook of Public Health Practice. Oxford University Press.

Perel, P., Avezum, A., Huffman, M., Pais, P., Rodgers, A., Vedanthan, R., Wood, D., Yusuf, S., 2015. Reducing Premature Cardiovascular Morbidity and Mortality

in People With Atherosclerotic Vascular Disease: The World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease. gh 10, 99. https://doi.org/10.1016/j.gheart.2015.04.003

Petrou, S., Gray, A., 2011. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. BMJ 342, d1766. https://doi.org/10.1136/bmj.d1766

Petticrew, M., 2011. When are complex interventions 'complex'? When are simple interventions 'simple'? European Journal of Public Health 21, 397–398. https://doi.org/10.1093/eurpub/ckr084

Phillips, C.J., 2008. Health Economics: An Introduction for Health Professionals. John Wiley & Sons.

Piepoli, M.F., Corrà, U., Adamopoulos, S., Benzer, W., Bjarnason-Wehrens, B., Cupples, M., Dendale, P., Doherty, P., Gaita, D., Höfer, S., McGee, H., Mendes, M., Niebauer, J., Pogosova, N., Garcia-Porrero, E., Rauch, B., Schmid, J.P., Giannuzzi, P., 2014. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: A Policy Statement from the Cardiac Rehabilitation Section of the European Association for. European Journal of Preventive Cardiology 21, 664–681. https://doi.org/10.1177/2047487312449597

Piepoli, M.F., Corrà, U., Dendale, P., Frederix, I., Prescott, E., Schmid, J.P., Cupples, M., Deaton, C., Doherty, P., Giannuzzi, P., Graham, I., Hansen, T.B., Jennings, C., Landmesser, U., Marques-Vidal, P., Vrints, C., Walker, D., Bueno, H., Fitzsimons, D., Pelliccia, A., 2016. Challenges in secondary prevention after acute myocardial infarction: A call for action. European Journal of Preventive Cardiology 23, 1994–2006. https://doi.org/10.1177/2047487316663873

Plass, D., Vos, T., Hornberg, C., Scheidt-Nave, C., Zeeb, H., Krämer, A., 2014. Trends in Disease Burden in Germany. Deutsches Ärzteblatt international. https://doi.org/10.3238/arztebl.2014.0629

Ramsey, S., Willke, R., Briggs, A., Brown, R., Buxton, M., Chawla, A., Cook, J., Glick, H., Liljas, B., Petitti, D., Reed, S., 2005. Good research practices for cost-effectiveness analysis alongside clinical trials: The ISPOR RCT-CEA Task Force report. Value in health : the journal of the International Society for

Pharmacoeconomics and Outcomes Research 8, 521–33. https://doi.org/10.1111/j.1524-4733.2005.00045.x

Roberts, M., Russell, L.B., Paltiel, A.D., Chambers, M., McEwan, P., Krahn, M., 2012. Conceptualizing a Model: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–2. Med Decis Making 32, 678–689. https://doi.org/10.1177/0272989X12454941

Roth, G.A., Mensah, G.A., Johnson, C.O., Addolorato, G., Ammirati, E., Baddour, L.M., Barengo, N.C., Beaton, A.Z., Benjamin, E.J., Benziger, C.P., Bonny, A., Brauer, M., Brodmann, M., Cahill, T.J., Carapetis, J., Catapano, A.L., Chugh, S.S., Cooper, L.T., Coresh, J., Criqui, M., DeCleene, N., Eagle, K.A., Emmons-Bell, S., Feigin, V.L., Fernández-Solà, J., Fowkes, G., Gakidou, E., Grundy, S.M., He, F.J., Howard, G., Hu, F., Inker, L., Karthikeyan, G., Kassebaum, N., Koroshetz, W., Lavie, C., Lloyd-Jones, D., Lu, H.S., Mirijello, A., Temesgen, A.M., Mokdad, A., Moran, A.E., Muntner, P., Narula, J., Neal, B., Ntsekhe, M., Moraes de Oliveira, G., Otto, C., Owolabi, M., Pratt, M., Rajagopalan, S., Reitsma, M., Ribeiro, A.L.P., Rigotti, N., Rodgers, A., Sable, C., Shakil, S., Sliwa-Hahnle, K., Stark, B., Sundström, J., Timpel, P., Tleyjeh, I.M., Valgimigli, M., Vos, T., Whelton, P.K., Yacoub, M., Zuhlke, L., Murray, C., Fuster, V., GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group, 2020. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol 76, 2982–3021. https://doi.org/10.1016/j.jacc.2020.11.010

Rütten, A., Abu-Omar, K., Banzer, W., Burlacu, I., Ferrari, N., F??z??ki, E., Gediga, G., Geidl, W., Graf, C., Hartung, V., Klamroth, S., Messing, S., Pfeifer, K., Ungerer-R??hrich, U., V??lker, K., Vogt, L., 2016. National Recommendations for Physical Activity and Physical Activity Promotion.

Rütten, A., Abu-Omar, K., Messing, S., Weege, M., Pfeifer, K., Geidl, W., Hartung, V., 2018. How can the impact of national recommendations for physical activity be increased? Experiences from Germany. Health Research Policy and Systems 16, 121. https://doi.org/10.1186/s12961-018-0396-8

Sallis, J.F., Grossman, R.M., Pinski, R.B., Patterson, T.L., Nader, P.R., 1987. The development of scales to measure social support for diet and exercise behaviors. Prev Med 16, 825–836. https://doi.org/10.1016/0091-7435(87)90022-3

Sarkar, S., Taylor, W.C., Lai, D., Shegog, R., Paxton, R.J., 2016. Social support for physical activity: Comparison of family, friends, and coworkers. Work 55, 893–899. https://doi.org/10.3233/WOR-162459

Schmid, T., 2015. Costs of treating cardiovascular events in Germany: a systematic literature review. Health Econ Rev 5, 27. https://doi.org/10.1186/s13561-015-0063-5

Sehested, T.S.G., Bjerre, J., Ku, S., Chang, A., Jahansouz, A., Owens, D.K., Hlatky, M.A., Goldhaber-Fiebert, J.D., 2019. Cost-effectiveness of Canakinumab for Prevention of Recurrent Cardiovascular Events. JAMA Cardiology 4, 128–135. https://doi.org/10.1001/jamacardio.2018.4566

Severens, J.L., Milne, R.J., 2004. Discounting health outcomes in economic evaluation: the ongoing debate. Value Health 7, 397–401. https://doi.org/10.1111/j.1524-4733.2004.74002.x

Skinner, B.F., 1953. Science and human behavior, First Free Press Paperback edition. ed. The Free Press, New York, NY.

Skivington, K., Matthews, L., Simpson, S.A., Craig, P., Baird, J., Blazeby, J.M., Boyd, K.A., Craig, N., French, D.P., McIntosh, E., Petticrew, M., Rycroft-Malone, J., White, M., Moore, L., 2021. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ 374, n2061. https://doi.org/10.1136/bmj.n2061

Smolina, K., Wright, F.L., Rayner, M., Goldacre, M.J., 2012. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circulation: Cardiovascular Quality and Outcomes 5, 532–540. https://doi.org/10.1161/CIRCOUTCOMES.111.964700

Sonnenberg, F.A., Beck, J.R., 1993. Markov models in medical decision making: a practical guide. Med Decis Making 13, 322–338. https://doi.org/10.1177/0272989X9301300409

Sox, H.C., Higgins, M.C., Owens, D.K., 2013. Medical Decision Making. John Wiley & Sons.

Squires, H., Chilcott, J., Akehurst, R., Burr, J., Kelly, M.P., 2016. A Framework for Developing the Structure of Public Health Economic Models. Value Health 19, 588–601. https://doi.org/10.1016/j.jval.2016.02.011

Stampfer, M.J., Hu, F.B., Manson, J.E., Rimm, E.B., Willett, W.C., 2000. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 343, 16–22. https://doi.org/10.1056/NEJM200007063430103

Stewart, R.A.H., Held, C., Hadziosmanovic, N., Armstrong, P.W., Cannon, C.P., Granger, C.B., Hagström, E., Hochman, J.S., Koenig, W., Lonn, E., Nicolau, J.C., Steg, P.G., Vedin, O., Wallentin, L., White, H.D., 2017. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. Journal of the American College of Cardiology 70, 1689–1700. https://doi.org/10.1016/j.jacc.2017.08.017

Stone, S.G., Serrao, G.W., Mehran, R., Tomey, M.I., Witzenbichler, B., Guagliumi, G., Peruga, J.Z., Brodie, B.R., Dudek, D., Möckel, M., Brener, S.J., Dangas, G., Stone, G.W., 2014. Incidence, predictors, and implications of reinfarction after primary percutaneous coronary intervention in st-segment-elevation myocardial infarction: The harmonizing outcomes with revascularization and stents in acute myocardial infarction trial. Circulation: Cardiovascular Interventions 7, 543–551. https://doi.org/10.1161/CIRCINTERVENTIONS.114.001360

Strohacker, K., Galarraga, O., Williams, D.M., 2014. The Impact of Incentives on Exercise Behavior: A Systematic Review of Randomized Controlled Trials. Annals of Behavioral Medicine 48, 92–99. https://doi.org/10.1007/s12160-013-9577-4

Tappenden, P., Chilcott, J., Brennan, A., Squires, H., Stevenson, M., 2012. Whole Disease Modeling to Inform Resource Allocation Decisions in Cancer: A Methodological Framework. Value in Health 15, 1127–1136. https://doi.org/10.1016/j.jval.2012.07.008

Thaler, R.H., 2016. Behavioral Economics: Past, Present, and Future. American Economic Review 106, 1577–1600. https://doi.org/10.1257/aer.106.7.1577

Thokala, P., Dodd, P., Baalbaki, H., Brennan, A., Dixon, S., Lowrie, K., 2020. Developing Markov Models From Real-World Data: A Case Study of Heart Failure Modeling Using Administrative Data. Value in Health 23, 743–750. https://doi.org/10.1016/j.jval.2020.02.012

Torgerson, D.J., Byford, S., 2002. Economics Notes: Economic modelling before clinical trials. Bmj 325, 98–98. https://doi.org/10.1136/bmj.325.7355.98

Trerayapiwat, K., Jinatongthai, P., Vathesatogkit, P., Sritara, P., Paengsai, N., Dilokthornsakul, P., Nathisuwan, S., Le, L.M., Chaiyakunapruk, N., 2022. Using real world evidence to generate cost-effectiveness analysis of fibrinolytic therapy in patients with ST-segment elevation myocardial infarction in

Thailand. The Lancet Regional Health – Western Pacific 26. https://doi.org/10.1016/j.lanwpc.2022.100503

Tršan, J., Košuta, D., Rajkovič, U., Fras, Z., Jug, B., Novaković, M., 2021. Vascular Function in Patients After Myocardial Infarction: The Importance of Physical Activity. Front Physiol 12, 763043. https://doi.org/10.3389/fphys.2021.763043

Tudor-Locke, C., Aguiar, E.J., Han, H., Ducharme, S.W., Schuna, J.M., Barreira, T.V., Moore, C.C., Busa, M.A., Lim, J., Sirard, J.R., Chipkin, S.R., Staudenmayer, J., 2019. Walking cadence (steps/min) and intensity in 21-40 year olds: CADENCE-adults. Int J Behav Nutr Phys Act 16, 8. https://doi.org/10.1186/s12966-019-0769-6

Tudor-Locke, C., Sisson, S.B., Collova, T., Lee, S.M., Swan, P.D., 2005. Pedometer-determined step count guidelines for classifying walking intensity in a young ostensibly healthy population. Can J Appl Physiol 30, 666–676. https://doi.org/10.1139/h05-147

Unal, B., Capewell, S., Critchley, J.A., 2006. Coronary heart disease policy models: A systematic review. BMC Public Health 6, 1–10. https://doi.org/10.1186/1471-2458-6-213

van Baal, P.H.M., Polder, J.J., de Wit, G.A., Hoogenveen, R.T., Feenstra, T.L., Boshuizen, H.C., Engelfriet, P.M., Brouwer, W.B.F., 2008. Lifetime medical costs of obesity: prevention no cure for increasing health expenditure. PLoS Med 5, e29. https://doi.org/10.1371/journal.pmed.0050029

Verhoef, T.I., Trend, V., Kelly, B., Robinson, N., Fox, P., Morris, S., 2016. Cost-effectiveness analysis of offering free leisure centre memberships to physically inactive members of the public receiving state benefits: a case study. BMC Public Health 16, 616. https://doi.org/10.1186/s12889-016-3300-x

Visseren, F.L.J., Mach, F., Smulders, Y.M., Carballo, D., Koskinas, K.C., Bäck, Maria, Benetos, A., Biffi, A., Boavida, J.-M., Capodanno, D., Cosyns, B., Crawford, C., Davos, C.H., Desormais, I., Di Angelantonio, E., Franco, O.H., Halvorsen, S., Hobbs, F.D.R., Hollander, M., Jankowska, E.A., Michal, M., Sacco, S., Sattar, N., Tokgozoglu, L., Tonstad, S., Tsioufis, K.P., van Dis, I., van Gelder, I.C., Wanner, C., Williams, B., ESC Scientific Document Group, De Backer, G., Regitz-Zagrosek, V., Aamodt, A.H., Abdelhamid, M., Aboyans, V., Albus, C., Asteggiano, R., Bäck, Magnus, Borger, M.A., Brotons, C., Čelutkienė, J., Cifkova, R., Cikes, M., Cosentino, F., Dagres, N., De Backer, T., De Bacquer, D., Delgado, V., Den Ruijter, H., Dendale, P., Drexel, H., Falk,

V., Fauchier, L., Ference, B.A., Ferrières, J., Ferrini, M., Fisher, M., Fliser, D., Fras, Z., Gaita, D., Giampaoli, S., Gielen, S., Graham, I., Jennings, C., Jorgensen, T., Kautzky-Willer, A., Kavousi, M., Koenig, W., Konradi, A., Kotecha, D., Landmesser, U., Lettino, M., Lewis, B.S., Linhart, A., Løchen, M.-L., Makrilakis, K., Mancia, G., Marques-Vidal, P., McEvoy, J.W., McGreavy, P., Merkely, B., Neubeck, L., Nielsen, J.C., Perk, J., Petersen, S.E., Petronio, A.S., Piepoli, M., Pogosova, N.G., Prescott, E.I.B., Ray, K.K., Reiner, Z., Richter, D.J., Rydén, L., Shlyakhto, E., Sitges, M., Sousa-Uva, M., Sudano, I., Tiberi, M., Touyz, R.M., Ungar, A., Verschuren, W.M.M., Wiklund, O., Wood, D., Zamorano, J.L., Smulders, Y.M., Carballo, D., Koskinas, K.C., Bäck, Maria, Benetos, A., Biffi, A., Boavida, J.-M., Capodanno, D., Cosyns, B., Crawford, C.A., Davos, C.H., Desormais, I., Di Angelantonio, E., Franco Duran, O.H., Halvorsen, S., Richard Hobbs, F.D., Hollander, M., Jankowska, E.A., Michal, M., Sacco, S., Sattar, N., Tokgozoglu, L., Tonstad, S., Tsioufis, K.P., Dis, I. van, van Gelder, I.C., Wanner, C., Williams, B., 2021. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal 42, 3227–3337. https://doi.org/10.1093/eurheartj/ehab484

Vlaev, I., King, D., Darzi, A., Dolan, P., 2019. Changing health behaviors using financial incentives: a review from behavioral economics. BMC Public Health 19, 1059. https://doi.org/10.1186/s12889-019-7407-8

Wahlich, C., Beighton, C., Victor, C., Normansell, R., Cook, D., Kerry, S., Iliffe, S., Ussher, M., Whincup, P., Fox-Rushby, J., Limb, E., Furness, C., Harris, T., 2017. “You started something … then I continued by myself”: a qualitative study of physical activity maintenance. Prim Health Care Res Dev 18, 574–590. https://doi.org/10.1017/S1463423617000433

Wang, J., Liu, H., Chen, C., Chang, W., Ma, Y., Zhao, C., Smith, S.C.J., Han, J., Yu, M., Ma, J., Qi, J., Xing, Y., 2020. Physical Activity and Factors Affecting Its Maintenance Among Patients With Coronary Heart Disease Not Undergoing Cardiac Rehabilitation in China. Journal of Cardiovascular Nursing 35, 558–567. https://doi.org/10.1097/JCN.0000000000000698

Weinstein, M.C., Coxson, P.G., Williams, L.W., Pass, T.M., Stason, W.B., Goldman, L., 1987. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. Am J Public Health 77, 1417–1426. https://doi.org/10.2105/ajph.77.11.1417

Weinstein, M.C., O'Brien, B., Hornberger, J., Jackson, J., Johannesson, M., McCabe, C., Luce, B.R., ISPOR Task Force on Good Research Practices--Modeling Studies, 2003. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Health 6, 9–17. https://doi.org/10.1046/j.1524-4733.2003.00234.x

Wilkinson, T., Sculpher, M.J., Claxton, K., Revill, P., Briggs, A., Cairns, J.A., Teerawattananon, Y., Asfaw, E., Lopert, R., Culyer, A.J., Walker, D.G., 2016. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. Value Health 19, 921–928. https://doi.org/10.1016/j.jval.2016.04.015

Wisløff, T., Selmer, R.M., Halvorsen, S., Fretheim, A., Norheim, O.F., Kristiansen, I.S., 2012. Choice of generic antihypertensive drugs for the primary prevention of cardiovascular disease - A cost-effectiveness analysis. BMC Cardiovascular Disorders 12, 26. https://doi.org/10.1186/1471-2261-12-26

World Health Organization, 2020. Noncommunicable diseases: progress monitor 2020. World Health Organization, Geneva.

Yan, A.F., Stevens, P., Wang, Y., Weinhardt, L., Holt, C.L., O'Connor, C., Feller, T., Xie, H., Luelloff, S., 2015. mHealth text messaging for physical activity promotion in college students: a formative participatory approach. Am J Health Behav 39, 395–408. https://doi.org/10.5993/AJHB.39.3.12

Yusuf, S., Hawken, S., Ounpuu, S., Bautista, L., Franzosi, M.G., Commerford, P., Lang, C.C., Rumboldt, Z., Onen, C.L., Lisheng, L., Tanomsup, S., Wangai, P., Razak, F., Sharma, A.M., Anand, S.S., INTERHEART Study Investigators, 2005. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 366, 1640–1649. https://doi.org/10.1016/S0140-6736(05)67663-5

Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. The Lancet 364, 937–952. https://doi.org/10.1016/S0140-6736(04)17018-9

7 Appendix

Appendix 1: Consolidated Health Economic Evaluation Reporting Standards 2022 Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Cover page
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	pp. I-II
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	pp. 1-10
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	p. 15
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	pp. 11-13
Setting and location	6	Provide relevant contextual information that may influence findings.	pp. 11-13
Comparators	7	Describe the interventions or strategies being compared and why chosen.	pp. 11-13
Perspective	8	State the perspective(s) adopted by the study and why chosen.	p. 16, pp. 21-22

Time horizon	9	State the time horizon for the study and why appropriate.	p. 17, p. 25
Discount rate	10	Report the discount rate(s) and reason chosen.	p. 22
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	p. 24
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	pp. 16-25
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	pp. 22-24
Measurement and valuation of resources and costs	14	Describe how costs were valued.	pp. 21-22, Appendix 2
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	pp. 21-22, Appendix 2
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	pp. 15-25
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	pp. 13-24
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	pp. 16-20, pp. 24-25
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	N/A
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the	pp. 23-25, Appendix 4

		analysis.	
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	pp. 11-13
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	pp. 15-25, Appendices 2-4
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	pp. 26-29
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	pp. 27-30
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	pp. 13-14
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	pp. 31-42
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	N/A
Conflicts of interest	28	Report authors conflicts of interest	N/A

		according to journal or International Committee of Medical Journal Editors requirements.	

Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. BMJ. 2022;376:e067975.

Appendix 2: Cost data for health states

Annual direct medical costs for the “history of MI” state were based on a German cost analysis (Lutter et al., 2019). Reported healthcare usage among a cohort with previous myocardial infarction was multiplied with German unit costs (price year 2013 in Euros) (Bock et al., 2015). Unit costs varied depending on the service, which included ambulatory physician visits, hospital treatments, rehabilitation costs and medication costs.

Annual direct medical costs for the “reinfarction” state were based on a systematic economic review (Schmid et al., 2016) on the costs of treating cardiovascular events in Germany (price year 2014 in Euros). Estimates relied on real-world administrative data by a German sickness fund and a resource utilization evaluation by a Delphi expert panel (Bäumler et al., 2012). The administrative cost measurement used reimbursement data, employing the detailed German system of diagnosis-related groups (G-DRG) that calculates cost weights based on average provider costs for the reimbursement of in-hospital patients. In the expert cost analysis, the resource utilization for inpatient, outpatient, rehabilitation and pharmaceutical treatments was assessed and costed based on the respective charges.

Annual direct medical costs for the “post-reinfarction” state were based on a German cost analysis and a cost-effectiveness analysis on recurrent cardiovascular events (Lutter et al., 2019; Sehested et al., 2019). Following Sehested et al. (2019), previously published costs for standard of care treatment for the “history of MI” state was used, adding an increase in costs following recurrent myocardial infarction to account for the assumed development of heart failure in 20% of patients (Voigt et al., 2014).

References:

Bäumler M, Stargardt T, Schreyögg J, Busse R. Cost effectiveness of drug-eluting stents in acute myocardial infarction patients in Germany: results from administrative data using a propensity score-matching approach. Appl Health Econ Health Policy. 2012 Jul 1;10(4):235-48.

Bock J, Brettschneider C, Seidl H, Bowles D, Holle R, Greiner W, et al. Calculation of standardised unit costs from a societal perspective for health economic evaluation. Gesundheitswesen. 2015;77(1):53–61 (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany).

Brüggenjürgen, B., Rupprecht, H. J., Willich, S. N., Spannagl, M., Ehlken, B., Smala, A., et al. Cost of atherothrombotic diseases—myocardial infarction, ischaemic stroke and peripheral arterial occlusive disease—in Germany. Journal of public health, 2015;13, 216-224.

Schmid T, Xu W, Gandra SR, Michailov GV. 'Costs of treating cardiovascular events in Germany: a systematic literature review'. Health Econ Rev. 2016 Dec;6(1):1.

Sehested TSG, Bjerre J, Ku S, Chang A, Jahansouz A, Owens DK, Hlatky MA, Goldhaber-Fiebert JD. Cost-effectiveness of Canakinumab for Prevention of Recurrent Cardiovascular Events. JAMA Cardiol. 2019 Feb 1;4(2):128-135. doi: 10.1001/jamacardio.2018.4566.

Voigt J, Sasha John M, Taylor A, Krucoff M, Reynolds MR, Michael Gibson C. A reevaluation of the costs of heart failure and its implications for allocation of health resources in the United States. Clin Cardiol. 2014;37(5):312-321.

Appendix 3: Cost estimation of INPHY

Intervention - financial	€ per Person
Fitness Tracker	120
Smartphone	100
financial incentive	420
Staff	329,46
Total Cost	**969,46**

Staff - Intervention	h per Person
Recruiting	1
Equipment with Devices	2
Technical Help	4
Managing Data	4
Managing Financial Incentive	6
Total Working Hours	**17**
Staff Cost per Hour	19,38

Intervention - social	€ per Person
Fitness Tracker	120
Smartphone	100
Staff	290,7
Total Cost	**510,7**

Staff - Intervention	h per Person
Recruiting	1
Equipment with Devices	2
Technical Help	4
Managing Data	4
Managing Social Incentive	4
Total Working Hours	**15**
Staff Cost per Hour	19,38

Evaluation RCT - financial	€ per Person
Fitness Tracker	120
Smartphone	100
Insurance	17,5
Questionnaire license	1,4
Travel compensation	90
financial incentive	420
Staff	966,14
Total Cost	**1715,04**

Evaluation RCT - social	€ per Person
Fitness Tracker	120
Smartphone	100
Insurance	17,5
Questionnaire license	1,4
Travel compensation	90
Staff	888,85
Total Cost	**1217,75**

Staff - RCT	h per Person
Recruiting	1
Equipment with Devices	2
Technical Help	4
Managing Data	4
Questionnaire	6
Fitness Test	2
Managing Financial Incentive	6
Total Working Hours	**25**
Staff Cost per Hour	38,65

Staff - RCT	h per Person
Recruiting	1
Equipment with Devices	2
Technical Help	4
Managing Data	4
Questionnaire	6
Fitness Test	2
Managing Social Incentive	4
Total Working Hours	**23**
Staff Cost per Hour	38,65

Appendix 4: Distributions in the Probabilistic Sensitivity Analysis

Distribution	**Parameters**
Fixed (not changed)	Transition probabilities
Log-Normal	Relative risks
Normal	Physical activity parameters at beginning
Binomial	Days of adherence
Gamma	Costs

Danksagung

Ich möchte mich bei den folgenden Personen bedanken, ohne die ich nicht in der Lage gewesen wäre, diese Dissertation abzuschließen!

Mein besonderer Dank gilt meiner Doktormutter, meiner Mentorin und meiner Ratgeberin Frau Professorin Andrea Icks. Während meiner Zeit als Doktorand durfte ich unter deiner Betreuung lernen, wachsen und mich entwickeln. Deine stetige Förderung, deine ermutigenden E-Mails und deine wegweisenden Anrufe bleiben immer in Erinnerung.

Herrn Professor Christian Jung danke ich als Zweitbetreuer für die wertvollen Hinweise zur Arbeit. Das Einbringen Ihrer klinischen Perspektive auf das Projekt war sehr wertvoll.

Ewiger Dankbarkeit bin ich meiner Betreuerin Frau Dr. Katherine Ogurtsova verpflichtet. Ohne deine geduldige Anleitung und engagierte Unterstützung wäre diese Arbeit nicht zustande gekommen.

Ich möchte auch dem Institut für Versorgungsforschung und Gesundheitsökonomie danken, insbesondere den Projektmitgliedern Professorin Nadja Kairies-Schwarz, Dr. Markos Dintsios und Jan Dyczmons. Eure wohlüberlegten Ideen, Vorschläge und Kommentare haben mir geholfen, meine Dissertation zu verbessern.

Mein größter Dank gilt den besten Eltern, den besten Geschwistern und der besten Freundin dieser Welt. Danke Mama, danke Papa, für all das, was ihr für mich getan habt. Danke Maral, danke Armin, dass ihr mein Leben stets wie Blumen aus dem gleichen Garten versüßt. Danke Kathi, dass du wie ein Fels in der Brandung meinen Rücken stärkst und immer für mich da bist.