Scaling up cost-effective physical activity interventions in a culturally diverse setting

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List of abbreviations

DALY	Disability-adjusted life-year
GBD	Global burden of disease
GP	General practitioner
ICER	Incremental cost-effectiveness ratio
MET	Metabolic equivalent of task
NCDs	Non-communicable diseases
PAF	Population attributable fraction
RCT	Randomized controlled trial
RR	Relative risk
SPACE	Swiss physical activity cost-effectiveness
WHO	World health organization

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Preface

This PhD thesis investigated the cost-effectiveness of physical activity interventions in the culturally diverse setting of Switzerland. After an abstract and an extended summary, the first chapter of the thesis elaborates on the background. Afterwards, the specific aims are described, which are then followed by the three papers forming part of this thesis. The thesis finishes with a chapter that summarizes the main findings, includes a general discussion, shows prospects for future research and finally draws overarching conclusions.

Abstract

Before this PhD project started, evidence showed that physical inactivity causes a substantial health and economic burden globally. For Switzerland, there was research available investigating the burden of physical inactivity. However, this research estimated the burden for the entire country without differentiating between sub regions although the prevalence of physical inactivity varies significantly between the French-, German- and Italian-speaking regions. Therefore, this thesis had three aims:

1. Estimating the health and economic burden of physical inactivity in Switzerland and for the French-, German- and Italian-speaking language regions separately
2. Systematically reviewing trial-based economic evaluations of interventions to reduce physical inactivity
3. Developing a health economic model that investigates the cost-effectiveness of physical activity interventions in Switzerland and its three language regions

The thesis showed that the burden of physical inactivity in Switzerland is substantial and that the French- and Italian-speaking regions are over-proportionally affected. These two regions distinguish themselves from the German-speaking region by having a higher prevalence of physical inactivity, higher per capita health care spending, and higher disease prevalence. Due to the substantial burden of physical inactivity, interventions aiming to increase physical activity should be considered. In the systematic review we conducted, we found evidence from randomized controlled trials indicating the cost-effectiveness of some physical activity interventions for primary prevention in adults. These interventions were then further evaluated in a cost-effectiveness model built for the Swiss setting. This model showed that Swiss policy makers have cost-effective options of physical activity promotion. We recommend that individualized advice and general practitioner referral be further evaluated as interventions and that decision-making considers the specifics of the Swiss language regions. Furthermore, we judge the cost-effectiveness model to be not only relevant for Switzerland but also for other multicultural countries. Based on similar data availability, our model has the potential to be applied beyond Switzerland, primarily to high-income countries with a comparable background, as a tool to guide societal efforts in primary prevention of physical-inactivity-related diseases.

Summary

Background and aims

Before this PhD project started, evidence showed that physical inactivity causes a substantial health and economic burden globally. For Switzerland, there was research available investigating the burden of physical inactivity. However, this research estimated the burden for the entire country without differentiating between sub regions although the prevalence of physical inactivity varies significantly between the French-, German- and Italian-speaking regions. Therefore, the aim of the first publication forming part of this PhD thesis was to estimate the burden of physical inactivity in Switzerland separately for the three language regions. In a systematic review that formed the basis of the second publication of this thesis, we aimed to identify cost-effective physical activity interventions that have been investigated in randomized controlled trials (RCTs). We then moved on and used findings from the first two PhD publications to develop a health economic model that investigates the cost-effectiveness of physical activity interventions in Switzerland and its three language regions.

Publication 1: Burden of physical inactivity in Swiss language regions

We estimated the burden of physical inactivity in Swiss adults from a societal perspective with a prevalence-based top-down approach using population attributable fractions (PAFs) and the latest data available for Switzerland. The following nine diseases related to physical inactivity were included in the analysis: coronary heart disease, hypertension, ischemic stroke, type 2 diabetes mellitus, breast cancer, colorectal cancer, osteoporosis, low back pain, and depression. Total disability-adjusted life-years (DALYs), health care costs, and productivity losses of these diseases were then retrieved from the global burden of disease study and a recent study on the costs of non-communicable diseases in Switzerland. In order to analyze the fraction of this total burden that is attributable to physical inactivity, we combined estimates of the prevalence of physical inactivity stemming from the Swiss Health Survey with literature-based estimates of disease incidence in the presence vs. absence of physical inactivity and resulting relative risks. The combination of these two types of parameters allowed us to estimate PAFs, which describe the proportion of disease occurrence that can be attributed to a certain risk factor.

The burden of physical inactivity in Switzerland in 2013 was estimated at CHF 1.610 billion (95%CI CHF 1.413-1.827 billion) plus 40,433 (95%CI 34,935-46,487) DALYs. The DALYs lost due to physical inactivity represented 2.0% (95%CI 1.7%-2.2%) of total DALYs lost in Switzerland. Health care costs caused by physical inactivity were estimated at CHF 0.802 billion (95%CI CHF 0.684-0.934 billion) or at 1.2% (95%CI 1.0%-1.3%) of total health care expenditures. This was equivalent to CHF 116 (95%CI CHF 99-135) per capita. Productivity

losses were valued at CHF 0.808 billion (95%CI CHF 0.653-0.983 billion) or CHF 117 (95%CI CHF 94-142) per capita. Furthermore, we found that the French- and Italian-speaking regions, which are home to 30% of the Swiss population, contribute more than 45% to the burden of physical inactivity. Reasons include a higher prevalence of physical inactivity, higher per capita health care spending, and higher disease prevalence than the German-speaking region. In addition, the per capita burden was twice as high in the French- and Italian-speaking regions compared to the German-speaking region.

In conclusion, this study showed that physical inactivity causes a substantial health and economic burden in Swiss adults and that the French- and Italian-speaking regions are over-proportionally affected. Investments in interventions aiming to increase physical activity should therefore be considered. Such interventions should be cost-effective and this study indicates that regional differences likely influence the cost-effectiveness of physical activity interventions.

Publication 2: Systematic review of cost-effectiveness of physical activity interventions

In this systematic review, we aimed to summarize evidence from RCT-based economic evaluations of primary prevention physical activity interventions in adult populations outside the workplace setting. We included cost-effectiveness analyses in which all data (except unit costs) came from one RCT. As the studies reported different physical activity outcomes, effect measures were standardized in metabolic equivalent of task (MET)-hours gained per person per day. We further calculated the mean differences in costs and outcomes between intervention and control as a basis for estimating the incremental cost-effectiveness ratio (ICER) in US$ per MET-hour gained. A benchmark between US$0.44 and US$0.63 per MET-hour gained, which was based on the health care costs and productivity losses of physical inactivity in Switzerland, was used to assess the cost-effectiveness of interventions.

Twelve studies published between 2000 and 2018 were included in the final analysis. In these twelve studies, 22 interventions were investigated. Interventions were based on advice, goal setting and follow-up support, exercise classes, financial incentives or teaching on behavioral change. The effects and costs of the interventions varied widely and so did the ICER. Four interventions showed an ICER below the applied benchmark. These four interventions were based on individualized advice delivered in four different ways: print (postal mail) or web (website and email) and in a basic form (standard advice) or with additional environmental components (e.g., walking and cycling routes). One other intervention that was based on general practitioner (GP) referral to behavior change counseling by telephone had an ICER of US$0.64 per MET-hour gained. One pedometer-based individualized goal-setting intervention had an ICER of US$0.67 per MET-hour gained. Another intervention was based on exercise prescription and had an ICER of US$0.85 per MET-hour gained. All other interventions had an ICER above US$1.00 per MET-hour gained.

In conclusion, we found evidence from RCTs indicating cost-effectiveness of some physical activity interventions for primary prevention in adults. However, cost-effectiveness results varied widely among interventions and the majority of interventions would not be cost-effective according to the benchmark applied. Four interventions that delivered individualized advice via print or web showed the best value (physical activity gains) for money (intervention costs).

Publication 3: Cost-effectiveness model of physical activity interventions

The cost-effectiveness model of physical activity interventions was built as a proportional multistate life table model for the Swiss adult population over their lifetime. We named it the Swiss Physical Activity Cost-Effectiveness (SPACE) model. In the model, a comprehensive set of diseases was included, namely breast cancer, colorectal cancer, type 2 diabetes mellitus, coronary heart disease, ischemic stroke, osteoporosis, low back pain and depression. The effect of interventions on diseases was modelled with data from recent meta-analyses. Interventions analyzed were individualized physical activity advice, pedometer with individualized goal setting, GP referral to telephone-based counseling and exercise prescription. Intervention effects were taken from RCTs, and intervention costs were based on a bottom-up approach with Swiss prices. Cost-effectiveness in terms of cost per DALY averted compared to “doing nothing” as well as cost-effectiveness between interventions were analyzed on the national level and separately for the French-, German- and Italian-speaking language regions. The frequently assumed tentative willingness-to-pay threshold of CHF 100,000 per DALY was used to assess the cost-effectiveness of interventions. Interventions that led to better health and were at the same time cost-saving were categorized as “dominant”.

From a societal perspective and irrespective of language region, all four interventions were cost-saving and more effective compared to “doing nothing”. At the national level and in the German-speaking region, individualized advice was the preferable intervention followed by GP referral. These two interventions dominated pedometer and exercise prescription. In the French- and Italian speaking regions, GP referral was the preferable intervention that dominated the three others. From a health care payer perspective, however, individualized advice was the preferable intervention followed by GP referral. The uncertainty underlying key model input parameters led to substantial variation in the modelled results, according to the probabilistic sensitivity analysis.

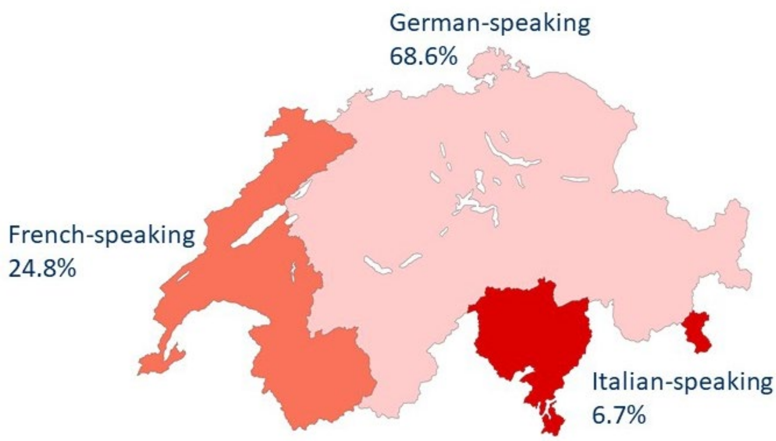
In conclusion, we hope to inform efficient resource allocation and evidence-based decision-making in primary prevention in Switzerland. We recommend that individualized advice and GP referral be further evaluated as interventions and that decision-making considers the specifics of the Swiss language regions. Furthermore, we judge the SPACE model to be not only relevant for Switzerland but also for other multicultural countries. Based on similar data availability, the SPACE model has the potential to be applied beyond Switzerland, primarily to high-income countries with a comparable background, as a tool to guide societal efforts in primary prevention of physical-inactivity-related diseases.

1. Background

1.1 Switzerland - a multilingual, multicultural country

Switzerland has a population size of about 8.5 million [4]. Influenced by its neighboring countries, there are three main language regions in this rather small country: German-speaking, French-speaking and Italian-speaking (Figure 1). The fourth national language is Romansh, which is spoken by a minority of about 0.5% of the population [5]. There are also many foreigners contributing to the linguistic diversity of Switzerland. The most commonly spoken foreign languages are English, Portuguese, Spanish, Serbian, Croatian and Albanian [5]. The relationship between language and culture has been extensively studied [6] and recent concepts suggest an interactional relationship between the two [7]. Due to its linguistic diversity, Switzerland can be considered a culturally diverse setting.

Figure 1: Switzerland and its three main language regions



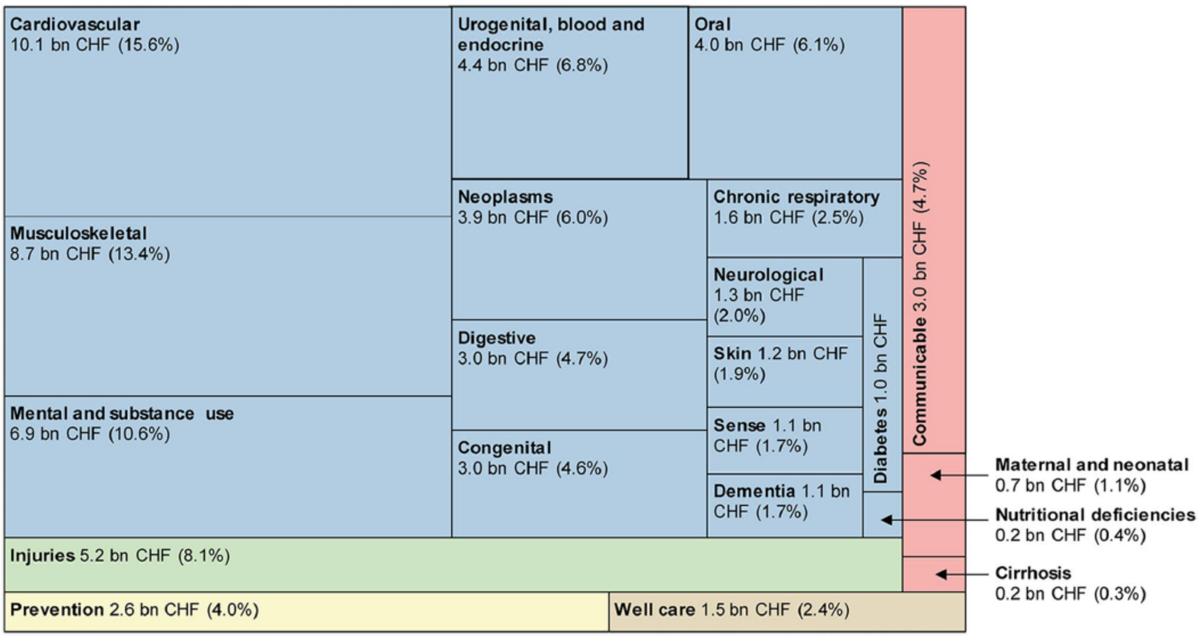
Interestingly, we see substantial differences in health behavior, self-perceived health status and health care resource use between the language regions. Examples include prevalence of smoking, alcohol abuse, unhealthy eating habits and physical inactivity that are on average higher in the French- and Italian-speaking regions compared to the German-speaking region [8]. Furthermore, self-perceived health status is highest in the German-speaking region, followed by the French-speaking and Italian-speaking regions [8]. In addition, there are more doctor's visits per year in the French- and Italian-speaking regions than in the German-speaking region [8]. Research also showed variation in the cost of care during the last year of life between Swiss language regions and highlighted the importance of cultural factors for the delivery and utilization of health care [9].

1.2 The relevance of non-communicable diseases in Switzerland

Switzerland has the second highest life expectancy worldwide, which is 84 years [10]. However, Switzerland also has the second highest health care expenditure with US$ 9836 per capita [11]. Non-communicable diseases (NCDs) such as cardiovascular diseases, musculoskeletal diseases and neoplasms cause 80% of the health and economic burden in Switzerland (Figure 2) [12, 13]. This substantial burden is the reason for the strategic initiative for the prevention of NCDs by the Swiss Federal Office of Public Health [14].

In addition to personal and environmental factors, modifiable lifestyle factors influence the incidence of NCDs and life expectancy [15-19]. Modifiable lifestyle factors include smoking, alcohol abuse, unhealthy eating habits and physical inactivity. All these lifestyle factors are common in Switzerland [8]. Furthermore, the health and economic burden due to smoking, alcohol abuse and physical inactivity has been shown to be substantial [20-22]. This PhD project focuses on one of these lifestyle factors: physical inactivity.

Figure 2: Health care expenditure in Switzerland by disease group and disease (from Wieser et al. [13])



1.3 Physical activity

Physical activity is defined as bodily movement produced by skeletal muscles that results in energy expenditure [23]. Physical activity occurs for different reasons in different domains throughout the day. The four domains are occupational, transportation, household and leisure-time physical activity [24].

Physical activity is associated with a wide range of health benefits. Higher levels of physical activity lead to reduced all-cause mortality [25-29]. Furthermore, physical activity reduces the risk of several NCDs such as coronary heart disease, ischemic stroke, type 2 diabetes mellitus, colorectal cancer, breast cancer, depression and low back pain [30-32].

Due to the health-enhancing effects of physical activity, the world health organization (WHO) recommends at least 2.5 hours of physical activity with moderate intensity per week or 1.25 hours of physical activity with high intensity per week [33]. These WHO guidelines have been adopted by the Swiss Federal Office of Sports [34]. Most recent recommendations have been issued for the US [35]. The US guidelines specify higher levels of physical activity: adults should do at least 2.5 hours to 5 hours a week of moderate-intensity, or 1.25 hours to 2.5 hours a week of vigorous-intensity physical activity, or an equivalent combination of moderate- and vigorous-intensity activity. Adults should also do muscle-strengthening activities on two or more days a week. Children and adolescents should be physically active for at least one hour per day.

1.4 Physical inactivity in Switzerland

Physically inactive people do not comply with physical activity recommendations. Although physical inactivity can be considered a global pandemic, the problem is of particular concern in high-income countries. In 2016, the prevalence of physical inactivity in high-income countries was twice that in low-income countries (36.8% versus 16.2%) [36].

In Switzerland, 24.3% of the population over the age of 15 is physically inactive [8]. However, the prevalence of physical inactivity shows significant regional differences: 21.0% of the adult population in the German-speaking region is physically inactive whereas 32.6% are physically inactive in the French-speaking region and 31.5% in the Italian-speaking region. These regional differences can also be seen in children: during an average school day, 21% of the children in the German-speaking region are physically active for less than one hour whereas this number is 31% in the other two language regions [37]. People with higher education and higher income generally tend to be more active. Recent studies, however, showed that the regional differences of physical inactivity in Switzerland cannot be explained by such socio-demographic differences or differences in the built environment [38-41].

1.5 The burden of physical inactivity in Switzerland

Cost-of-illness studies estimate the burden of specific health problems at the population level in terms of losses of quality and length of life, health care resource use and productivity losses. Cost-of-illness studies are often used to demonstrate the importance of particular health problems to policy makers and the public. In these circumstances, the magnitude of a health problem is used to justify or guide resource allocation, e.g. the allocation of intervention/prevention programs or the allocation of research funding [42, 43]. Although cost-of-illness studies are of a descriptive nature, they can also be used to analyze the magnitude of a certain aspect of a health problem. In addition, cost-of-illness studies define the upper limit of resources that could be saved through interventions and therefore serve as a framework for cost-effectiveness analyses of interventions [44, 45].

The global burden of physical inactivity is substantial. In 2015, 1.6 million deaths and 34.6 million disability-adjusted life-years (DALYs) were attributable to physical inactivity [46]. Furthermore, the health problem is getting worse as deaths and DALYs attributable to physical inactivity increased by more than 17% between 2005 and 2015. The major health burden of physical inactivity has also been shown in other studies [47]. Besides the substantial health burden, physical inactivity also causes an associated economic burden worldwide [48-50].

In a recent study, we estimated health care costs due to physical inactivity at CHF 1.2 billion or at 1.8% of total health care expenditures in Switzerland in 2011 and productivity losses at CHF 1.4 billion [22]. Furthermore, 326,310 cases of disease and 1,153 deaths were attributable to physical inactivity in 2011. Although the prevalence of physical inactivity varies significantly between Swiss language regions, this study estimated costs for the entire country without differentiating between sub regions. Therefore, the aim of the first publication forming part of this PhD thesis was to estimate the burden of physical inactivity in Switzerland separately for the German-, French- and Italian-speaking regions.

1.6 Physical activity interventions

Physical activity behavior is determined by individual, social and environmental factors (Figure 3) [51]. Physical activity interventions initially were targeting individual-level health, and interventions intending to change physical activity on a population level emerged later. More recently, a systems approach that acknowledges the complex interaction of individual- and population-level interventions has been promoted (Figure 4) [52]. In accordance with this systems approach, the Global Advocacy for Physical Activity defined the following seven “best investments” for physical activity with good evidence of effectiveness and worldwide applicability: school-based interventions, transport, urban design, primary health care, public education (including mass media), community-based interventions (including workplace) and the sports system [53].

Figure 3: Adapted ecological model of the determinants of physical activity (from Bauman et al. [51])

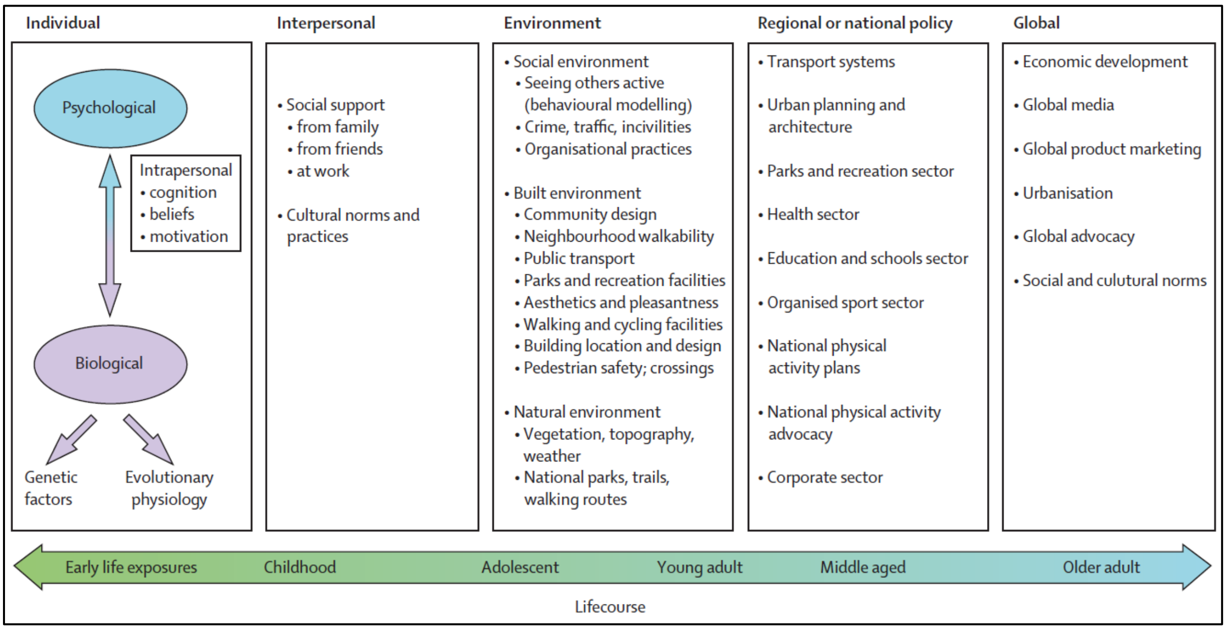


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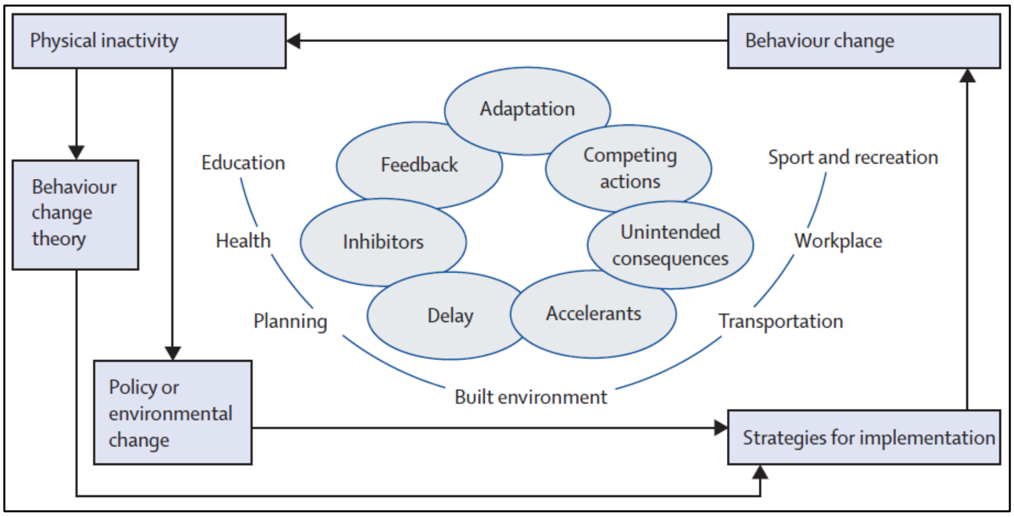
Figure 4: Systems approach to physical activity (from Kohl et al. [52])



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There are hundreds of primary studies investigating the effectiveness of physical activity interventions, and it is not surprising that systematic reviews are also numerous [54-71]. However, with limited resources available, policy makers are interested in interventions that provide best value for money. Therefore, interventions aiming to increase physical activity should not only prove effectiveness in terms of health outcomes but also cost-effectiveness.

1.7 Cost-effectiveness analyses

Cost-effectiveness analyses compare costs and outcomes of an intervention with a comparator and are also called full economic evaluations [72]. In full economic evaluations, costs can be reported from different perspectives, e.g. intervention costs, health care costs offset due to interventions or productivity losses offset due to interventions. There are also different outcome measures that can be used such as MET-hours per week gained, DALYs averted or quality-adjusted life-years (QALYs) gained (strictly, the latter two would be named cost-utility analyses instead of cost-effectiveness analyses). The difference in costs between intervention and comparator is divided by the difference in the effect between intervention and comparator to estimate the incremental cost-effectiveness ratio (ICER). The ICER describes how much it would cost to gain one MET-hour per week, how much it would cost to avert one DALY or how much it would cost to gain one QALY. This ICER can then be compared between interventions in order to find the most cost-effective one. Some countries also know an ICER threshold and if the ICER of an intervention lies above this threshold, the intervention is no longer considered to be cost-effective. Consequently, cost-effectiveness analyses investigate value for money. However, there is a second relevant question in economic evaluations and that is the one about affordability. Affordability is investigated in budget impact analyses. Budget impact analyses estimate expected changes in health care expenditure after the introduction of a new intervention [73]. However, a budget impact analysis can also be useful for budget or resource planning.

There are two different approaches in economic evaluations: trial-based economic evaluations and model-based economic evaluations [74]. However, the transition between the two is smooth. In a trial-based economic evaluation, costs are measured alongside a clinical trial investigating the effect of the intervention [75-78]. In a model-based economic evaluation, data on the effect and the costs from different sources are combined in a decision-analytic model [79, 80]. Both methodological approaches have strengths and weaknesses [81-85]. The main strengths of a trial-based economic evaluation are related to the methodological strength of randomized controlled trials (RCTs), i.e. the exclusion of potential biasing factors [80]. However, RCTs have weaknesses when directly used for policy making that are related to the efficacy versus effectiveness discussion [80]: areas of potential concern include choice of comparator, protocol-driven costs and outcomes, artificial environment, intermediate versus final outcomes, inadequate participant follow-up, and selected patient and provider populations [80]. Model-based economic evaluations have the strength that they can synthesize the best evidence available in case relevant head-to-head clinical trials are missing, costs were not measured within trials, intermediate endpoints were captured or trial follow-up was short-term [74]. Nevertheless, inappropriate use of clinical data, bias in observational data, difficulties of extrapolation and concerns about transparency or validity of models are major problems [74]. These strengths and weaknesses make it evident that for policy-making reasons the two methods are better used complementarily than alternatively [81].

Several systematic reviews have investigated the cost-effectiveness of physical activity interventions [86]. Most reviews focused on specific settings (e.g. school, workplace, community) and did not pay much attention to the methodological approaches (trial-based or model-based) chosen in the identified economic evaluations [86]. The availability of trial-based economic evaluations of physical activity interventions seems to be limited [54, 60, 87, 88], and to the best of our knowledge, no systematic review has focused on this topic. Consequently, the second publication forming part of this PhD thesis aimed to systematically review trial-based economic evaluations of interventions to increase physical activity.

1.8 Modelling cost-effectiveness of physical activity interventions

Policy makers have to make decisions on a national or even regional level and cost-effectiveness of physical activity interventions may differ between regions. This could be specifically the case in Switzerland where the prevalence of physical inactivity but also health care resource use substantially differs between language regions. Therefore, policy makers need to know the cost-effectiveness of physical activity interventions regionally in order to allocate resources efficiently. Health economic modelling can support decision-making, particularly in the absence of region-specific data [74, 79].

A variety of model structures have been presented for the economic evaluation of public health interventions for NCDs [89]. Previous models investigating the cost-effectiveness of physical activity interventions include decision trees [90, 91], Markov models [92-96], microsimulation models [97, 98] as well as multistate life table models [99-102]. Most models were built for the UK [90-94, 97-99, 103-108], Australia [100, 102, 109-111] and the USA [96, 112-114]. However, no such model is yet available for Switzerland. Therefore, the aim of the third publication forming part of this PhD thesis was to develop a health economic model that investigates the cost-effectiveness of physical activity interventions in Switzerland and its three language regions.

To the best of our knowledge, all previous models investigating physical activity interventions were built from a health care payer perspective. Therefore, our aim was to develop a model not only from a health care payer perspective but also from a societal one, meaning we also included productivity losses [115]. Furthermore, we aimed to account for the fact that the use of certain resources does not increase when scaling up the interventions (fixed costs) [115]. The term ‘scaling up’ describes “the ambition or process of expanding the coverage of health interventions, but can also refer to increasing the financial, human and capital resources required to expand coverage” [116] and it originates from the time when the HIV/AIDS pandemic was the most relevant public health issue. Nowadays, physical inactivity is also seen as a pandemic and it is not surprising to see similar considerations regarding scaling up of interventions in this field [52, 117, 118]. It is suggested that cost-effective and financially feasible interventions should be considered for scaling up [119-121].

2. Aims

The aims of this PhD project were:

1. Estimating the health and economic burden of physical inactivity in Switzerland and for the French-, German- and Italian-speaking language regions separately
2. Systematically reviewing trial-based economic evaluations of interventions to reduce physical inactivity
3. Developing a health economic model that investigates the cost-effectiveness of physical activity interventions in Switzerland and its three language regions

3. Publication 1: Physical inactivity caused economic burden depends on regional cultural differences

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ORIGINAL ARTICLE

WILEY

Physical inactivity caused economic burden depends on regional cultural differences

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Physical inactivity is a major risk factor for numerous non-communicable diseases which dominate the overall burden of disease in Switzerland. We aimed to estimate the burden attributable to adult physical inactivity in Switzerland and its three culturally different language regions from a societal perspective in terms of disability-adjusted life years (DALYs), medical costs, and productivity losses. The burden of physical inactivity was estimated with a population attributable fractions (PAFs) approach. PAFs were calculated based on the prevalence of physical inactivity in the Swiss Health Survey and literature-based adjusted risk ratios of disease incidence. These PAFs were then applied to the total burden of the diseases related to physical inactivity. Physical inactivity was responsible for 2.0% (95%CI 1.7%-2.2%) of total DALYs lost and 1.2% (95%CI 1.0%-1.3%) of total medical costs in 2013. This is equivalent to 116 (95%CI 99-135) Swiss francs per capita per year. Productivity losses were valued at 117 (95%CI 94-142) Swiss francs per capita per year. The two diseases which caused the highest economic burden were low back pain and depression. The analysis of regional differences revealed that the per capita burden of physical inactivity is about twice as high in the French- and Italian-speaking regions compared to the German-speaking region. Reasons include a higher prevalence of physical inactivity, higher per capita health care spending, and higher disease prevalence. Cost-effectiveness analysis of related interventions should consider regional differences for optimal resource allocation in physical activity promotion policies.

KEYWORDS
chronic disease, cost of illness, disease burden, physical activity, regional differences

1 | INTRODUCTION

Physical inactivity is a major risk factor for numerous non-communicable diseases, which are responsible for a large share of the morbidity and mortality in Switzerland.[1] The prevalence of physical inactivity in adults in Switzerland is 28% but differs substantially among the three language regions (German-, French-, and Italian-speaking).[2] In fact, language region has been shown to be a strong correlate of physical activity independent of socio-demographic or environmental factors.[3] For example, French-speaking parents have been observed to be more likely to drive their children to school compared to German-speaking parents, indicating that habits and beliefs about the proper way of performing everyday tasks may differ between Swiss language regions.[4] Differences in habits and beliefs are often referred to as cultural differences and have been shown to influence physical activity behavior.[5] Therefore, Switzerland and its language regions form an interesting case for analyzing the influence of cultural differences on the burden of physical inactivity especially as nationwide health policies and regulations apply (including health insurance law and benefit package) and uniform nationwide data exist.

Disability-adjusted life years (DALYs) in combination with economic burden can be used to measure the burden of a disease or a health behavior such as physical inactivity imposes on society.[6] DALYs combine in one measure years of life lost due to premature mortality (YLL) and years lived with disability (YLD). Therefore, they measure the difference between the current situation and an ideal situation in which everyone would live up to the age of standard life expectancy and in perfect health. The economic burden is described by medical costs and productivity losses caused by the disease or health behavior.

An early study estimated the economic burden of physical inactivity in Switzerland at 2.384 billion Swiss francs in the year 2000.[7] However, this study did not analyze language region-specific differences and did not estimate DALYs. Furthermore, the prevalence of physical inactivity has decreased over the last years. Although this decrease can be observed in all language regions, the gap between the German-speaking region, where the prevalence of physical inactivity is lower, and the French- and Italian-speaking regions is widening.[2]

A better understanding and awareness of the regional differences in the burden of physical inactivity and their consequences are needed to support the optimal allocation of resources in physical activity promotion policies in Switzerland and might also be of interest for other multicultural societies. Furthermore, this study contributes to the international literature by considering some conditions not included in many previous studies, namely low back pain and depression, using population attributable fractions (PAFs) based on risk ratios (RR) adjusted for confounders and addressing uncertainty with sensitivity analyses to estimate robust and transparent results.[8] This study estimates the current Disability-adjusted life years, medical costs and productivity losses of physical inactivity in Switzerland and for the three language regions separately.

2 | MATERIALS AND METHODS

2.1 | Overview

We estimated the burden of physical inactivity from a societal perspective with a prevalence-based top-down approach using population attributable fractions (PAFs) and the latest data available for Switzerland. In a first step, we identified from previous studies the diseases for which physical inactivity is a recognized risk factor. Total DALYs, medical costs, and productivity losses of these diseases were then retrieved from the global burden of disease (GBD) study and a recent study on the costs of non-communicable diseases in Switzerland.[1,9] In order to analyze the fraction of this total burden that is attributable to physical inactivity, we combined estimates of the prevalence of physical inactivity stemming from the most recent Swiss Health Survey with literature-based estimates of disease incidence in the presence vs. absence of physical inactivity and resulting risk ratios (RR). The combination of these two types of parameters allowed us to estimate PAFs, which describe the proportion of disease occurrence that can be attributed to a certain risk factor. In other words, the PAFs describe the proportion of a disease occurrence that could be prevented by entirely eliminating the risk factor for physical inactivity. Figure 1 gives an overview of the methods. This study follows the recently published checklist for reporting estimates of the economic burden of risk factors.[8]

2.2 | Diseases included in the analysis

Epidemiological studies consistently show substantial association between physical inactivity and the occurrence of the following diseases: coronary heart disease, hypertension, stroke, diabetes type 2, breast cancer, colon cancer, osteoporosis, back pain, and depression. We included all of these nine diseases in our analysis. Most of these diseases were also considered in previous studies investigating the burden of physical inactivity.[6,10,11] However, only one previous study included back pain and depression.[7] Although these two diseases have no impact on mortality, they incur a substantial economic burden due to high treatment costs and productivity losses.[9] Consequently, we decided to include them as well.

2.3 | National data on economic cost and health burden of diseases

Estimates of the annual total medical costs of the diseases for which physical inactivity is a recognized risk factor stem from the most recent study on the costs of non-communicable diseases in Switzerland.[9] This study took into account total medical costs of all health care services (inpatient and outpatient services and drugs), irrespective of the actual payer. Costs for hypertension were not reported in this study. We therefore used estimates from a recent study specifically investigating costs of antihypertensive therapy in Switzerland.[12] In our study, we extrapolated all costs to the year 2013 based on the increase in health care spending.

Annual productivity losses were estimated with a human capital approach. For all diseases except hypertension, results from the above-described study by Wieser et al[9] were used. To estimate productivity losses for hypertension, we used the Cause of Death Statistic, the Swiss Labor Force Survey and the Swiss Earnings Structure Survey.[13-15] Future productivity losses due to premature mortality were discounted to present value at a 2% rate. Details are described in Supporting Information Section 1. We extrapolated productivity losses to the year 2013 according to the nominal wage increase.

We estimated DALYs per disease based on the GBD study 2013.[1] We used the following groups: hypertensive heart disease for hypertension, ischemic heart disease for coronary heart disease, ischemic stroke for stroke, diabetes mellitus for diabetes type 2, breast cancer for breast cancer, colon and rectal cancer for colon cancer, falls for osteoporosis, low back pain for back pain, and depressive disorders for depression.

2.4 | Estimation of burden per language region

We divided the national disease burden by the number of prevalent disease cases in Switzerland (Supporting Information Section, Table S1) and then multiplied the resulting burden per case (Supporting Information Section, Table S2) with the number of prevalent disease cases in each language region to estimate the regional disease burden. The prevalent disease cases were estimated from the data of the 2012 Swiss Health Survey and the National Institute for Cancer Epidemiology and Registration.[16-18] Details about this survey are described in Supporting Information Section 2. All prevalence of disease data were adjusted for the year 2013 based on population data from the Swiss Federal Statistical Office. To allow for regional differences in health care spending, we estimated age- and gender-standardized per capita health care spending for each language region based on the statistics of the Swiss risk compensation scheme.[19] For the productivity losses, we considered regional differences by estimating median wages for each language region based on the Swiss Earnings Structure Survey.[15]

2.5 | Prevalence of physical inactivity

We estimated the prevalence of physical inactivity in cases eventually developing a given disease of interest by performing a propensity score matching using the data of the 2012 Swiss Health Survey.[16,20] This survey identified self-reported physical activity levels. A person was considered as physically inactive, if she/he did not meet the current minimal recommendations for health-enhancing physical activity by the WHO[21]: at least 2.5 hours of physical activity with moderate intensity per week or 1.25 hours of sports with high intensity per week. Covariates included in the propensity score matching were behavior (smoking, alcohol use, eating habits, lifestyle), personal characteristics (sex, bmi, education), and environmental factors (stress at work, language region, urban/rural). More details about the propensity score matching can be found in Supporting Information Section 3.

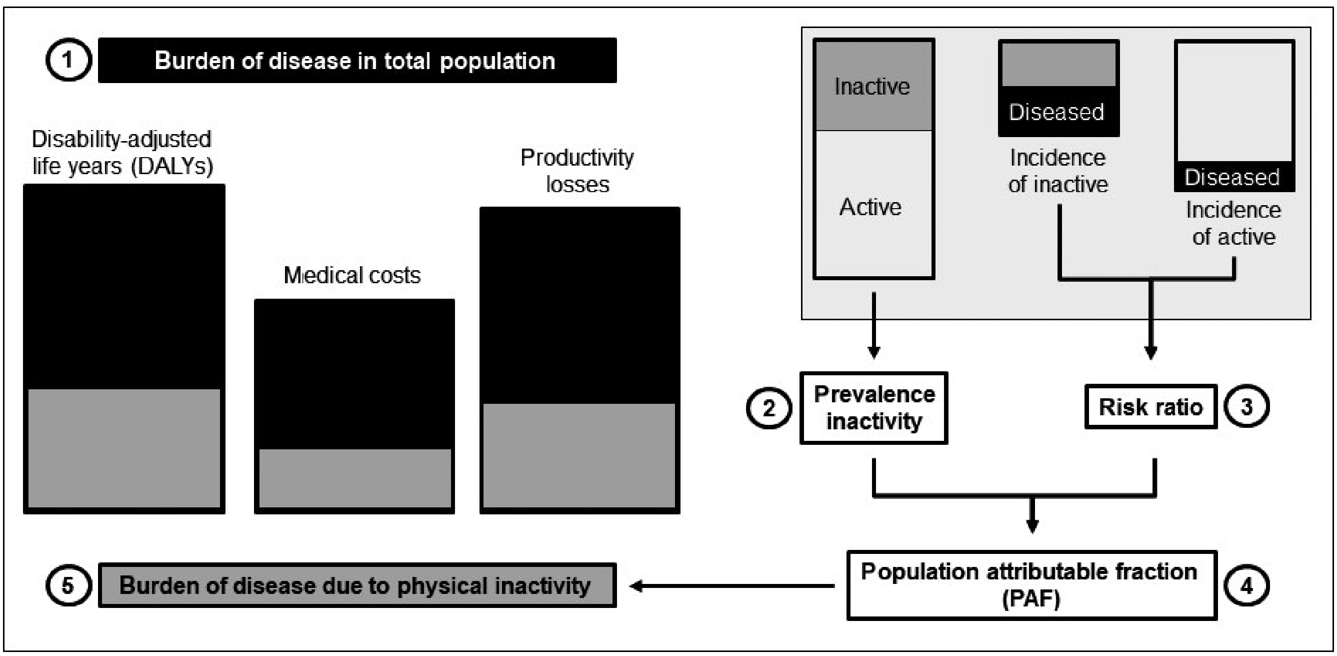

FIGURE 1 Overview of methods. The burden of disease in the total population was extracted from literature (1). The prevalence of physical inactivity in the Swiss Health Survey (2) and literature-based risk ratios of disease incidence (3) were then combined to get the population attributable fraction (PAF) (4). In the last step, the PAF was multiplied with the disability-adjusted life years (DALYs), medical costs and productivity losses in the total population to estimate the burden attributable to physical inactivity (5)

2.6 | Quantification of risk ratios

We quantified the confounding-adjusted RR for disease incidence resulting from physical inactivity vs. physical activity based on previously published meta-analyses investigating causality between physical activity and a specific disease (Table 1). Where RR were estimated for different exposure levels, we used the ones closest to our definition of physical activity and inactivity. In case the RR was reported for active people, we used the following formula to obtain the RR for inactive people: RR(inactive) = 1/RR(active).

2.7 | Calculation of population attributable fractions

We estimated the population attributable fractions (PAFs) based on the prevalence of physical inactivity reported in the latest Swiss Health Survey and RR for disease incidence extracted from the literature. PAFs can be calculated with different formulae. The most common formula uses the prevalence of the exposition in the total population and the unadjusted RR (formula (1)).

$$\text{PAF}(\%) = \frac{\text{prevalence}_{\text{exposition total population}}\left(\text{RR}_{\text{unadj}}-1\right)}{\text{prevalence}_{\text{exposition total population}}\left(\text{RR}_{\text{unadj}}-1\right)+1} \times 100 \quad (1)$$

The unadjusted RR do not account for confounding between exposure and disease. Consequently, this formula is only valid if there is no risk of confounding of the association between exposure and disease.[22,23] In the context of physical inactivity, most recent studies recommend using an alternative formula (formula (2)).[6,24] This formula considers the prevalence of the exposition in cases finally developing the disease together with the RR adjusted for confounding. In our study, we used formula (2) to calculate PAFs related to physical inactivity.

$$\text{PAF}(\%) = \frac{\text{prevalence}_{\text{exposition in cases}}\left(\text{RR}_{\text{adj}}-1\right)}{\text{RR}_{\text{adj}}} \times 100 \quad (2)$$

2.8 | Sensitivity analysis

We conducted two scenario analyses and a probabilistic sensitivity analysis. In scenario analysis 1, we used PAF formula (1) instead of formula (2) to analyze the influence of the formula on the national burden of disease attributable to physical activity. In scenario analysis 2, we assumed that the only difference between the language regions would be the prevalence of physical inactivity. Therefore, in scenario analysis 2, we neglected the fact that there are differences in disease prevalence, differences in per capita health care spending, and differences in salaries among the three language regions. The probabilistic sensitivity analysis was conducted to estimate 95% credible intervals (CI). We used the following distributions for this analysis: lognormal distribution for the RR, beta distribution for the prevalence of physical inactivity, uniform distribution for the medical costs and the productivity losses, and gamma distribution for the DALYs. 10 000 Monte Carlo simulations were run. The entire model including the sensitivity analyses was implemented in Excel 2010 (Microsoft, Redmond, Washington, USA).

3 | RESULTS

3.1 | National burden due to physical inactivity

On a national level, we estimated PAFs for physical inactivity at 4.1% (95%CI 1.7%-6.3%) for back pain, 4.3% (95%CI 1.2%-7.2%) for coronary heart disease, 5.0% (95%CI 2.6%-7.1%) for depression, 5.3% (95%CI 2.7%-7.8%) for diabetes type 2, 5.4% (95%CI 2.5%-8.3%) for stroke, 6.7% (95%CI

TABLE 1 Risk ratios (RR) for disease incidence used in the study

Disease	RR-value	95% CI lower bound	95% CI higher bound	References
Hypertension	1.36	1.28	1.45	Janssen[11]
Coronary heart disease	1.16	1.04	1.30	Sattelmair et al[40]
Stroke	1.18	1.08	1.28	Wendel-Vos et al[41]
Diabetes type 2	1.20	1.10	1.33	Jeon et al[42]
Breast cancer	1.33	1.26	1.42	Lee et al[24]
Colon cancer	1.32	1.23	1.39	Wolin et al[43]
Osteoporosis	1.57	1.38	1.77	Janssen[11]
Back pain	1.16	1.06	1.27	Shiri and Falah-Hassani[44]
Depression	1.20	1.11	1.32	Schuch et al[45]

5.2%-8.4%) for colon cancer, 6.9% (95%CI 5.3%-8.4%) for breast cancer, 7.7% (95%CI 6.2%-9.0%) for hypertension, and 10.5% (95%CI 7.9%-13.2%) for osteoporosis.

Based on the estimated PAFs for the above-mentioned diseases, medical costs caused by physical inactivity in Switzerland in 2013 were estimated at 0.802 (95%CI 0.684-0.934) billion Swiss francs or at 1.2% (95%CI 1.0%-1.3%) of total health care expenditures. This is equivalent to 116 (95%CI 99-135) Swiss francs per capita. Of these medical costs, 35.4% were attributed to cardiovascular diseases (coronary heart disease, stroke, and hypertension), 20.9% to back pain, 17.5% to depression, and the remaining 26.2% to osteoporosis, diabetes type 2, colon cancer, and breast cancer (Table 2). Productivity losses were valued at 0.808 (95%CI 0.653-0.983) billion Swiss francs or 117 (95%CI 94-142) Swiss francs per capita and were mainly caused by back pain (38.2%), depression (20.0%), and cardiovascular diseases (17.9%).

We estimated the DALYs lost due to physical inactivity at 40 433 DALYs (95%CI 34 935-46 487) or at 2.0% (95%CI 1.7%-2.2%) of total DALYs lost in Switzerland in 2013. Osteoporosis contributed 34.4% of the total DALYs, back pain 17.7%, cardiovascular diseases 21.9%, and depression 8.3%.

In the scenario analysis 1, in which we applied a different PAF formula (formula (1)), the medical costs due to physical inactivity in Switzerland in 2013 were estimated at 0.837 billion Swiss francs or at 1.2% of total health care expenditures. Productivity losses were estimated at 0.840 billion Swiss francs and the DALYs lost due to physical inactivity at 44 932 DALYs (Table 3). These results are 4.0% (productivity losses) to 4.4% (medical costs) higher compared to the base case analysis.

3.2 | Burden of physical inactivity in the three language regions

In the German-speaking region (68.6% of the Swiss population), the prevalence of physical inactivity is 23.6%; in the French-speaking region (24.8% of the population), the prevalence is 37.0%; and in the Italian-speaking region (6.7% of

TABLE 2 Medical costs, productivity losses, and DALYs due to physical inactivity in Switzerland in 2013 (95%CI)

Disease	Medical costs (million Swiss francs)	Productivity losses (million Swiss francs)	DALYs
Hypertension	48 (38-61)	4 (3-5)	318 (248-402)
Coronary heart disease	138 (72-209)	93 (48-143)	6108 (3255-8771)
Stroke	98 (61-143)	47 (29-68)	2416 (1525-3350)
Diabetes type 2	51 (33-72)	72 (46-102)	2652 (1733-3694)
Breast cancer	32 (24-40)	75 (57-96)	2283 (1874-2740)
Colon cancer	69 (53-89)	46 (35-60)	2237 (1877-2641)
Osteoporosis	58 (44-75)	-	13 913 (10 910-17 554)
Back pain	167 (100-248)	309 (179-459)	7142 (4207-10684)
Depression	141 (93-196)	162 (106-227)	3364 (2128-4973)
Sum	802 (684-934)	808 (653-983)	40 433 (34 935-46 487)

TABLE 3 Results of sensitivity analysis using scenario 1

Disease	Medical costs (million Swiss francs)	Productivity losses (million Swiss francs)	DALYs
Hypertension	57	5	373
Coronary heart disease	133	90	5916
Stroke	83	40	2049
Diabetes type 2	50	70	2605
Breast cancer	38	91	2745
Colon cancer	83	55	2677
Osteoporosis	73	-	17 659
Back pain	173	320	7402
Depression	146	169	3505
Sum	837	840	44 932

the population), the prevalence is 39.1%. Due to these differences in the prevalence of physical inactivity, language region-specific PAFs were highest in the Italian-speaking region, followed by the French-speaking region and the German-speaking region (Figure 2). In addition, most of the diseases for which physical inactivity is a recognized risk factor have a higher prevalence in the Italian- and French-speaking regions compared to the German-speaking region (Supporting Information Section , Table S1). Per capita health care spending was 3523 Swiss francs in the French-speaking region, 3258 Swiss francs in the Italian-speaking region, and 3174 Swiss francs in the German-speaking region. Finally, the median monthly gross salary was 6481 Swiss francs in the German-speaking region, 6419 Swiss francs in the French-speaking region, and 5437 Swiss francs in the Italian-speaking region.

We estimated per capita medical costs due to physical inactivity in the German-speaking region in 2013 at 87 Swiss francs, productivity losses at 96 Swiss francs, and DALYs per 1000 persons at 4.5. Medical costs in the French-speaking region were estimated at 179 Swiss francs per capita, productivity losses at 164 Swiss francs, and DALYs at 8.9 per 1000 persons. In the Italian-speaking region, per capita medical costs were valued at 172 Swiss francs, productivity losses at 153 Swiss francs, and DALYs at 8.6. Figure 3 shows the relative contribution of each language region to the national burden of physical inactivity in 2013.

In the scenario analysis 2, in which we assumed that the only difference between the language regions would be the prevalence of physical inactivity, the German-speaking region contributed to 57.9% of the national burden due to physical inactivity, while the French-speaking region contributed 32.8% and the Italian-speaking region 9.4%. Compared to the base case analysis, the per capita medical costs due to physical inactivity were overestimated by 7% in the German-speaking region and underestimated by 18% in the French-speaking region and by 10% in the Italian-speaking region.

4 | DISCUSSION

This study estimated the burden of physical inactivity at 1.610 (95%CI 1.413-1.827) billion Swiss francs plus 40433 (95%CI 34 935-46 487) DALYs in Switzerland in 2013. Low back pain and depression, two diseases not included in most previous studies investigating the burden of physical inactivity,

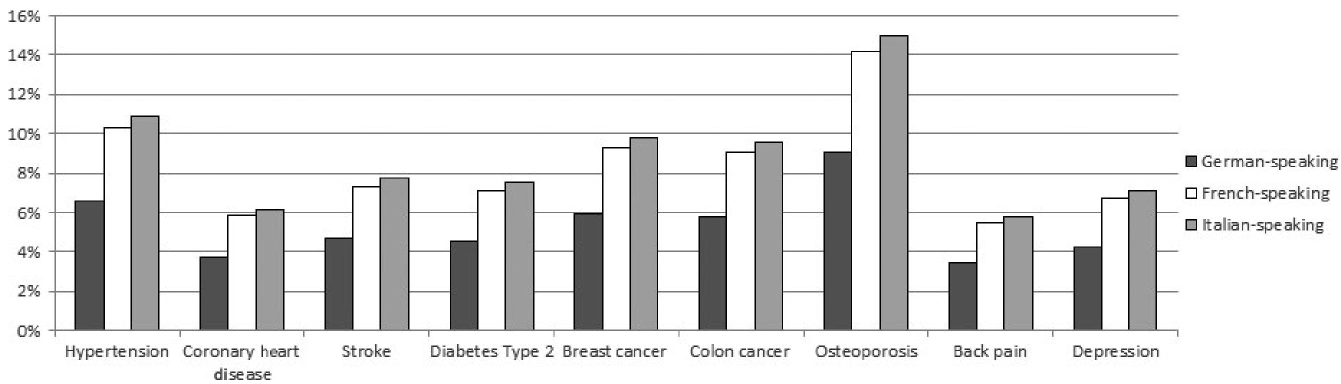

FIGURE 2 Estimated PAFs for physical inactivity for each language region in Switzerland

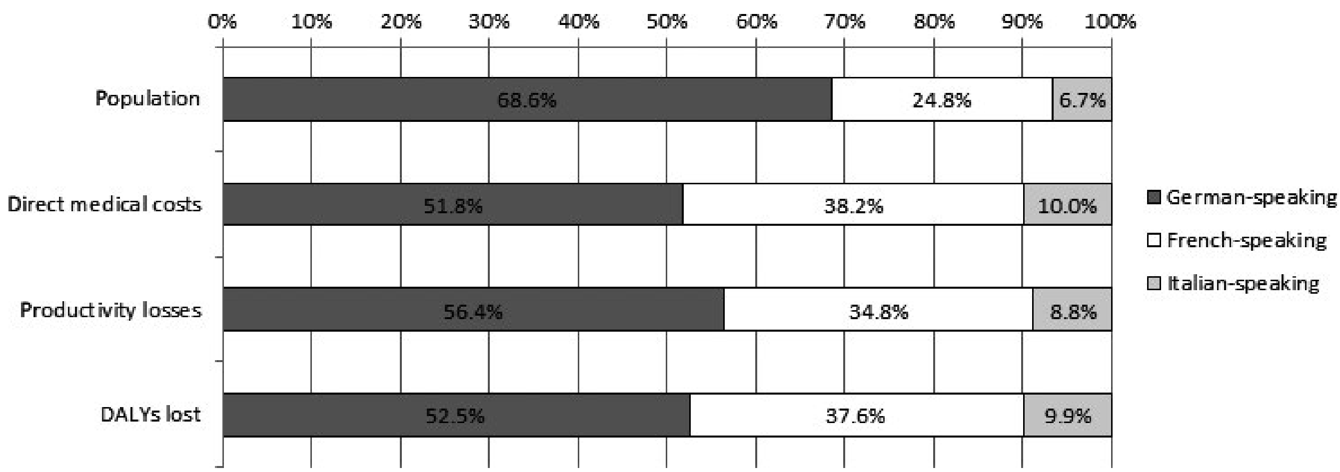

FIGURE 3 Contribution of each language region to the national burden of physical inactivity

added substantially to the results. Furthermore, the analysis of regional differences revealed that the per capita burden of physical inactivity is about twice as high in the French- and Italian-speaking regions compared to the German-speaking region.

Our results correspond to previous findings from international studies. 0.6% (95%CI 0.4%-0.7%) of health care costs could be attributed to physical inactivity in Switzerland in 2013 when only considering coronary heart disease, stroke, diabetes type 2, breast cancer, and colon cancer. Based on the same set of diseases, Ding et al[6] reported a proportion of 0.6% (95%CI 0.1%-2.2%) for Germany (prevalence of physical inactivity: 21.1%), of 0.4% (95%CI 0.1%-0.9%) for France (prevalence: 23.4%), and of 0.5% (95%CI 0.1%-1.8%) for Italy (prevalence: 33.2%). Our findings are thus in line with these results for the neighboring countries of Switzerland. Previous international studies estimated proportions between 1.0% and 3.8%.[11,25,26] Our results are somewhat lower due to the lower prevalence of physical inactivity in Switzerland and, as showed in the first scenario analysis, due to the more conservative PAF formula used in our study.[27]

Only a small number of previous studies included productivity losses in their analysis of the economic burden of physical inactivity and due to different methodological approaches, the results of these studies differ widely. Productivity losses four times smaller than the medical costs were reported in one study that used a friction cost approach.[6] Two other studies used a human capital approach.[11,28] They estimated productivity losses in the amount of the medical costs and twice the amount of the medical costs, respectively. We also used a human capital approach in our study and estimated productivity losses in the amount of the medical costs. A recent study estimated that physical inactivity is responsible for approximately 1.5% of global DALYs.[29] When considering similar diseases, we estimated the proportion at 0.8% (95%CI 0.6%-0.9%). Our lower proportion of 0.8% is mainly due to a relatively low prevalence of physical inactivity in Switzerland.

The findings of our study are also comparable to the results reported by Martin et al[7] who estimated total costs due to physical inactivity in Switzerland in 2000 at 2.384 billion Swiss francs, 48% higher than our estimation for 2013 (medical costs: 1.579 billion Swiss francs, 96.8% higher than our estimation; productivity losses: 0.805 billion Swiss francs, 0.4% lower than our estimation). In comparison with this study, we considered similar diseases, but used up to date medical costs, productivity losses, and RR estimates. As shown in the first scenario analysis, we also used a more conservative PAF formula. When comparing these two studies, it should also be considered that self-reported physical activity behavior changed in Switzerland in recent years. In 2002, 37% of the Swiss population reported to be physically inactive, whereas this proportion decreased to 28% in 2012.[2]

To the best of our knowledge, this is the first study that investigated the economic burden of physical inactivity in the three language regions of Switzerland. Although a small country, Switzerland is an interesting case for analyzing the influence of regional cultural differences. Cultural differences often refer to differences in habits and beliefs. There is evidence for different health habits and believes between Swiss language regions. Bringolf et al[3] showed that the environment for physical activity is more favorable, and the socioeconomic status is higher in the German-speaking region compared to the French-speaking region. In their study, however, language region was a strong correlate of physical activity independent of individual, social, and environmental factors. Interestingly, differences between language regions were found also for other health behaviors than physical activity. Faeh et al[30] showed that smoking and daily alcohol consumption were less frequent in the German-speaking region compared to the French-speaking region. Furthermore, cause-specific mortality substantially differed between language regions although all-cause mortality did not differ. Another study investigated Swiss adolescents and showed that self-reported low physical fitness is more frequent in the French-speaking region than in the German- and Italian-speaking regions.[31] In contrast, unfavorable self-rated health was less frequent in the French-speaking region than in the German- and Italian-speaking regions.

We found that the French- and Italian-speaking regions, which are home to 30% of the Swiss population, contribute more than 45% to the burden of physical inactivity. Reasons include a higher prevalence of physical inactivity, higher per capita health care spending, and higher disease prevalence than the German-speaking region. However, higher disease prevalence in the French- and Italian-speaking regions might be due to regional differences in screening and management.[32] Underdiagnosis of diseases in the German-speaking region could thus have led to an overestimation of regional differences. The second scenario analysis, in which we assumed that the only difference between the language regions would be the prevalence of physical inactivity, changed the results by 10%. Therefore, as many relevant aspects as possible should be considered when comparing different regions. Our PAFs for the German- and Italian-speaking regions also correspond very well with the PAFs for Germany and Italy from a recent study.[6] Due to differences in the prevalence of physical inactivity (French-speaking region of Switzerland 37.0%, France 23.4%), our PAFs for the French-speaking region are approximately 2% (absolute) higher compared to the PAFs for France from the same study. These observations support the plausibility of our estimates of regional differences. They also indicate that the propensity score matching using Swiss data led to estimates of the prevalence of physical inactivity in cases eventually developing the disease similar to those reported in a recent study investigating the burden of physical inactivity on a global level.[6]

Strengths of our study are the variety of diseases and outcomes (DALYs, medical costs, and productivity losses) considered. Furthermore, the data source for the medical costs addressed a frequent criticism of cost of illness studies, namely that the sum of the cost estimates for single diseases may exceed the aggregate total cost of health care. As Wieser et al[9] decomposed total Swiss health care costs to diseases, double counting of medical costs is not an issue in our study. The GBD study does also adjust the YLD for comorbidities to address potential overestimation of total health loss. In addition, we were able to estimate country-specific correction factors to approximate the prevalence of physical inactivity in cases eventually developing the disease by applying propensity score matching to data from the Swiss Health Survey. This allowed us to use the recommended PAF formula for physical inactivity.[6,24,33]

The main limitation of our study is the uncertainty arising from the use of secondary data sources. For example, the RR we used for our calculations are not based on a standardized definition and measurement of physical activity and a standardized assessment of confounding. We also assumed equal RR across gender and age-groups. Although we used RR maximally adjusted for confounding and included relevant risky health behaviors such as smoking and alcohol use in the propensity score matching, we cannot preclude that residual joint effects of risky health behaviors may have influenced our results.[34] In addition, there may be other diseases for which physical inactivity will be established as a risk factor. For example, a recent study reported a PAF for physical inactivity and dementia in Europe of 3.7% (95%CI 1.5%-6.9%).[33] However, we were not able to include this disease in our analysis due to limited data availability for Switzerland. Obesity is not included as a specific primary disease; however, it is reflected in the secondary cardiovascular and metabolic diseases. A further limitation is that response in the Swiss Health Survey was non-random. For instance, responders were of higher average socioeconomic status and reported better subjective health than non-responders.[35] This may have affected our estimates of the burden of physical inactivity. Furthermore, we may have underestimated the prevalence of physical inactivity as the Swiss Health Survey investigates self-reported activity levels. A recent study from Switzerland reported that time spent physically active was 4.2 times higher according to self-reported questionnaires than measured with accelerometers.[36] Several other studies also showed substantial differences between self-reported physical activity and objective measurements.[37] The available RR estimates are also based on self-reported activity levels. Assuming a decreasing risk of disease for increasing physical activity, we would expect higher RR based on accelerometer measurements than based on self-reporting.[38] Our effect estimates are consistent in the sense that both prevalence and RR were based on self-reported physical activity levels, but we would still expect higher PAFs and consequently a higher estimated burden if physical activity was measured objectively with accelerometers. It is also noteworthy that we only investigated the impact of physical activity on primary prevention. There are several diseases in which physical activity is an effective modifier of the course of clinical disease, and one could argue that there is an additional burden related to inactive patients. Furthermore, we did not include home-based and leisure-based production losses in our analysis. Finally, we did not consider costs of myocardial infarctions occurring during physical activity and costs of sport injuries. However, there is evidence that sport injuries especially happen to people that are not regularly active.[39]

5 | PERSPECTIVES

This study shows that low back pain and depression substantially add to the burden of physical inactivity. Consequently, future studies should consider these two diseases when estimating the burden of physical inactivity. Policy makers aiming at assessing the regional burden of physical inactivity should consider not only the regional prevalence of physical inactivity but also regional disease prevalence and health care spending.

In regard to Switzerland, this study shows that physical inactivity causes a substantial disease burden in Swiss adults and that the French- and Italian-speaking regions are overproportionally affected. Investments in interventions aiming to increase physical activity should therefore be considered. Research is needed to identify effective interventions to promote physical activity in the different language regions. Furthermore, we recommend the consideration of regional differences when assessing the cost-effectiveness of such interventions, as regional differences may have consequences for the optimal resource allocation in physical activity promotion policies. This latter aspect may not only be relevant for Switzerland but also for other multicultural countries and other health promotion settings.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supporting information

Section 1: Estimation of productivity losses for hypertension

For hypertension, we used the Cause of Death Statistic[1] provided by the Swiss Federal Statistical Office to estimate the costs due to death before the statutory retirement age. Future losses due to premature mortality were discounted to present value at a 2% discount rate. This interest rate corresponded to the interest rate of long-term bonds from the Swiss government in the last 20 years.[2] Information regarding age group- and gender-specific labor market participation and average weekly workload stem from the Swiss Labor Force Survey[3] and were used in order to account for early retirement and reduction of employment. Furthermore, we used age group- and gender-specific median wages from the Swiss Earnings Structure Survey.[4] A proportion of 10% was added to these wages to account for employers' contributions to the mandatory Swiss pension scheme. Wages were extrapolated to the year 2013 according to the nominal wage increase.

Section 2: Estimation of burden per language region

The prevalent disease cases (Table S1) were estimated from the data of the 2012 Swiss Health Survey[5] to calculate the burden per case (Table S2). We used survey weights provided by the Swiss Federal Statistical Office to estimate results representative for the Swiss population older than 15 years. In this survey, respondents were asked whether they currently were or had ever been in medical treatment for a number of specific diseases. If respondents had not been in medical treatment in the past 12 months, they were asked if they still suffered from the disease. In addition, respondents reported drug use related to a number of specific diseases in the past seven days. We did not consider drug use to estimate the prevalence of osteoporosis, since the relevant medications are often used for prevention. Furthermore, we were not able to distinguish diabetes type 2 from type 1 in the Swiss Health Survey, i.e. the prevalence of diabetes represents the prevalence of diabetes type 1 and type 2. The Swiss Health Survey also investigated cancer without differentiating between specific types of cancer. In consequence, this information on total cancer prevalence was only used to model differences between the language regions. To estimate the prevalence of breast cancer and colon cancer, data from the National Institute for Cancer Epidemiology and Registration (NICER)[6,7] were used.

TABLE S1 Prevalence of the diseases for which physical inactivity is a recognized risk factor per Swiss language region in 2013

	German-speaking		**French-speaking**		**Italian-speaking**	
	N	**%**	**N**	**%**	**N**	**%**
Population size	4753973	100%	1716268	100%	463763	100%
Hypertension	923085	19%	312011	18%	101743	22%
Coronary Heart Disease	305232	6%	150325	9%	45497	10%
Stroke	49244	1%	26603	2%	4094	1%
Diabetes Type 2	208368	4%	85054	5%	25136	5%
Breast cancer	15575	0.3%	6725	0.4%	1493	0.3%
Colon cancer	8766	0.2%	3785	0.2%	840	0.2%
Osteoporosis	138611	3%	74038	4%	15493	3%
Back pain	330372	7%	115810	7%	34862	8%
Depression	354695	7%	133353	8%	42694	9%

TABLE S2 Direct medical costs, productivity losses and DALYs per case per year in Switzerland in 2013

Disease	Direct medical costs (Swiss francs)	Productivity losses (Swiss francs)	DALYs
Hypertension	463	43	0.003
Coronary Heart Disease	5916	4133	0.267
Stroke	21174	10371	0.530
Diabetes Type 2	2907	4172	0.153
Breast Cancer	18503	45212	1.354
Colon Cancer	73613	50498	2.412
Osteoporosis	2241	-	0.549
Back Pain	8368	15756	0.360
Depression	5132	6053	0.124

Section 3: Prevalence of physical inactivity

Respondents from the Swiss Health Survey suffering from a disease for which physical inactivity is a recognized risk factor were matched with respondents not suffering from this disease by propensity score matching.[8] A propensity score was calculated for each participant using a logit regression model. The propensity score was defined as the participant's conditional probability of being exposed to a specific disease given the observed covariates. Covariates included were: behavior (smoking, alcohol use, eating habits, lifestyle), personal characteristics (sex, bmi, education) and environmental factors (stress at work, language region, urban/rural). Two participants with a similar propensity score had an equal estimated probability of having the disease. The participants were matched using a kernel matching algorithm.[9] Common support was guaranteed by minima and maxima comparison.[10] The propensity score matching was implemented without distinguishing between language regions. The prevalence of physical inactivity in the matched participants without the specific disease was divided by the prevalence of physical inactivity in the total Swiss population to estimate disease specific correction factors (Table S3). Corresponding 95% confidence intervals (CI) were estimated based on the Clopper-Pearson method. The correction factors were then multiplied with the physical inactivity levels of each language region, thus estimating the prevalence of physical inactivity in the cases eventually developing the disease. Stata, version 14.2 (StataCorp, College Station, Texas, USA) was used for propensity score matching.

TABLE S3 Correction factors resulting from the propensity score matching and correction factors reported in previous studies

Disease	**Value**	**95% CI lower bound**	**95% CI higher bound**	***Range from literature***	***Source*** *(given range only includes European studies)*
Hypertension	1.05	1.00	1.11	*not available*	
Coronary Heart Disease	1.14	1.05	1.23	*1.13 - 1.34*	*Lee et al.*[11]
Stroke	1.32	1.08	1.56	*1.21 - 1.47*	*Ding et al.*[12]
Diabetes Type 2	1.15	1.04	1.27	*1.20 - 1.31*	*Lee et al.*[11]
Breast Cancer	1.01	0.87	1.16	*0.77 - 1.11*	*Lee et al.*[11]
Colon Cancer	1.01	0.87	1.16	*1.17 - 1.54*	*Lee et al.*[11]
Osteoporosis	1.05	0.92	1.20	*not available*	
Back Pain	1.07	0.97	1.17	*not available*	
Depression	1.09	1.00	1.18	*not available*	

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4. Publication 2: Physical activity interventions for primary prevention in adults: a systematic review of randomized controlled trial-based economic evaluations

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Abstract

Background: Physical inactivity is a worldwide pandemic associated with major chronic diseases. Given limited resources, policy makers are in need of physical activity interventions that provide best value for money.

Objective: To summarize evidence from RCT-based economic evaluations of primary prevention physical activity interventions in adult populations outside the workplace setting.

Design: Systematic review of health economic evaluations. Incremental cost-effectiveness ratios (ICERs) in US$ per MET-hour gained were estimated on the basis of mean differences in intervention costs and standardized effects between intervention and control groups.

Data sources: Identification of relevant studies via systematic searches in electronic databases (MEDLINE, Embase and NHSEED).

Eligibility criteria: Cost-effectiveness analyses in which all data (except unit costs) came from one RCT investigating physical activity interventions for primary prevention or health promotion in an adult population in high-income countries.

Results: In twelve eligible studies, 22 interventions were investigated. Interventions were based on advice, goal setting and follow-up support, exercise classes, financial incentives or teaching on behavioral change. The ICER varied widely among the interventions and four interventions showed an ICER below the applied benchmark of US$0.44 to US$0.63 per MET-hour gained. These four interventions were based on individualized advice via print or web.

Conclusion: We found evidence from RCTs indicating cost-effectiveness of some physical activity interventions for primary prevention in adults. However, the majority of interventions assessed would not be cost-effective according to the benchmark applied. Furthermore, our study showed that trial-based evidence on cost-effectiveness of physical activity interventions is scarce. Therefore, we recommend that future studies investigating the

efficacy or effectiveness of such interventions consider costs as an additional outcome and assess cost-effectiveness.

Key points

- We found evidence from RCTs indicating cost-effectiveness of some physical activity interventions for primary prevention in adults. However, cost-effectiveness results varied widely among interventions. Four interventions that delivered individualized advice via print or web showed best value (physical activity gains) for money (intervention costs).
- Our study shows that trial-based evidence on cost-effectiveness of physical activity interventions is relatively scarce.
- We recommend that future studies investigating the efficacy or effectiveness of interventions aimed at increasing physical activity consider costs as an additional outcome and assess cost-effectiveness.

1 Introduction

Physical inactivity is a worldwide pandemic that causes substantial health and economic burden [1-3]. Established health consequences of physical inactivity include cardiovascular diseases, diabetes and different types of cancer [3]. However, there is growing evidence that physical inactivity is also related to musculoskeletal and mental health problems [4-6], which has not been explored in the majority of studies. This may result in an underestimation of the true burden of physical inactivity. The substantial burden of physical inactivity calls for interventions aiming to increase physical activity.

With limited resources available, policy makers are interested in interventions that provide best value for money. Therefore, interventions aiming to reduce physical inactivity should not only prove effectiveness on health outcomes but also cost-effectiveness. Economic evaluation studies compare costs and outcomes of an intervention with a comparator. In the area of physical activity, the comparator is often doing nothing, non-physical activity related advice or standard physical activity advice [7].

There are two different approaches in economic evaluations: trial-based economic evaluations and model-based economic evaluations [8]. In a trial-based economic evaluation, costs are measured within a randomized controlled trial (RCT) investigating the effect of the intervention [9]. In a model-based economic evaluation, data on the effect and the costs from different sources are combined in a decision-analytic model [10]. Both methodological approaches have strengths and weaknesses [9-11]. The main strengths of a trial-based economic evaluation are related to the methodological strength of RCTs, i.e. the exclusion of potential biasing factors [12]. However, RCTs have weaknesses when directly used for policy making that are related to the efficacy versus effectiveness discussion [12]: Areas of potential concern include choice of comparator, protocol-driven costs and outcomes, artificial environment, intermediate versus final outcomes, inadequate participant follow-up, and selected patient and provider populations [12]. Model-based economic evaluations have the strength that they can synthesize the best evidence available in case relevant head-to-head clinical trials are missing, costs were not measured within trials, intermediate endpoints were captured or trial follow-up was short-term [8]. Nevertheless, inappropriate use of clinical data, bias in observational data, difficulties of extrapolation and concerns about transparency or validity of models are major concerns [8]. These strengths and weaknesses make it evident that for policy making reasons the two methods are better used complementarily than alternatively [13]. In any case, the review of available evidence, e.g. trial-based economic evaluations, remains a prerequisite for conducting model-based economic evaluations.

Several systematic reviews have investigated the cost-effectiveness of physical activity interventions but most of these reviews focused on specific settings (e.g. school, workplace, community) and did not pay much attention to the methodological approaches (trial-based or model-based) chosen in the identified economic evaluations [14]. The availability of trial-based economic evaluations of physical activity interventions seems to be limited [7, 15-17], and to the best of our knowledge, no systematic review has focused on this topic. Consequently, this study aims to systematically review trial-based economic evaluations of interventions to reduce physical inactivity in the general adult population.

2 Methods

We conducted our study according to current recommendations for systematic reviews of health economic evaluations [18-20].

2.1 Eligibility criteria

We defined the following inclusion criteria:

Population: General adult population (≥18 years) in high-income countries as defined according to the World Bank [21]. We focused on populations in which physical activity would be considered to be primary prevention or health promotion. Consequently, we excluded studies investigating physical activity as secondary or tertiary prevention in patients with diseases such as stroke, diabetes, obesity, COPD, multiple sclerosis or mental health issues. As we focused on interventions that can be implemented on a population-level, we excluded studies on specific populations such as worksite populations, students or soldiers.

Intervention: Any intervention aimed to increase physical activity.

Comparator: No intervention (doing nothing), non-physical activity related advice or any other intervention aimed to increase physical activity.

Outcomes: Effectiveness (e.g. change in physical activity minutes, change in walking time, change in steps per day, change in the number of physically active individuals) and intervention costs. We excluded studies that did not report specific physical activity outcomes, e.g. studies only reporting quality-adjusted life-years as part of pure cost-utility analyses.

Study design: Cost-effectiveness analyses in which all data (except unit costs) came from one RCT of any follow-up duration. Consequently, we excluded health economic modelling studies and cost-effectiveness analyses from trials with a design other than RCT.

We focused on recently published studies since the year 2000 written in English or German.

2.2 Search strategy

We searched for studies using the following electronic databases: MEDLINE (via Pubmed), Embase and NHSEED. The search strategy was defined using the PRESS checklist [22]. As detailed in Table 1, we created a search string for physical activity and one for economic evaluations. These strings were then combined to identify economic evaluations of physical activity interventions. The search strategy was validated with the cost-effectiveness studies identified by Foster et al. [16]. The final search was conducted on 31 July 2019.

Table 1 Detailed search strategy

Concept 1 physical activity	**Mesh/Emtree Search**
	• Mesh (for Pubmed): Exercise [Mesh] (not one level higher (Motor Activity [Mesh]) as otherwise getting many animal studies); Physical Fitness [Mesh] • Emtree for Embase: Physical activity; Physical inactivity; Fitness
	Expressions from titles/abstracts used to describe physical activity – Keyword Search
	• physical activity OR physically active OR physical inactivity OR physically inactive OR physical fitness OR active lifestyle OR inactive lifestyle OR sedentary lifestyle OR sedentary behavior OR sedentary behaviour • biking OR bike* OR bicycling • walk* (only in title, otherwise too broad) OR pedestrian* OR running (only in title, otherwise too broad) OR jogging OR stair climbing OR climbing stairs • active travel* OR active commut* OR built environment OR environment* design OR environment* planning OR city planning OR urban planning
Concept 2 economic evaluations	**Mesh/Emtree Search**
	• Mesh (for Pubmed): Cost-Benefit Analysis [Mesh] • Emtree for Embase: Cost effectiveness analysis; Cost benefit analysis; Cost utility analysis
	Expressions from titles/abstracts used to describe cost-effectiveness – Keyword Search
	• economic analy* OR economic evaluation OR economic assess* • cost-effective* OR cost-benefit* OR cost-utility OR benefit-cost OR cost-effica*

2.3 Study selection

Identified studies were exported into Endnote and duplicates were removed. Prior to the screening of the identified studies, training sessions took place to ensure high consistency between reviewers. Afterwards, two reviewers (RM, RF) screened all studies separately. Title/abstracts were screened first, followed by a full-text screening. Disagreements between reviewers after screening title/abstracts and the assessment of full-text were resolved by consensus. Unclear cases were discussed with a third reviewer (MS).

2.4 Data extraction

We extracted data on the study design including random sequence generation, allocation concealment and blinding. Furthermore, we collected information regarding the definition of the study population, details about the intervention and control groups, outcome definition and measurement, and results. A data extraction form was created in Microsoft Excel, pilot tested independently by two reviewers and subsequently adapted to ensure all relevant data being captured. Data were then extracted by one reviewer and confirmed by a second reviewer. Disagreements were again resolved by consensus. In case required information was not reported in the publication, data were extracted from additional publications relating to the same study, e.g. study protocols.

2.5 Risk of bias and quality assessment

Risk of bias was assessed using the criteria from the Cochrane risk of bias tool and the consensus on health economics criteria (CHEC) list [23, 24]. Two reviewers evaluated the selected studies independently and any disagreement was again resolved by consensus. As in previous systematic reviews of interventions promoting physical activity, we did not rate studies on whether participants were blinded to their allocation to intervention or control groups [7], because it would be impossible to blind participants to a physical activity intervention. For the assessment of the performance bias, we therefore considered blinding of the personnel and if this may have affected the outcome. If publications from the same study were referenced, we also checked these additional references for information supporting the risk of bias assessment.

2.6 Data synthesis

The studies included in the review reported different physical activity outcomes. In order to compare the results between studies, effect measures were standardized. The standardized effect measure was the metabolic equivalent of task (MET) measured in MET-hours gained per person per day. One MET is defined as the resting energy expenditure, which is equivalent to an oxygen consumption of 3.5 ml/kg/min. The MET of an activity is a multiplicator of the resting energy expenditure and represents the intensity of an activity. To calculate the volume of physical activity we multiplied frequency by duration of physical activity as MET-hours. The formula by Wu et al. [17] was used to translate physical activity outcomes to MET-hours gained per person per day. For these calculations, 3.0 METs were assigned to moderate physical activity, 4.5 METs to moderate-to-vigorous physical activity and 6.0 METs to vigorous physical activity [17]. We choose these relatively low values to be consistent with other studies in the field [17, 25] and because of the well-documented large overestimation of physical activity intensity by self-report [26-28]. Whenever possible, the results of a twelve-month follow-up interval were taken to make the studies comparable.

Physical activity interventions cause different types of costs, e.g. intervention costs, costs to participants, healthcare costs or production losses [29]. We therefore extracted the costs separately for each type. Cost types included in all studies (i.e. intervention costs) were used to compare costs between studies. The costs were converted to US dollars (US$) using purchasing power parity conversion factors for the reference year [30]. Costs were then extrapolated to the year 2018 using the total consumer price index for the US [31].

We further calculated the mean differences in costs and outcomes between intervention and control as a basis for estimating the incremental cost-effectiveness ratio (ICER) in US$ per MET-hour gained. The outcome in MET-hours per person per day was multiplied with the number of days of follow-up to make the outcome comparable to the costs and, therefore, allow us to compare interventions with different follow-up times. Wu et al. [17] used a benchmark of US$0.50 to US$1.00 per MET-hour gained to assess cost-effectiveness of physical activity interventions. This benchmark is based on the per capita health care costs of physical inactivity in the US and the recommendation for health-enhancing physical activity by the WHO [32]. This means at least 2.5 hours per week of physical activity with moderate intensity or 1.25 hours per week of physical activity with vigorous intensity [32]. We used the same approach as Wu et al. [17] but applied current health care costs and productivity losses of physical inactivity in Switzerland [33]. Based on the lower and upper bound of the 95% uncertainty interval reported, we estimated a benchmark between US$0.44 and US$0.63 per MET-hour gained [33]. Swiss health care costs were extrapolated from 2013 to 2018 according to the increase in per capita health care spending and productivity losses were extrapolated using the wage index [34, 35].

3 Results

3.1 Study identification

Our searches retrieved 5060 potentially relevant studies (Fig. 1). After removing 1288 duplicates, 3772 title/abstracts were screened. Many studies had to be excluded as they investigated populations not matching our inclusion criteria or the study design was not an RCT. After screening of title and abstract, 36 full-text publications were assessed for eligibility. Of these 36 publications, 24 were excluded because the population was not fulfilling our inclusion criteria (10 publications), the physical activity (5 publications) or cost outcome (6 publications) was not reported in sufficient detail, the study was a model-based evaluation of an initial trial that was included in our analysis (1 publication), the study investigated a follow-up intervention after an initial physical activity intervention (1 publication), the journal publication reported a study that was included in our analysis based on the earlier published and more detailed Health Technology Assessment report (1 publication). Twelve studies were included in the final evaluation.

3.2 Description of included studies

Details of the twelve included studies are provided in Table 2. Three trial-based cost-effectiveness analyses were conducted in New Zealand [36-38], three in the UK [39-41], three in the USA [42-44], two in the Netherlands [45, 46], and one in Australia [47]. Eight studies recruited the participants through GPs [36-41, 46, 47], three studies used different channels for advertisements [42-44] and one study recruited participants with invitation letters [45]. The mean age of participants in the twelve studies ranged from 45 years to 74 years. Female participants were more frequent in all of the studies except for the Dutch study conducted by van Keulen et al. [46], in which 45% of the participants were female. Four studies were clustered RCTs [37, 39, 40, 45]. In three studies, the trial arms had less than 100 participants [42, 44, 47]. All the other studies had more than 100 participants per arm.

Table 2 Overview on included studies

Reference	Country	Population[a]	Intervention[b]	Control[c]	Follow-up[d]	Effect measures	Cost measures
Harris et al. [39]	UK	Adults aged 45-74 years recruited by their GP by invitation letter, physically inactive, able to walk outside the home and no contraindications to increase moderate to vigorous physical activity Mean age (years): not reported; range: 45-74 Males (%): (1) 37; (2) 37; (C) 34	(1) pedometer, individual targets for step counts over a period of 12 weeks and dairy for daily step counts all provided by post (n=339) (2) pedometer, individual targets for step counts over a period of 12 weeks and dairy for daily step counts all provided by a nurse plus three individually tailored physical activity consultations by a nurse at week 1, 5 and 9 (n=346)	Doing nothing: Participants were advised to continue their usual physical activity and were not offered the 12-week intervention	12 months	Weekly minutes of moderate to vigorous physical activity (in ≥ 10-minute bouts) as measured with 7-day accelerometry with a belt at the hip	NHS perspective 2 types of costs: intervention costs (set-up costs and delivery costs), healthcare costs
Ewald et al. [47]	Australia	Adults aged >18 years recruited by their GP, average daily step count lower than 7000 steps per week, many participants with inactivity-related health problems Mean age (years): 57 Males (%): 30	Physical activity behavior change counseling delivered in two ways: (1) five face-to-face visits with an exercise physiologist (n=68) (2) one face-to-face visit with an exercise physiologist, followed by four sessions delivered by phone (n=64)	Standardized print brochure encouraging physical activity (n=71)	12 months	Step count for one week with pedometer	Payer perspective Intervention costs
Golsteijn et al. [45]	Netherlands	Adults aged >50 years recruited based on matched neighborhoods from municipal health council regions Mean age (years): (1) 63; (2) 64; (3) 62; (4) 61; (C) 64 Males (%): (1) 46; (2) 45; (3) 52; (4) 51; (C) 50	Computer-tailored physical activity advice at three time-points (2 weeks, 2 months and 4 months after baseline) delivered as either print (mail) or web (website and email) and in either a basic form (standard advice) or with additional environmental components (e.g., walking and cycling routes and PA possibilities and initiatives in participants' own neighborhood and home exercises): (1) print-delivered basic (n=439) (2) print-delivered environmental (n=435) (3) web-based basic (n=423) (4) web-based environmental (n=432)	Doing nothing: Participants in the control group were invited to complete 4 questionnaires about physical activity during the upcoming year and they were told that they would receive physical activity advice after one year as a reward for their cooperation (n=411)	12 months	MET-hours per week based on the Dutch SQUASH [48]	Societal perspective Intervention costs (fixed and variable), healthcare costs, participant and family costs (buying sports equipment, paying membership fees,…), productivity losses

Iliffe et al. [40]	UK	Adults aged ≥65 years recruited by their GP with stable medical conditions, living independently, walking independently both indoors and outdoors (with or without a walking aid and without help from another person) Mean age (years): 73 Males (%): 38	2 intervention arms: (1) class-based exercise: FaME program, weekly classes plus home exercises for 24 weeks and encouraged walking (n=387) (2) home-based exercise: OEP, home exercises supported by peer mentors for 24 weeks and encouraged walking (n=411)	Doing nothing: Participants in the control group were not offered either the OEP or FaME program, but were free to participate in any other exercise just as they would if they were not participating in the trial (n=458)	12 months after the end of the intervention period	Proportion reaching the recommended physical activity target of 150 minutes of moderate to vigorous physical activity per week based on the CHAMPS questionnaire [49]	NHS and participant perspective Setup and management of the intervention; hire of facilities; equipment; human resources; travel and phone expenses related to delivering the intervention; participants' out-of-pocket expenses related to exercising (incl. FaME)
Leung et al. [38]	New Zealand (Auckland)	Adults aged ≥65 years recruited by their GP from communities in Auckland, who did not achieve the recommended 150 minutes of at least moderate physical activity per week; 97% of participants were of New Zealand European ethnicity Mean age (years): 74 Males (%): 46	Face-to-face advice, step-related goal setting, followed by phone counseling: initial face-to-face advice on engaging in physical activity from GP including goal setting, followed up by 3 phone counseling sessions by trained physical activity counselors over 3 to 4 months. Goal setting based on steps and participants were encouraged to use their pedometer to monitor steps. Goals were handed to participants on a green prescription card (n=165)	Face-to-face advice, time-related goal setting, followed by phone counseling: Participants in the control group received the same intervention as participants in the intervention group with the exception that counseling focused on accumulating physical activity around time-related goals rather than step-related goals (n=165)	12 months	Minutes of weekly leisure walking assessed with the Auckland Heart Study Physical Activity Questionnaire [50]	Public health care system and participant perspective Three categories: (i) Community care costs, which included GPs, nurses, physiotherapists, other allied health professionals, home help, and the cost of the pedometer. (ii) Exercise and community care costs, which included the prior category plus all personal sport and exercise equipment and physical activity costs. (iii) All costs, which included the prior category plus all hospital-related costs such as specialist consultations, outpatient procedures and inpatient stays. (Costs of coordinating the GRx program and of phone counseling were excluded as these costs were common to both patient groups)

Elley et al. [36]	New Zealand	Women aged 40-74 years recruited by their GP and not achieving 30 minutes of at least moderate-intensity exercise such as brisk walking on 5 days or more per week Mean age (years): 59 Males (%): 0	Face-to-face advice, goal setting and follow-up by a face-to-face meeting and phone counseling: 10 minutes of brief advice and a written exercise prescription given by a primary healthcare nurse, face-to-face follow-up at 6 months and phone support for 9 months from an exercise facilitator. The recommended goal was at least 30 min of moderate-intensity physical activity five times per week (n=544)	Doing nothing: Participants in the control group received usual care from GP (n=545)	24 months	Minutes of moderate or vigorous physical activity per week assessed with the NZ Physical Activity Questionnaire [51]	Societal perspective Direct and indirect costs including program delivery costs, participant exercise costs, primary and secondary care costs, allied healthcare costs and productivity costs
Van Keulen et al. [46]	Netherlands	Adults aged 45-70 years recruited by their GP who failed to meet at least two out of three Dutch public health guidelines (physical activity, fruit and vegetable consumption), 50% diagnosed as hypertensive Mean age (years): 57 Males (%): 55	3 intervention arms: (1) TPC: four printed, tailored letters (1. letter: 4 pages about physical activity, 2. and 4. letter: 5 pages about fruits and vegetables, 3. letter: 3 pages about physical activity) (n=405) (2) TMI: four phone calls, the order of the conversation topics in the first and third interviews could be chosen by participants (if PA was preferred in the first interview, fruit and vegetables consumption was discussed in the second and vice versa) (n=407) (3) Combined: two tailored print letters and two phone motivational interviews, the first letter and interview focused on physical activity, the second letter and interview on fruit and vegetables consumption (n=408)	Doing nothing: Participants in the control group received one tailored letter after the last follow-up questionnaire (n=409)	73 weeks (approx. 17 months)	Proportion reaching the recommended physical activity target of 150 minutes of moderate to vigorous physical activity per week measured with the modified CHAMPS physical activity questionnaire [52] (added to this was the summary question of the SQUASH [48])	Payer and participant perspective Fixed and variable costs involved in implementing the intervention (e.g. printing and mailing letters for TPC, call charges for TMI) and the costs of the time invested by participants

Finkelstein et al. [42]	USA	Adults aged ≥50 years recruited through advertisements in two free local newspapers and a free online website of classified ads, self-reported as healthy and sedentary (currently exercising for less than 2h per week and if exercising, engaging in walking as their primary form of exercise) Mean age (years): (I) 59; (C) 61 Males (%): (I) 24; (C) 27	Financial incentive: The intervention group was offered \$50 for base participation in the study as well as a variable incentive payment depending on participants' aerobic minutes during each of the 4 weeks of the study: - \$0 if averaging less than 15 aerobic minutes per day each week - \$10 if averaging at least 15 and less than 25 aerobic minutes per day each week - \$15 if averaging at least 25 and less than 40 aerobic minutes per day each week - \$20 if averaging 40 or more aerobic minutes per day each week (n=21)	Fixed financial incentive: The control group received a fixed payment of \$75 for attending a 90-minute kickoff meeting, wearing a pedometer daily and returning all study materials (n=30)	4 weeks	Daily aerobic minutes measured with pedometers over 4 weeks	Payer perspective Only costs due to incentives were included in the study
Sevick et al. [44]	USA	Adults aged 18-65 years recruited from the community using advertisements in the newspaper and in a local hospital; participants were considered as healthy but sedentary (< 90 minutes per week of at least moderate or vigorous physical activity) based on a phone call from a research assistant Mean age (years): 45 Males (%): 18	2 intervention arms. Participants in both arms mailed in physical activity logs and brief surveys each month, which were used to generate individualized feedback with the goal to increase physical activity. Feedback was communicated to participants either via mail or phone: (1) a phone-based, individualized motivationally-tailored feedback intervention (n=80) (2) a print-based, individualized motivationally-tailored feedback (n=81)	Doing nothing: The participants in the control group received mailings unrelated to physical activity on the same schedule as phone and print participants, as well as a packet of health information at the beginning of the study (n=78)	12 months	Minutes of physical activity per week as assessed in a 7-day physical activity recall interview [53]	Payer perspective Intervention costs including those costs that would be borne by and outcomes that would be relevant to a health plan or insurer offering the intervention as part of their covered services
Isaacs et al. [41]	UK	Adults aged 40-74 years recruited from their GP, not currently physically active, with at least one cardiovascular risk factor but without pre-existing overt cardiovascular disease, uncontrolled hypertension, uncontrolled insulin-dependent diabetes, psychiatric conditions or physical disabilities that would prevent participation in an exercise class Mean age (years): 57 Males (%): 33	10-week physical activity program with advice on how to continue and financial incentive: (1) a 10-week program of supervised exercise classes, two to three times a week in a local leisure center (n=317) (2) a 10-week instructor-led walking program, two to three times a week (n=311) Both with provision for continuing exercise at the end of the program. This included advice on how to continue being active and a financial incentive (a book of 20 half-price tickets for the leisure center). No charge was made to attend any of the exercise sessions during the 10-week period	Individualized advice: The advice-only control group received tailored advice and information on physical activity including information on local exercise facilities. After 6 months the control group were re-randomized to one of the other trial arms (n=315)	12 months	Minutes of moderate and/or vigorous activity per week as measured with a 7-day recall questionnaire [54]	NHS and participant perspective 3 types of costs: intervention costs (facilities, exercise trainers, administrative support), participants costs (time, travel, pay for childcare, equipment), healthcare costs

Elley et al. [37]	New Zealand	Adults aged 40-79 years recruited by their GP, "less active" meaning those who were not achieving the recommended 2.5 hours of at least moderate activity per week Mean age (years): (I) 57; (C) 59 Males (%): (I) 33; (C) 34	Face-to-face advice, goal setting and follow-up by phone counseling: The intervention was verbal advice to increase physical activity with exercise goals written on a green prescription card by the GP. The prescription was then faxed to exercise specialists in Sports Foundations who provided phone support on three occasions over the following three months to each intervention patient and sent written material including newsletters (n=451)	Doing nothing: The control group received usual care that may have included some verbal advice about physical activity (n=427)	12 months	Minutes of leisure exercise per week as measured with a self-administered questionnaire which prompts recall of physical activity over three months [50]	Societal perspective Intervention costs; health funder costs; patient costs; productivity costs
Sevick et al. [43]	USA	Adults aged 35-60 years recruited through mass media (print, radio, TV), word of mouth and recontacting volunteers from previous studies. Participants were sedentary but healthy (meaning no history of myocardial infarction, stroke, insulin-dependent diabetes mellitus, osteoporosis, or osteoarthritis) Mean age (years): (I) 46; (C) 46 Males (%): (I) 50; (C) 49	Lifestyle intervention: Teaching of behavior modification and cognitive-behavior modification techniques for behavior change in small group meetings. During the 18-month tapered phase, all participants received a quarterly newsletter and a monthly calendar of activities. (n=121)	Exercise prescription: Participants in the control group received typical exercise prescription as described by the American College of Sports Medicine, involving an exercise intensity of 50%–85% of maximal aerobic power and exercise of 20 to 60 minutes duration at each session. During the 18-month tapered phase, all participants received a quarterly newsletter and a monthly calendar of activities. (n=114)	24 months	Energy expenditure per day from physical activity using the 7-day Physical Activity Recall questionnaire [53]	Payer perspective Intervention staff time, computerized tracking system, curriculum materials, printing and postage, facilities, health club memberships.

Legend: Studies ordered by year of publication, CHAMPS = Community Healthy Activities Model Program For Seniors scale, FaME = Falls Management Exercise, OEP = Otago Exercise Program, SQUASH = Short Questionnaire to Assess Health Enhancing Physical Activity, TMI = Telephone Motivational Interviewing, TPC = Tailored Printed Communication

[a] description of the population investigated including how the participants were recruited followed by mean age of the population and sex distribution, (I) refers to intervention group, (C) refers to control group, in case of more than one trial arm (1) refers to trial arm one, (2) refers to trial arm two and so on

[b] description of the intervention including the number of participants (n), in case of more than one trial arm (1) refers to trial arm one, (2) refers to trial arm two and so on

[c] description of the control group including the number of participants (n)

[d] last follow-up time point

Twenty-two interventions were analyzed in the twelve studies. The interventions investigated in eight studies were advice and goal setting conducted in different ways such as face-to-face, by telephone, using printed material or web contact/communication with different kinds of follow-up support [36-39, 44-47]. Exercise classes were researched in two studies [40, 41]. One study investigated financial incentives [42] and one study examined teaching on behavioral change [43]. In seven studies, the control group did not receive any information regarding physical activity during the study period, unless it was part of usual care [36, 37, 39, 40, 44-46]. The other five studies compared the intervention group to a control group that also received an intervention that aimed at increasing physical activity [38, 41-43, 47]. As an example, in one study the control group received mailings unrelated to physical activity compared to the intervention arm with participants, who received telephone-based or print-based individually tailored feedback [44]. In another example, the control group received fixed financial incentives, and the intervention group received incentives based on the amount of physical activity [42].

The duration of follow-up was one month in one study [42], twelve months in eight studies [37-41, 44, 45, 47], 17 months in one study [46] and 24 months in two studies [36, 43]. The effect on physical activity was measured with self-reported questionnaires in eight studies [36-38, 40, 41, 43, 45, 46]. Two studies used pedometers in addition to activity logs and questionnaires to measure the outcome [42, 47] and one study used face-to-face interviews [44]. One study measured physical activity objectively by accelerometry [39].

Costs were assessed using different perspectives. Three studies conducted the analysis from a societal perspective and included intervention costs, costs to participants, healthcare costs and production losses [36, 37, 45]. Two studies included intervention costs, costs to participants and healthcare costs [38, 41]. Three studies assessed intervention costs and costs to participants [40, 43, 46] and one study included intervention costs and healthcare costs [39]. Three studies only included intervention costs [42, 44, 47]. In general, intervention costs were assessed using study records. Costs to participants and production losses were mainly quantified based on questionnaires. Healthcare costs were assessed using either questionnaires or healthcare practice records. A separate and detailed reporting of resource consumption and unit cost was not done in most of the studies, except for the ones originating from New Zealand [36-38] and a recent study from UK [39]. Costing year was not specifically reported in four studies [41, 43, 46, 47]. Only two studies separately reported fixed and variable costs [45, 46].

3.3 Risk of bias and quality assessment

Risk of bias was assessed for each study with the Cochrane risk of bias tool [24] and results are summarized in Table 3. Six out of twelve studies provided enough information to judge that random sequence generation and allocation concealment were adequate. Adequate blinding of personnel and blinding of outcome assessment was reported in four studies. Incomplete outcome data were addressed in eight studies. Risk of reporting bias was judged to be low in eleven studies. The quality assessment using the CHEC list [23] showed that most studies did not investigate costs from an appropriate perspective (societal), many studies did not report the costing year and several studies did not conduct an appropriate sensitivity analysis (see electronic supplementary Table S1).

Table 3 Risk of bias summary table

Reference	Additional references	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
Harris et al. [39]		+	+	-	+	+	+
Ewald et al. [47]	[55, 56]	+	+	+	+	?	+
Golsteijn et al. [45]	[57]	?	?	?	?	+	+
Iliffe et al. [40]		+	+	-	-	+	+
Leung et al. [38]	[58]	-	-	+	+	+	+
Elley et al. [36]	[59]	+	+	+	+	+	+
Van Keulen et al. [46]	[60]	+	?	?	?	+	+
Finkelstein et al. [42]		+	+	-	?	+	+
Sevick et al. [44]	[61]	?	?	?	?	?	?
Isaacs et al. [41]		+	+	-	-	+	+
Elley et al. [37]	[62]	+	?	?	?	?	+
Sevick et al. [43]	[63-65]	?	?	+	+	-	+

Coding of judgment: “+” low risk of bias; “?” unclear risk of bias; “-“ high risk of bias

3.4 Results of trial-based economic evaluations

Effects of the interventions varied widely. The highest effect on physical activity was seen in an intervention using financial incentives (Table 4). The effect was a gain of 1.17 MET-hours per day. However, it should be considered that this study had a follow-up duration of 4 weeks, which is much smaller than all the other studies, which had a follow-up of at least 1 year. Another intervention that was based on printed individualized motivationally tailored feedback showed a gain of 1.01 MET-hours per day, which can be considered equivalent to 20 minutes of moderate physical activity per day [44]. Five interventions gained between 0.5 and 1 MET-hour per day. These interventions included behavior change counseling or teaching, a combination of advice, goal setting and follow-up counseling, individualized feedback by telephone and instructor-led walking [36, 41, 43, 44, 47]. One intervention that used computer-tailored physical activity advice communicated via website and email had a negative effect (-0.06 MET-hours per day) [45]. All the other interventions had an effect between 0.1 and 0.5 MET-hours per day.

Costs of interventions varied widely. The most expensive interventions were based on individualized motivationally tailored feedback communicated via telephone (US$1260 per person) or print (US$638 per person) [44]. However, these costs included recruitment and facility costs that were not included in any of the other studies. Four other interventions had costs higher than US$300 per person: One intervention combining advice, goal setting and follow-up counseling, two interventions based on exercise classes, and one behavior change teaching intervention [38, 40, 41, 43]. Seven interventions had costs lower than US$100 per person: three interventions with computer tailored physical activity advice communicated via print, two similar interventions communicated via web, one individualized step-related goal setting intervention plus one intervention combining advice, goal setting and follow-up counseling [36, 39, 45, 46]. All the other interventions had costs between US$100 per person and US$250 per person.

The ICER varied widely among the interventions (Fig. 2). Four interventions showed an ICER below our benchmark between US$0.44 and US$0.63 per MET-hour gained, which is based on the health care costs and productivity losses of physical inactivity in Switzerland. These four interventions were based on individualized advice delivered in four different ways [45]: print (postal mail) or web (website and email) and in a basic form (standard advice) or with additional environmental components (e.g., walking and cycling routes and physical activity possibilities and initiatives in participants' own neighborhood and home exercises). One other intervention that was based on behavior change counseling by telephone had an ICER of US$0.64 per MET-hour gained [47]. One pedometer-based individualized step-related goal setting intervention had an ICER of US$0.67 per MET-hour gained [39]. Another intervention was based on face-to-face advice, goal setting, follow-up face-to-face meeting and follow-up telephone counseling [36]. This intervention had an ICER of US$0.85 per MET-hour gained. All other interventions had an ICER above US$1.00 per MET-hour gained.

Table 4 Detailed MET-hours gained, intervention costs and ICER of included studies

Reference	Follow-up (months)	Study arms	MET-hours gained per person per day	MET-hours gained per person	Intervention costs per person (US$ 2018)	Δ effect (MET-hours gained)	Δ costs (US$ 2018)	ICER (US$ 2018 per MET-hour gained)	Comments
Harris et al. [39]	12	(C) doing nothing	0.05	19.6	0.0				
		(I1) pedometer, individualized step-related goal setting print	0.40	144.7	83.5	125.1	83.5	0.67	
		(I2) pedometer, individualized step-related goal setting face-to-face plus counseling	0.35	129.1	238.4	109.5	238.4	2.18	
Ewald et al. [47]	12	(C) standardized brochure encouraging physical activity	0.14	49.8	0.0				Costs of control group (brochure) not plausible
		(I1) behavior change counseling face-to-face	0.34	123.6	194.2	73.8	194.2	2.63*	
		(I2) behavior change counseling telephone	0.84	307.1	163.6	257.4	163.6	0.64*	
Golsteijn et al. [45]	12	(C) doing nothing	-0.31	-114.7	0.0				
		(I1) individualized advice print basic	0.43	156.4	34.4	271.1	34.4	0.13	
		(I2) individualized advice print environmental	0.39	140.8	41.7	255.5	41.7	0.16	
		(I3) individualized advice web basic	0.10	36.5	20.7	151.2	20.7	0.14	
		(I4) individualized advice web environmental	-0.06	-20.9	25.1	93.9	25.1	0.27	
Iliffe et al. [40]	12	(C) doing nothing	0.02	7.6	0.0				
		(I1) class-based exercise	0.36	132.0	381.6	124.4	381.6	3.07	
		(I2) home-based exercise	0.08	28.7	146.1	21.1	146.1	6.92	
Leung et al. [38]	12	(C) face-to-face advice, goal setting and follow-up telephone counseling	0.17	61.1	318.4				
		(I) face-to-face advice, step-related goal setting, followed by telephone counseling	0.30	109.9	397.4	48.9	79.0	1.62*	
Elley et al. [36]	12	(C) doing nothing	0.38	137.6	0.0				
		(I) face-to-face advice, goal setting and follow-up face-to-face meeting and telephone counseling	0.61	224.2	73.3	86.6	73.3	0.85	
Van Keulen et al. [46]	17	(C) doing nothing	0.25	125.9	0.0				
		(I1) individualized advice print	0.29	147.8	81.4	21.9	81.4	3.71	
		(I2) individualized advice telephone	0.26	131.4	152.7	5.5	152.7	27.89	
		(I3) individualized advice print and telephone	0.31	158.8	114.2	32.9	114.2	3.48	
Finkelstein et al. [42]	1	(C) fixed financial incentive	0.65	18.2	90.8				
		(I) variable financial incentives	1.17	32.7	145.3	14.5	54.5	3.77*	
Sevick et al. [44]	12	(C) doing nothing	0.45	163.3	191.4				Costs include general office activities, recruitment cost and facilities costs
		(I1) individualized feedback on physical activity telephone	0.58	211.8	1260.3	48.5	1068.8	22.03	
		(I2) individualized feedback on physical activity print	1.01	369.7	638.1	206.4	446.7	2.16	
Isaacs et al. [41]	12	(C) individualized advice only	0.17	61.2	0.0				Costs of control group (advice only) not plausible
		(I1) exercise classes, advice and financial incentive	0.18	64.9	375.7	3.7	375.7	101.48*	
		(I2) instructor-led walking program, advice and financial incentive	0.50	181.1	186.2	119.9	186.2	1.55*	
Elley et al. [37]	12	(C) doing nothing	0.12	43.8	0.0				
		(I) face-to-face advice, goal setting and follow-up telephone counseling	0.39	142.4	164.1	98.6	164.1	1.66	

Sevick et al. [43]	24	(C) exercise prescription	0.69	503.7	1002.3			
		(I) behavior change teaching face-to-face	0.84	613.2	348.6	109.5	-653.7	-5.97*

Legend: * ICER based on a comparator other than “doing nothing”; C = comparator; I = intervention; Δ = intervention – control group; ICER = incremental cost-effectiveness ratio; MET-hours gained per person = MET-hours gained per person per day multiplied with the number of days of follow-up to make the effect comparable to the costs and, therefore, allow to compare interventions with different follow-up times.

4 Discussion

To the best of our knowledge, this study is the first to systematically review RCT-based economic evaluations of physical activity interventions for primary prevention or health promotion in adults. Four interventions that delivered individualized advice via print or web showed best value (physical activity gains) for money (intervention costs) with ICERs below the benchmark between US$0.44 and US$0.63 per MET-hour gained [45]. However, cost-effectiveness results varied widely among interventions and only a small number of interventions would be cost-effective according to the benchmark applied. Furthermore, this study shows that trial-based evidence on cost-effectiveness of physical activity interventions is relatively scarce, confirming a finding from the first Economics of Physical Inactivity Consensus (EPIC) conference [15].

Our focus on the rigorous RCT study design may be one reason why we found only a small number of cost-effective interventions [17]. Wu et al. [17] also showed higher effects in studies using subjective physical activity measures compared to objective measures. Therefore, it seems noteworthy that one study using accelerometry showed an ICER just above the benchmark although rather conservative results would be expected with such an objective measure [39]. Another study using pedometers also showed an ICER very close to the benchmark [47]. This intervention that was based on behavior change counseling by telephone, had a reasonable incremental effect of 0.71 MET-hours gained per person per day and showed an ICER of US$0.64 per MET-hour gained [47]. However, the ICER for this intervention was based on a comparator intervention other than “doing nothing”. It seems likely that the ICER would lie below the benchmark if compared to “doing nothing”. One other intervention was dominant, i.e. better and cheaper than the comparator [43]. However, the comparator was an active one (specifically, exercise prescription) and, therefore, the ICER cannot be directly compared to ICERs from studies with a “doing nothing” comparator.

Intervention effects and costs from the studies included in our analysis are comparable to previous findings from studies that investigated evidence from trials (controlled trial, pre–post trial, or postmeasure-comparison approach) or model-based economic evaluations [17, 25, 66]. The highest effect on physical activity (gain of 1.17 MET-hours per day compared to baseline) was observed in an intervention using variable financial incentives [42]. However, this study had a very short follow-up of 4 weeks and the intervention effect may not lead to substantial health benefits in a longer-term perspective. The second highest effect (gain of 1.01 MET-hours per day) was shown for a print-based individualized motivationally tailored feedback intervention [44]. These interventions with the highest effect required more resources and therefore showed high costs. Although such more intensive interventions may not be cost-effective at the population level, they may be cost-effective in more targeted populations [17]. In Switzerland for example, we see a higher prevalence of physical inactivity in the French- and Italian-speaking language regions compared to the German-speaking region [33]. In addition, populations with lower socioeconomic status show higher prevalence of physical inactivity. Targeting populations with similar cultural and socioeconomic characteristics may increase cost-effectiveness of physical activity interventions.

The intervention by Goldsteijn et al. [45] that provided individualized advice delivered via web and included additional environmental components is a good example for showing a problematic aspect of cost-effectiveness analyses in the field. The intervention itself had a negative effect of -0.06 MET-hours gained per person per day when comparing physical activity at the one year follow-up versus baseline. However, compared to the "doing nothing" control group the incremental effect was 0.26 MET-hours gained per person per day, which is equivalent to approximately five minutes of moderate physical activity per person per day. Although this is a positive effect, it can be considered a relatively low incremental physical activity gain that is not sufficient to lead to substantial health benefits [67]. The annual intervention costs were US$25.14 per person. This leads to an ICER of US$0.27 per MET-hour gained, which is below the benchmark. Therefore, the intervention is considered cost-effective although the physical activity gain can be considered as not sufficient to lead to substantial health benefits. This issue was already raised by Wu et al. [17], who showed that some interventions that increased physical activity levels only by small amounts, such as stair climbing prompts, may be very cost-effective due to the very low intervention costs. Consequently, relying on cost-effectiveness alone might favor interventions that are unable to add substantial health benefits. The specifics of each intervention should therefore be considered and additional criteria such as minimal clinically relevant effectiveness thresholds might be used in future health policy decision-making.

Cost-effectiveness may vary among settings and a previous study showed the limited comparability, generalizability and transferability of results from economic evaluations of physical activity interventions due to a high variability in costing methods [68]. Trial-based and model-based economic evaluations are complementary methods to assess cost-effectiveness [13]. Our research shows the limited evidence available from trial-based economic evaluations. Consequently, transferability of trial-based economic evaluations and the use of data from trial-based economic evaluations as input for model-based economic evaluations gain in importance. As explained above, in model-based economic evaluations, data on the effect and the costs from different sources are combined in a decision-analytic model.

We therefore agree with the EPIC statement that asks for high-quality RCTs with appropriate power and follow-up [15]. The statement also discusses other methodological challenges for economic evaluations of physical activity interventions such as the objective measurement of the intervention effect. Focusing more on the health economic aspects, we would stress the need to use available guidelines when conducting and reporting economic evaluations of physical activity interventions [23, 69]. Furthermore, we see an urgent need in reporting resource consumption and unit costs separately. This would not only increase transparency but also transferability of the results to other settings. In addition, the separate reporting of fixed and variable costs would facilitate the consideration of the cost-effectiveness when scaling-up physical activity interventions [70]. When reporting costs and effects, future studies should not only report means but also descriptors of statistical uncertainty. Another requirement for future studies is the use of “doing nothing” control groups, as this would increase the comparability of ICERs among studies.

Several limitations need to be considered. The studies included in our analysis investigated different populations, comparators, settings, and follow-up durations and used different outcome measures. Therefore, interventions were too diverse to warrant mathematical comparison and it was decided to not provide summary estimates using meta-analysis techniques. In order to improve comparability, effect measures were standardized to MET-hours gained per person per day. Although this method was used in previous studies, it may have some limitations when applied to broad outcomes such as step gains or proportions of populations meeting physical activity guidelines [17, 25]. In addition, many studies did not report sufficient statistical detail and, therefore, we were not able to properly address uncertainty. In order to assess the level of cost-effectiveness, we introduced a benchmark similar to that used in previous studies [17, 25]. Our benchmark was based on the health care costs and productivity losses of physical inactivity in Switzerland. Settings with different levels of prevalence of physical inactivity, health care spending or wages might choose different benchmarks for assessing cost-effectiveness of interventions to increase physical activity. The ICERs estimated in our study are based on the intervention costs and do not include potentially saved health care costs. Furthermore, we focused on interventions that can be implemented on a population-level and therefore excluded studies investigating the workplace setting. Some interventions focusing on the workplace setting have been previously shown to be cost-effective [71]. By limiting the study design to RCTs, we also excluded interventions targeting the built environment [17, 25, 72, 73]. As we excluded studies that did not report specific physical activity outcomes, we did not include studies only reporting quality-adjusted life-years as part of pure cost-utility analyses [74-76]. These studies showed varying results in terms of cost per quality-adjusted life-years gained by physical activity interventions.

5 Conclusion

We found evidence from RCTs indicating cost-effectiveness of some physical activity interventions. However, the majority of interventions assessed would not be cost-effective according to the benchmark applied. Some interventions increased physical activity levels only by small amounts, but were still cost-effective due to the very low intervention costs. Some interventions with relatively large intervention effects required more resources and, therefore, showed higher costs. Although such more intensive interventions may not be cost-effective at the population level, they may be cost-effective in more targeted populations (e.g. for Switzerland: populations with similar cultural background or with similar socioeconomic status).

Due to the relatively scarce trial-based evidence on the cost-effectiveness of physical activity interventions, we recommend that future studies investigating the efficacy or effectiveness of interventions aimed at reducing physical inactivity consider costs as an additional outcome of the study in order to assess cost-effectiveness. Such studies may not only investigate physical activity but overall lifestyle and consider well-being as an additional, separate outcome.

Author Contributions: RM and MS conceived the design of the study. RM and RF screened the studies. RM and MES extracted the data. RM, MES, SW, AST, MS were involved in the data analysis. RM drafted the manuscript. All authors were involved in the interpretation of the data and commented on and edited the final manuscript.

Compliance with Ethical Standards

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Data Availability: Any additional information (e.g. review protocol) is available upon request from the corresponding author.

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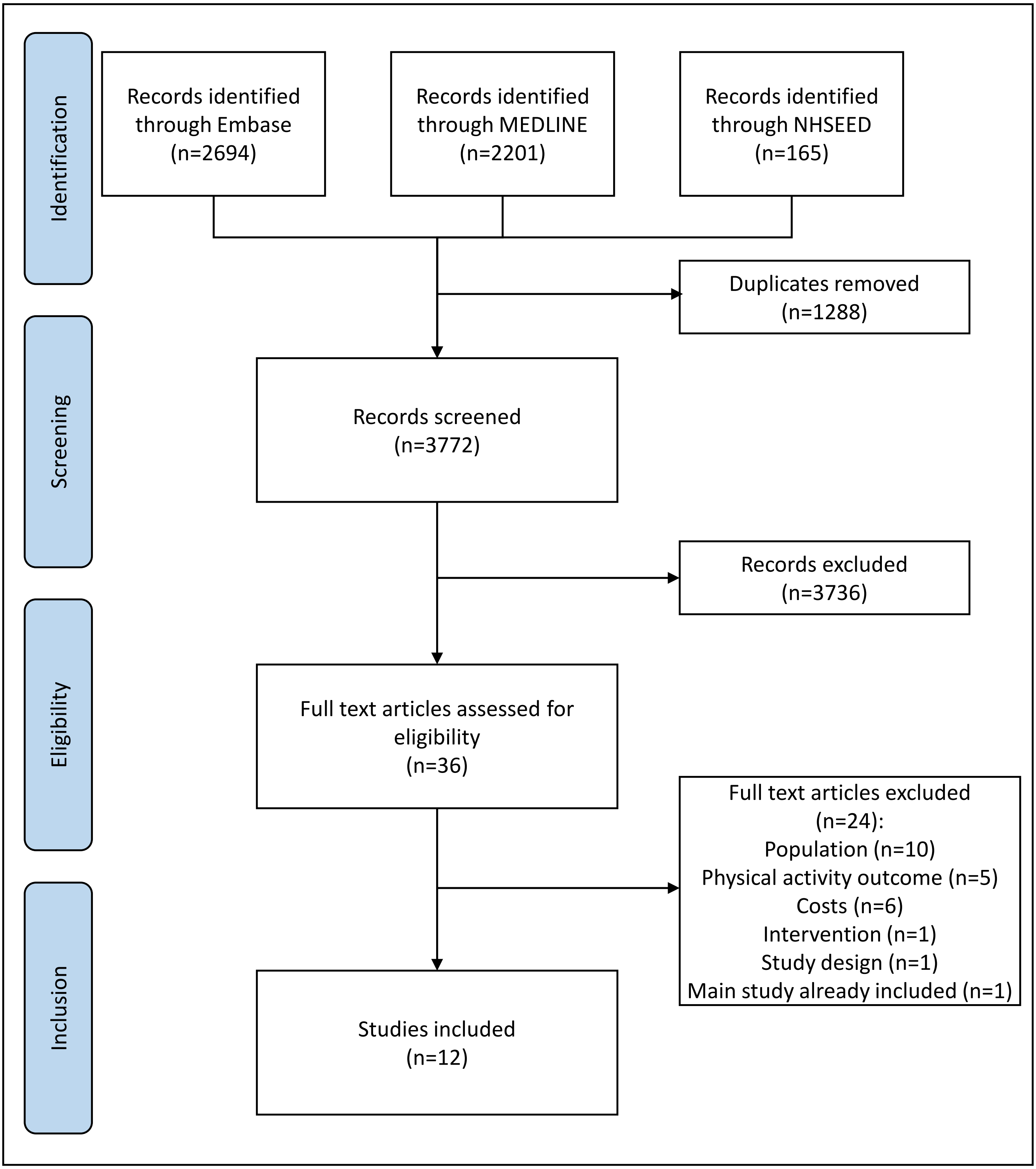
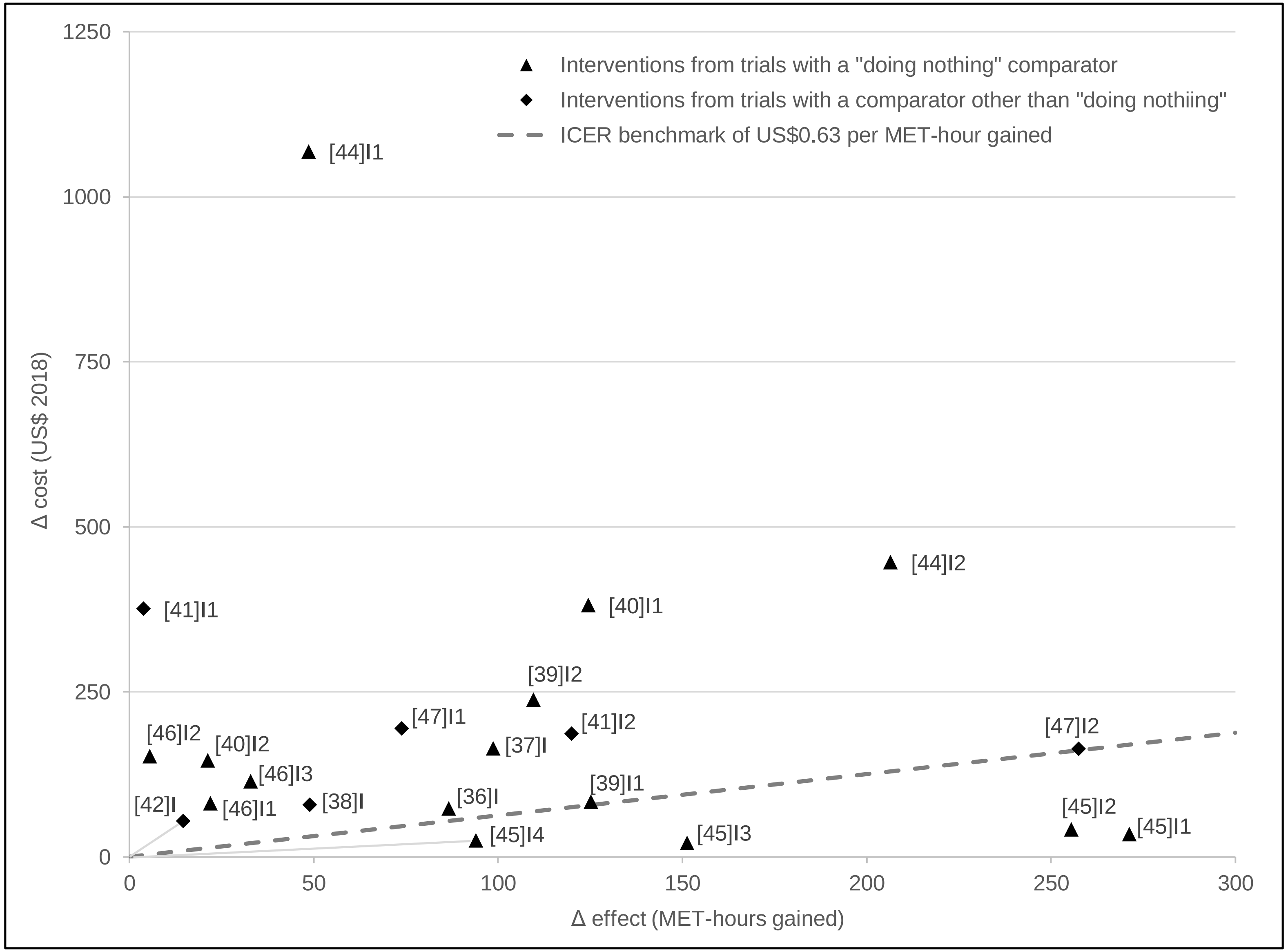
Figure Captions and Legends

Fig. 1 PRISMA flow diagram of the systematic review

Fig. 2 Incremental intervention costs and MET-hours gained (ICERs) in trial-based economic evaluations of physical activity interventions

Legend: Δ refers to intervention minus comparator. The results from the study by Sevick et al. [43] were removed from the figure, as the cost difference was negative (US$ -654); this was based on a comparator intervention other than “doing nothing” (specifically, exercise prescription).


Identification
Screening
Eligibility
Inclusion
Records identified through Embase (n=2694)
Records identified through MEDLINE (n=2201)
Records identified through NHSEED (n=165)
Duplicates removed (n=1288)
Records screened (n=3772)
Records excluded (n=3736)
Full text articles assessed for eligibility (n=36)
Full text articles excluded (n=24):
Population (n=10)
Physical activity outcome (n=5)
Costs (n=6)
Intervention (n=1)
Study design (n=1)
Main study already included (n=1)
Studies included (n=12)



1250
1000
750
500
250
0
Δ cost (US$ 2018)
0
50
100
150
200
250
300
Δ effect (MET-hours gained)
Interventions from trials with a "doing nothing" comparator
Interventions from trials with a comparator other than "doing nothiing"
ICER benchmark of US$0.63 per MET-hour gained
[44]I1
[44]I2
[41]I1
[40]I1
[39]I2
[47]I1
[41]I2
[47]I2
[46]I2
[40]I2
[37]I
[46]I3
[39]I1
[42]I
[38]I
[36]I
[45]I2
[46]I1
[45]I4
[45]I3
[45]I1

Electronic supplementary Table S1: CHEC list summary table

CHEC list item	Harris et al. [39]	Ewald et al. [47]	Golsteijn et al. [45]	Iliffe et al. [40]	Leung et al. [38]	Elley et al. [36]	Van Keulen et al. [46]	Finkelstein et al. [42]	Sevick et al. [44]	Isaacs et al. [41]	Elley et al. [37]	Sevick et al. [43]
Is the study population clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are competing alternatives clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Suboptimal	Yes	Yes	Yes	Yes
Are the structural assumptions and the validation methods of the model properly reported?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Is the actual perspective chosen appropriate?	No	No	Yes	No	No	Yes	No	No	No	No	Yes	No
Are all important and relevant costs for each alternative identified?	Yes	Yes	Yes	Yes	Suboptimal	Yes	Yes	Suboptimal	Yes	Yes	Yes	Yes
Are all costs measured appropriately in physical units?	Yes	Suboptimal	Yes	Yes	Yes	Yes	Suboptimal	Yes	Yes	Yes	Yes	Yes
Are costs valued appropriately?	Yes	Suboptimal	Yes	Yes	Yes	Yes	Suboptimal	Suboptimal	Yes	Suboptimal	Yes	Suboptimal
Are all important and relevant outcomes for each alternative identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are all outcomes measured appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are outcomes valued appropriately?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	Yes	Suboptimal	Yes	Suboptimal	Yes	Yes	Yes	Suboptimal	Yes	Yes	Yes	Yes
Are all future costs and outcomes discounted appropriately?	NA	NA	NA	NA	NA	No	NA	NA	NA	NA	NA	Yes
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Suboptimal	Yes	Suboptimal	Suboptimal	Yes	Yes	No	Suboptimal	Yes	Yes	Yes
Do the conclusions follow from the data reported?	Yes	Suboptimal	Yes	Yes	Yes	Yes	Yes	Suboptimal	Yes	Yes	Yes	Yes
Does the study discuss the generalizability of the results to other settings and patient/client groups?	Yes	Yes	Suboptimal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes	Suboptimal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are ethical and distributional issues discussed appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

5. Publication 3: Cost-effectiveness analysis of physical activity interventions in a multicultural setting: a modelling study

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Abstract

Background Physical inactivity causes a substantial health and economic burden globally. This study evaluated the cost-effectiveness of physical activity interventions for primary prevention with a health economic model presented for Switzerland as a conceivable example for other countries.

Methods We built a proportional multistate life table model with a lifetime perspective for the adult population. Interventions evaluated included: individualized advice, pedometer, general practitioner (GP) referral and exercise prescription. Intervention effects were derived from randomized controlled trials and intervention costs based on a bottom-up approach. The effect of interventions on a comprehensive set of diseases was modelled with data from recent meta-analyses. Cost-effectiveness was evaluated in terms of cost per disability-adjusted life-year averted compared to “doing nothing” as well as incremental cost-effectiveness between interventions at national and language region level.

Findings All four interventions were cost-saving and more effective compared to “doing nothing”, from a societal perspective. At national level and in the German-speaking region, individualized advice was the preferable intervention followed by GP referral. These two interventions dominated pedometer and exercise prescription. In the French- and Italian speaking regions, GP referral was the preferable and dominating intervention. However, results were subject to substantial uncertainty in the underlying key model input parameters.

Interpretation We recommend that individualized advice and GP referral be further evaluated as interventions and that decision-making considers the specifics of the Swiss language regions. Furthermore, we judge the SPACE model to not only be relevant for Switzerland but also for other multicultural countries.

Funding Health Promotion Switzerland.

Research in context

Evidence before this study: Physical inactivity causes substantial health and economic burden. This burden calls for interventions promoting physical activity. Such interventions should provide best value for money. Therefore, cost-effectiveness of physical activity interventions has been investigated in several health economic models designed for specific countries.

Added value of this study: Our model assessed the cost-effectiveness of physical activity interventions at the Swiss national level and in the three language, thus cultural, regions from a societal perspective. A comprehensive set of diseases was included in the model.

Implications of all the available evidence:

Swiss policy makers have cost-effective options of physical activity promotion and should consider the specifics of language regions in order to allocate resources efficiently. Our model has the potential to be applied beyond Switzerland, primarily to high-income countries, as a tool to guide societal efforts in primary prevention of physical inactivity-related diseases.

Keywords

Physical activity, intervention, cost-effectiveness, economic evaluation, model

Introduction

Physical inactivity causes a substantial health and economic burden globally.[1,2] Detrimental health consequences related to physical inactivity have been confirmed for cardiovascular diseases, diabetes, different types of cancer as well as musculoskeletal and mental health problems.[3,4] The World Health Organization (WHO) recommends weekly physical activity of at least 150 minutes with moderate intensity or 75 minutes with vigorous intensity to achieve a health enhancing effect.

In Switzerland, about one quarter of the population does not fulfill the WHO recommendations. However, the proportion of physically inactive people substantially differs between the three Swiss language regions: in the German-speaking region 21·0% of the adult population are physically inactive, whereas 32·6% are physically inactive in the French-speaking region and 31·5% in the Italian-speaking region.[5] In fact, language region has been shown to be a strong correlate of physical activity independent of socio-demographic or environmental factors.[6] Furthermore, the relationship between language and culture has been extensively studied and current concepts suggest an interactional relationship between the two.[7] Therefore, Switzerland may serve as interesting example for other multicultural high-income countries.

The burden of physical inactivity in Switzerland has been shown to be substantial and the French- and Italian-speaking regions were over-proportionally affected.[8] This considerable Swiss behavioral burden calls for interventions promoting physical activity. Policy makers should consider interventions that provide best value for money.[9] Physical activity interventions, therefore, should not only be effective in improving health outcomes but also cost-effective.

Several systematic reviews have investigated the cost-effectiveness of physical activity interventions.[10] However, transferability of cost-effectiveness results between geographies and cultures can be challenging and subject to limitations.[11] Health economic modelling can support decision-making, particularly in the absence of setting-specific data.[12] Health economic models have been built for different countries to evaluate the cost-effectiveness of physical activity interventions.[13-17] In the absence of a Swiss-specific model, this study developed a health economic model to assess the cost-effectiveness of physical activity interventions in Switzerland and its three language regions from a health care payer and societal perspective, with a potential for application to other multicultural settings.

Methods

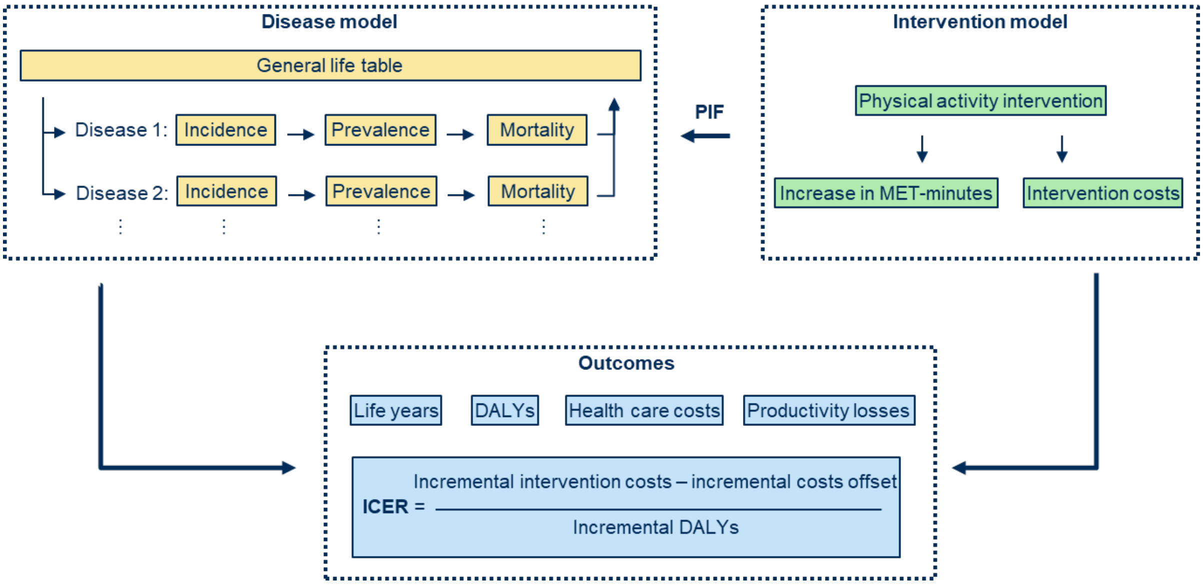
Model overview

We built the Swiss Physical Activity Cost-Effectiveness (SPACE) model as a proportional multistate life table model to evaluate the cost-effectiveness of physical activity interventions in Switzerland. SPACE adapted and further developed the ACE-Prevention approach from Australia.[15] In the SPACE model, the population was tracked in a general life table and multiple diseases were modelled in parallel in separate life tables (Figure 1, *disease model*).[15,18] The *intervention model,* as the second component of the SPACE model, estimated the impact of physical activity interventions on the modelled population in terms of metabolic equivalent (MET)-minutes gained. One MET is defined as the resting energy expenditure, which is equivalent to an oxygen consumption of 3·5 ml/kg/min. An increase in MET-minutes was fed back to the *disease model*, where it led to a decrease in disease incidence. Outcomes of the SPACE model were total physical activity intervention costs, costs offset due to averted health care spending and averted productivity losses, and health gains in terms of disability-adjusted life-years (DALYs). On this basis, incremental cost-effectiveness ratios (ICERs) between interventions and "doing nothing" were calculated as costs per DALY averted.[19]

At the national and language region level, we modelled the adult female and male population aged between 40 and 75 years in 2018. One-year age-sex cohorts were followed until death or a maximum age of 100 years. We purposeful chose a healthy population as a first step to provide a model in primary prevention.

Model input parameters and data sources are explained in the appendix pp. 3-13.

Figure 1 Schematic of the SPACE model



Source: Adapted from the ACE-Obesity Policy model.[20]

Disease model

Eight diseases were included in the analysis: breast cancer (in females only), colorectal cancer, type 2 diabetes mellitus, coronary heart disease, ischemic stroke, osteoporosis, low back pain and depression. The first five diseases can be considered a "core set" as they are frequently used in health economic studies investigating physical activity.[15,16] Osteoporosis, low back pain and depression have been taken into account less frequently.[8,21] However, recent studies have shown that physical activity reduces the incidence of all these diseases.[3,4,21] In the disease life tables, four different health states were modelled for each disease using the DisMod framework: healthy, diseased, dead from disease and dead from other cause.[15]

Intervention model

The intervention model considered the prevalence of different categories of physical activity and changes in energy expenditure within each category, expressed as MET-minutes per week, due to physical activity interventions. Four physical activity categories were modelled: inactive, partially active, sufficiently active, and exercising.

The intervention model influenced the disease model via the PIF. We applied the "RR shift" method of the PIF,[22] implying that physical activity interventions lower the relative risks (RRs) of disease within each physical activity category due to increased energy expenditure, but do not change the prevalence of each physical activity category. The lower category-level RRs due to interventions led to lower PIFs. PIFs were multiplied by the incidence rates in the disease model and lower PIFs, therefore, led to lower disease incidence. Consequently, physical activity interventions reduced the number of people with diseases.

We evaluated four interventions in SPACE that were the most cost-effective interventions based on a recent systematic review of randomized controlled trial-based economic evaluations of physical activity interventions for primary prevention in adults.[23] They reflect a range of concepts to promote physical activity and we judged their implementation to be feasible in Switzerland (Table 1):

- **Pedometer with individualized goal setting.** Pedometers are given to participants, who receive individual targets for step counts over a period of 12 weeks plus a diary for daily step counts, all by mail.[24]
- **General practitioner (GP) referral to telephone-based counselling.** GPs refer participants to an exercise physiologist for physical activity counselling. The counselling consists of one face-to-face session followed by four sessions delivered by phone over a period of 13 weeks.[25]
- **Individualized physical activity advice.** Participants receive computer-tailored physical activity advice that is based on "personal characteristics, motivational readiness for behavior change, and needs"[26] as assessed in a questionnaire. Text and illustrations are delivered to participants by mail at three time-points (2 weeks, 2 months and 4 months).

- **Exercise prescription.** Ten minutes of brief physical activity advice plus goal-setting (increasing physical activity to ≥30 minutes moderate-intensity physical activity five times per week) and a written exercise prescription given to participants by a primary healthcare nurse at the beginning of the intervention. The exercise prescription involves the provision of telephone-based physical activity counselling by an exercise facilitator over a period of 9 months (5 calls of 15 minutes each). In addition, a 30-minute face-to-face consultation with a nurse was scheduled at 6 months.[27]

Regarding intervention reach, we assumed that GP referral and exercise prescription would reach 10% of the population in the inactive and partially active categories. For pedometer and individualized advice, we assumed that 3% of the population in all physical activity categories would be reached. We applied intervention effects on physical activity from the second year onwards for three years (appendix p. 5). Applying intervention effects from the second year onwards accounted for the fact that intervention effects were based on 12-month follow-up data. In the first year with effect (second year in the model), we assumed a full intervention effect. Thereafter, we applied a relative annual decay rate of 50% of intervention effect on physical activity.[15,16]

Table 1 Overview of interventions evaluated in SPACE

Interventions	Intervention detail	Intervention effect in MET-min gained per week	Intervention cost in CHF 2018	
			Set-up (fixed) cost	Delivery of intervention (variable cost per person)
Pedometer	Pedometer and individualized step-related goal setting delivered by post	168·0	2,200,000	42·10
General practitioner (GP) referral	GP referral to behavior change counseling delivered by telephone	352·8	1,010,000	295·40
Individualized advice	Individualized physical activity advice delivered by post	180·6	3,100,000	8·60
Exercise prescription	Exercise prescription with telephone-based counselling	256·2	1,010,000	253·45

Abbreviations: CHF, Swiss francs; GP, general practitioner; MET, metabolic equivalent.
See appendix pp. 7-10 for intervention cost details

Model outcomes

Life years gained were directly extracted from the life tables in the disease model and DALYs were estimated using disability weights from prevalent years lived with disability (YLD). Health care costs related to the medical treatment of diseases were estimated based on the number of prevalent cases and annual costs per disease. Productivity losses due to morbidity (i.e. presenteeism, absenteeism and early retirement), premature mortality and informal care were estimated in the model using the human capital approach.

From a societal perspective, net costs were intervention costs minus averted health care costs (all direct medical costs irrespective of the payer) and averted productivity losses. From a health care payer perspective, net costs were intervention costs minus averted health care costs only. ICERs were estimated by dividing net costs by DALYs averted compared to “doing nothing”. In addition, an incremental analysis was conducted by comparing more cost-effective interventions with their next best alternatives. A willingness-to-pay threshold of CHF 100,000 per DALY was tentatively assumed to assess the cost-effectiveness of interventions. Interventions that led to more DALYs averted and were at the same time less costly compared to the alternative were categorized as “dominant”.[28]

Sensitivity analysis

We conducted multiple scenario analyses and a probabilistic sensitivity analysis ass detailed in the appendix p. 14. The SPACE model was developed in MS Excel (Microsoft, Redmond, WA) and used the Ersatz add-in to MS Excel to calculate outcomes for age-sex cohorts and to conduct PSA.[29]

Role of the funding source

Health Promotion Switzerland did partially fund this study. They were not involved in any of the following activities: in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Cost-effectiveness on the national level

Life years lived longer and health gains differed substantially between the four interventions (Table 2). GP referral had the highest gains of 134 life years and 306 DALYs over the cohorts' lifetime. The lowest gains were achieved with the pedometer intervention (41 life years and 133 DALYs). These differences in health gains were also reflected in differences in the reduction of health care costs and productivity losses. GP referral was responsible for the highest offsets of CHF -22·3 million (health care costs) and CHF -20·4 million (productivity losses). The pedometer intervention had the lowest offsets of CHF -10·4 million and CHF -8·9 million, respectively. Intervention costs also varied substantially. Individualized advice had the lowest costs with CHF 4·1 million and GP referral the highest with CHF 29·4 million.

From the *societal perspective*, all four interventions were cost-saving compared to "doing nothing", as intervention costs were offset by averted health care costs and productivity losses. Furthermore, they were dominant, as all four interventions also gained life years and averted DALYs. When comparing interventions incrementally, individualized advice was the most cost-effective intervention and the next best alternative was GP referral with an ICER of CHF 19,632 per DALY averted, which is below the frequently assumed tentative willingness-to-pay threshold of CHF 100,000 per DALY averted (appendix pp. 15-16). Pedometer and exercise prescription were dominated by the other two interventions.

From the *health care payer perspective*, the pedometer and individualized advice interventions remained dominant when compared to "doing nothing". For GP referral net costs were CHF 7·1 million and for exercise prescription CHF 9·1 million. This led to ICERs of CHF 23,044 and CHF 41,079 per DALY averted, respectively, for GP referral and exercise prescription. In the incremental analysis, individualized advice was the most cost-effective intervention and the next best alternative was GP referral with an ICER of CHF 86,503 per

DALY averted. Pedometer and exercise prescription were again dominated by the other two interventions.

Table 2 Cost-effectiveness of physical activity interventions as estimated in the deterministic base case analysis

							Societal perspective		Health care payer perspective	
Intervention	Population size	Population reached	DALYs averted	Health care cost offsets (million CHF)	Productivity losses offsets (million CHF)	Intervention cost (million CHF)	Net cost (million CHF)	ICER* (CHF/DALY)	Net cost (million CHF)	ICER* (CHF/DALY)
Pedometer	3,887,024	116,610	133	-10·4	-8·9	7·1	-12·2	dominant	-3·3	dominant
GP referral	3,887,024	96,039	306	-22·3	-20·4	29·4	-13·4	dominant	7·1	23,044
Individualized advice	3,887,024	116,610	143	-11·1	-9·6	4·1	-16·6	dominant	-7·0	dominant
Exercise prescription	3,887,024	96,039	222	-16·2	-14·8	25·4	-5·7	dominant	9·1	41,079

Abbreviations: GP, general practitioner; DALYs, disability-adjusted life-years; CHF, Swiss francs; ICER, incremental cost-effectiveness ratio
*compared to “doing nothing”

Cost-effectiveness in the three language regions

The results in the German-speaking region were comparable to the ones at the national level (Table 3). All four interventions were dominant from a societal perspective when compared to “doing nothing”. From a health care payer perspective, the pedometer and individualized advice interventions also remained dominant and the ICERs for GP referral and exercise prescription were below the tentatively assumed willingness-to-pay threshold of CHF 100,000 per DALY averted. In the incremental analysis, individualized advice was the most cost-effective intervention and the next best alternative was GP referral, with ICERs of CHF 45,977 and CHF 112,644 per DALY averted, respectively, from a societal and health care payer perspective. Pedometer and exercise prescription were dominated by the other two interventions.

In the French- and Italian-speaking regions, all four interventions were dominant from a societal perspective when compared to “doing nothing”. When comparing the interventions with each other, GP referral dominated all three other interventions as it averted most DALYs at lowest net costs. From a health care payer perspective, however, individualized advice was the preferable option followed by GP referral.

Table 3 Cost-effectiveness of physical activity interventions in the three language regions of Switzerland

							Societal perspective		Health care payer perspective	
Intervention	Population size	Population reached	DALYs averted	Health care cost offsets (million CHF)	Productivity losses offsets (million CHF)	Intervention cost (million CHF)	Net cost (million CHF)	ICER* (CHF/DALY)	Net cost (million CHF)	ICER* (CHF/DALY)
French-speaking region										
Pedometer	974,773	29,243	34	-2·9	-2·4	1·8	-3·5	dominant	-1·1	dominant
GP referral	974,773	32,118	101	-8·0	-6·9	9·7	-5·2	dominant	1·7	16,856
Individualized advice	974,773	29,243	37	-3·1	-2·5	1·0	-4·6	dominant	-2·1	dominant
Exercise prescription	974,773	32,118	74	-5·8	-5·0	8·4	-2·4	dominant	2·6	34,756
German-speaking region										
Pedometer	2,737,993	82,140	92	-7·0	-6·2	4·6	-8·7	dominant	-2·4	dominant
GP referral	2,737,993	58,321	186	-13·1	-12·5	17·7	-7·9	dominant	4·6	24,714
Individualized advice	2,737,993	82,140	99	-7·5	-6·7	2·3	-11·9	dominant	-5·2	dominant
Exercise prescription	2,737,993	58,321	135	-9·5	-9·1	15·3	-3·3	dominant	5·8	42,479
Italian-speaking region										
Pedometer	174,258	5,228	6	-0·5	-0·3	0·8	-0·1	dominant	0·3	42,391
GP referral	174,258	5,532	18	-1·4	-1·0	1·9	-0·4	dominant	0·5	29,589
Individualized advice	174,258	5,228	7	-0·5	-0·4	0·8	-0·1	dominant	0·3	41,567
Exercise prescription	174,258	5,532	13	-1·0	-0·7	1·7	-0·0	dominant	0·7	51,558

Abbreviations: GP, general practitioner; DALYs, disability-adjusted life-years; CHF, Swiss francs; ICER, incremental cost-effectiveness ratio
*compared to "doing nothing"

Sensitivity analysis

Pedometer and individualized advice remained cost-saving in all scenario analyses from a societal perspective (appendix pp. 17-20). GP referral was no longer cost-saving when the duration of effect was set at one year instead of three years. Exercise prescription was no longer cost-saving when the duration of effect was set at one year instead of three years; when the intervention effect was assumed 30% lower than in the base case analysis; when intervention costs were assumed 30% higher; and when health care costs and productivity losses were assumed 30% lower. DALYs averted were most influenced by the percentage of population reached and the duration of effect. The inclusion of osteoporosis, low back pain and depression had a substantial impact on the results, in such that without these three diseases only individualized advice remained cost-saving from a societal perspective.

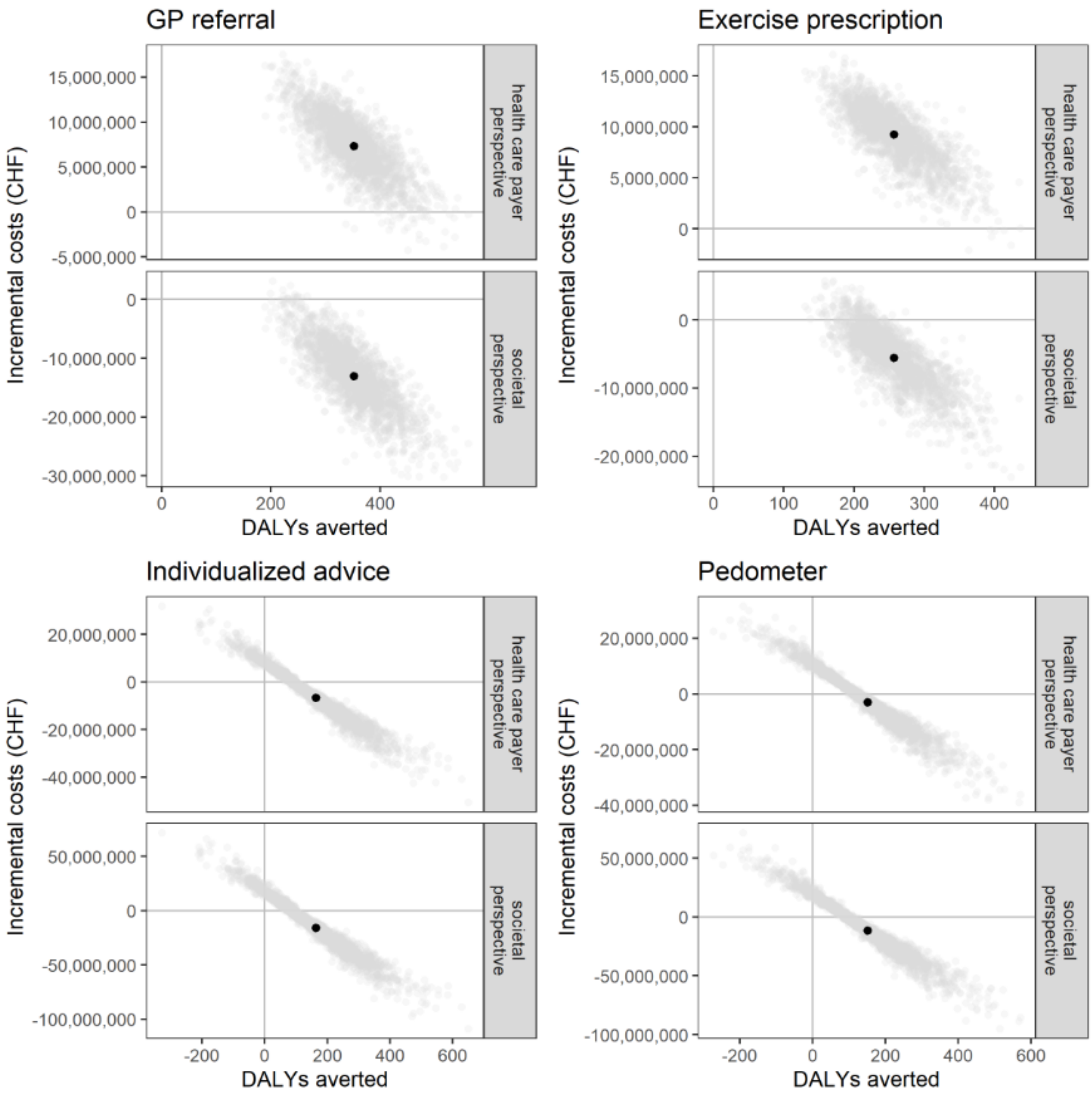
In the probabilistic sensitivity analysis, the uncertainty underlying some of the key model input parameters led to substantial variation in the model outcome (Figure 2). This is also reflected in the cost-effectiveness acceptability curves (Figure 3). From a societal perspective, the probability for being cost-saving was highest for individualized advice (73%) and lowest for exercise prescription (45%) (Table 4). The probabilities for an ICER below CHF 100,000 per DALY averted were 82% for GP referral and 72% for exercise prescription.

Table 4 Probabilistic sensitivity analysis results for physical activity interventions, compared to "doing nothing"

		Societal perspective			Health care payer perspective		
Intervention	DALYs averted (base case)*	Net cost in million CHF (base case)*	Probability of being cost-saving	Probability of being better than CHF100,000 /DALY averted	Net cost in million CHF (base case)*	Probability of being cost-saving	Probability of being better than CHF100,000 /DALY averted
Pedometer	149 (133)	-11·0 (-12·2)	68%	78%	-2·7 (-3·3)	61%	79%
GP referral	316 (306)	-2·8 (-13·4)	99%	100%	14·8 (7·1)	2%	100%
Individualized advice	162 (143)	-15·6 (-16·6)	74%	81%	-6·5 (-7·0)	73%	84%
Exercise prescription	229 (222)	2·9 (-5·7)	92%	100%	15·6 (9·1)	0%	100%

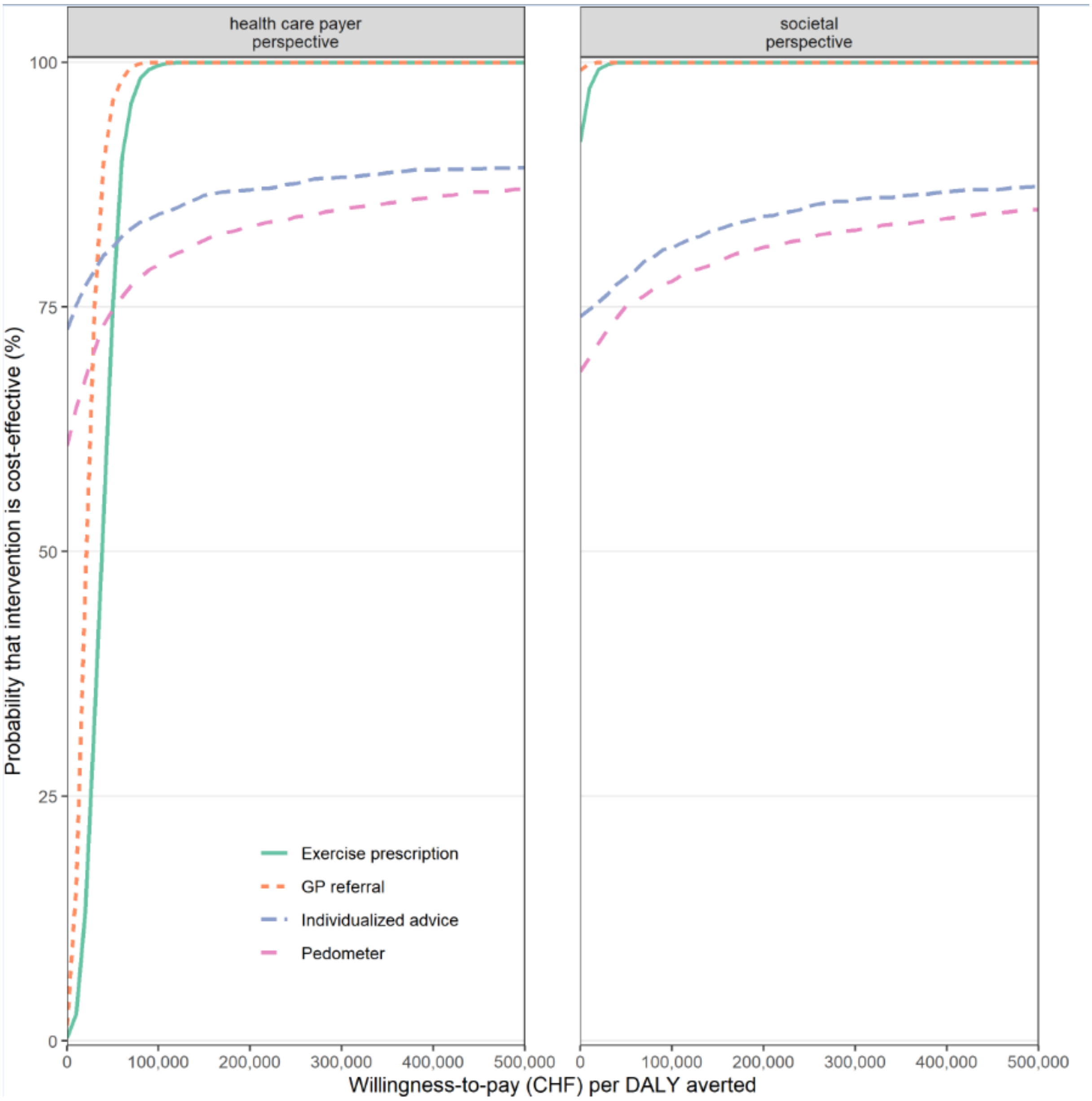
Abbreviations: GP, general practitioner; DALYs, disability-adjusted life-years; CHF, Swiss francs;
* Deterministic base case results for comparison.

Figure 2 Cost-effectiveness results of physical activity interventions from probabilistic sensitivity analysis



Abbreviations: GP, general practitioner; DALYs, disability-adjusted life-years; CHF, Swiss francs;
* Deterministic base case results for comparison.
Grey dots represent 2,000 simulations run as part of the probabilistic sensitivity analysis. Black dots indicate mean values from the probabilistic sensitivity analysis. Results are shown for both perspectives, health care payer and societal.

Figure 3 Cost-effectiveness acceptability curves for physical activity interventions



Abbreviations: GP, general practitioner; DALYs, disability-adjusted life-years; CHF, Swiss francs;
* Deterministic base case results for comparison.
This figure shows cost-effectiveness acceptability curves for all four interventions from the health care payer (left panel) and societal (right panel) perspectives. The curves indicate the probabilities of being cost-effective (y-axis) at different willingness-to-pay thresholds (x-axis).

Discussion

SPACE is the first health economic model to evaluate the cost-effectiveness of physical activity interventions in Switzerland. From a societal perspective and irrespective of language and thus cultural region, all four interventions, namely individualized advice, pedometer, GP referral and exercise prescription, were cost-saving and more effective compared to “doing nothing”. At the national level and in the German-speaking region, individualized advice was the preferable intervention followed by GP referral. These two interventions dominated pedometer and exercise prescription. In the French- and Italian speaking regions, GP referral was the preferable intervention that dominated the three others. From a health care payer perspective, however, individualized advice was the preferable intervention followed by GP referral. The uncertainty underlying key model input parameters led to substantial variation in the modelled results, according to the probabilistic sensitivity analysis.

In general, results for the health care payer perspective estimated in SPACE seemed to be comparable to the ones from previous physical activity models built for other countries. Compared to Cobiac et al.[15], who investigated the cost-effectiveness of physical activity interventions for Australia, results for the pedometer intervention were similar, the ICER for exercise prescription worse and the one for GP referral better. Our more favorable results for GP referral were explained by the use of intervention effects from a more recent study.[25] Furthermore, our results for the pedometer intervention were comparable to the ones by Anokye et al.[13] and more favorable than the ones estimated by Over et al.[17] and Gc et al.[16] because we included more diseases related to physical inactivity.

Although individualized advice was the most cost-effective strategy on the national level, it should be highlighted that health benefits in terms of DALYs averted were rather small (143 DALYs). The burden of physical inactivity in Switzerland was estimated at 40,433 DALYs for the year 2013.[8] Therefore, individualized advice would avoid less than 0·5% of the annual DALYs caused by physical inactivity. The issue of interventions that increase health benefits by small amounts only but may be cost-effective due to small intervention costs has already been raised in previous studies.[23,30] Consequently, relying on cost-effectiveness alone might favor interventions that are unable to add substantial health benefits. GP referral added more health benefits than individualized advice at different net costs. While individualized advice was the preferable option in the regions with lower prevalence of physical inactivity, GP referral was preferable in the regions with higher prevalence. This finding shows that more intensive interventions have the potential for being cost-effective in populations at higher risk despite not being cost-effective at the population level.[23]

We compared the four physical activity interventions under study with “doing nothing” and incrementally with each other. If the interventions were able to reach different sub-populations, they could be considered truly independent and leading to additive effects. This would support the comparison with “doing nothing”. In light of potential cost savings, it would imply that several of the studied interventions could sensibly be implemented in parallel. However, as individualized advice and pedometer both recruit participants via public campaigns, independence of the interventions is questionable. The same holds for GP referral and exercise prescription as both recruit participants via GPs. Therefore, our additional, incremental comparison assumed mutual exclusivity of the four interventions in the sense that they interact and lead to non-additive effects when implemented in the same population.[31] In reality, there be a situation of partial mutual exclusivity; one policy implication might be to consider co-implementation of individualized advice and GP referral in parallel. The available budget, and not just cost-effectiveness, may influence such choices.

According to our knowledge, this study is the first in the field to include productivity losses in the cost-effectiveness assessment of physical activity interventions, adopting a societal perspective. Previous studies mainly focused on health care costs, while the PRIMEtime CE model by Briggs et al.[14] also included social care costs for those aged above 75 years. The estimated averted productivity losses in the SPACE model were substantial, 10-15% lower than the averted health care costs. This is consistent with studies estimating the economic burden of physical inactivity.[32]

Fixed and variable intervention costs were modelled separately in SPACE to account for the fact that the use of certain resources is independent of the number of people receiving the intervention.[33] This separation of fixed and variable costs was another reason for different results between language regions besides the already mentioned influence of different prevalence of physical inactivity. In the Italian- and French-speaking regions, target populations were smaller and, thus, fewer people were reached by the interventions compared to the German-speaking region. Therefore, fixed intervention costs may substantially influence cost-effectiveness when the scale of the intervention substantially differs.

Strengths of our model, in summary, are the inclusion of a societal perspective of cost assessment, the consideration of fixed and variable intervention costs and intervention effects stemming from randomized controlled trials. In addition, we included osteoporosis, low back pain and depression to gain a comprehensive understanding of diseases related to physical inactivity. As shown in the scenario analysis, this had a substantial impact on the results. Furthermore, epidemiological data used were consistent, as derived from the GBD study.[34] Moreover, the language-region specific estimation of cost-effectiveness reflected previous findings which showed that the economic burden due to physical inactivity substantially differed between language regions.[8]

The main limitation of our model is the uncertainty arising from the use of a range of heterogeneous secondary data sources and assumptions. Although RRs for disease incidence were taken from recently published meta-analyses that investigated dose-response relationships, they were not based on a standardized definition and measurement of physical activity. Furthermore, we assumed equal RRs across gender and age-groups. We may have underestimated the prevalence of physical inactivity as the Swiss Health Survey investigates self-reported activity levels.[35] Irrespective of these common issues, our effect estimates are consistent in that both prevalence and RRs were based on self-reported physical activity levels. As a further limitation, productivity losses were likely underestimated because some domains such as presenteeism, early retirement and informal care could not be considered for some diseases due to limited data availability from literature. Although we tried to be comprehensive with diseases related to physical inactivity, there may be other diseases for which physical inactivity will be established as a risk factor, such as dementia and Alzheimer's disease. Due to currently conflicting evidence, these diseases were not included in our model.[36] Furthermore, multistate life table models assume independence in disease effects, while for example the occurrence of cardiovascular diseases is not independent from type 2 diabetes mellitus.[14] Our analysis was not comprehensive in terms of interventions considered. Focusing on interventions that can be implemented at the population-level, we excluded interventions targeting specific populations such as worksite populations.[37] In addition, we included only interventions that were investigated in randomized controlled trials. This implied the exclusion of interventions targeting the built environment.[30,38] The SPACE model currently focuses on the adult population and does not allow for a holistic life course approach. Such an approach may be taken in future models, which would then allow us to also analyze the cost-effectiveness of interventions targeting children.

In conclusion, we hope to inform efficient resource allocation and evidence-based decision-making in primary prevention in Switzerland. We recommend that individualized advice and GP referral be further evaluated as interventions and that decision-making considers the specifics of the Swiss language regions. Furthermore, we judge the SPACE model to be not only relevant for Switzerland but also for other multicultural countries. Based on similar data availability, the SPACE model has the potential to be applied beyond Switzerland, primarily to high-income countries with a comparable background, as a tool to guide societal efforts in primary prevention of physical-inactivity-related diseases.

Declaration of interests: Renato Mattli, Johannes Pöhlmann, Simon Wieser, Nicole Probst-Hensch, Arno Schmidt-Trucksäss and Matthias Schwenkglenks declare that they have no conflicts of interest relevant to the content of this article.

Availability of data and material Any additional information is available upon request from the corresponding author.

Authors' contributions RM and MS conceptualized the work. RM, JP, SW, NP, AS and MS contributed to the methodology and validation. RM and JP conducted the formal data analyses and built the model. RM prepared the original draft and JP, SW, NP, AS and MS read, reviewed, and edited subsequent drafts. All authors approved the final manuscript.

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Supplementary Appendix

1 Modelling approach

Although each modelling method has its advantages and disadvantages, we deemed the proportional multistate life table modelling approach implemented in SPACE to be a good fit for physical activity modelling as it allowed for relatively easy consideration of multiple diseases, comorbidity and increased life expectancy.[1-3] Previous models investigating cost-effectiveness of physical activity interventions included decision trees[4,5], Markov models[6-10], microsimulation models[11] as well as multistate life table models[12-15]. Multistate life table models were also used to assess other risk factors for non-communicable diseases such as smoking and unhealthy diet.[16-26]

2 Model input parameters and data sources

2.1 Disease model

Age- and sex-specific population counts and total mortality rates were obtained from the Swiss Federal Statistical Office.[27]

Disease life tables were mainly informed by data from the global burden of disease (GBD) 2017 study.[17] In an alternative scenario, we used Swiss-specific epidemiological data for the diseases for which we could source information from the Swiss National Institute for Cancer Epidemiology and Registration [28], the Swiss Health Survey [29] and mortality statistics.[27] (Table 1). We chose the GBD study as the primary source given the ready availability of detailed data and its wide use in the burden of disease and comparative risk assessment literature.[12,17,30] In addition, using GBD data implied that all epidemiological input data were estimated using the same methodological framework.[31] Epidemiological data were processed in the DisMod II software before serving as input data in SPACE in order to derive unknown epidemiological quantities and to create a set of consistent epidemiological parameter values.[32] The same approach was followed in previous public health economic modelling studies.[2,12-14,17,18]

Table 1 Overview of epidemiological input data

Disease	Incidence	Prevalence	Disease-specific mortality	Case-fatality rate	Remission
Breast cancer (female)	GBD 2017 [33]	BC: GBD 2017 AS: <u>NICER</u> [28]	GBD 2017	Dismod II	Dismod II
Colorectal cancer	GBD 2017	BC: GBD 2017 AS: *NICER*	GBD 2017	Dismod II	Dismod II
Type 2 diabetes mellitus	GBD 2017	BC: GBD 2017 AS: <u>SHS 2017</u> [34]	BC: GBD 2017 AS: <u>DeathStat 2016</u> [27]	Dismod II	Assumed no remission
Coronary heart disease	GBD 2017	GBD 2017	BC: GBD 2017 AS: <u>DeathStat 2016</u>	Dismod II	Assumed no remission
Ischemic stroke	BC: GBD 2017 AS: *SHS 2017* [35]	GBD 2017	BC: GBD 2017 AS: <u>DeathStat 2016</u>	BC: no input AS: SHS 2017 [35]	Assumed no remission
Osteoporosis (GBD category “falls”*)	GBD 2017	BC: GBD 2017 AS: <u>SHS 2017</u> [36]	GBD 2017	Dismod II	Assumed no remission
Low back pain	GBD 2017	BC: GBD 2017 AS: **SHS 2017** [37]	Assumed no disease-specific mortality	Dismod II	Dismod II
Depression (GBD category “major depressive disorder”)	GBD 2017	BC: GBD 2017 AS: **SHS 2017** [38]	Assumed no disease-specific mortality	Dismod II	BC: no input AS: 35.4% [39]

Abbreviations: AS, Alternative Scenario; BC, Base Case; DeathStat, Cause of Death and Stillbirth Statistics; GBD, Global Burden of Disease; NICER, National Institute for Cancer Epidemiology and Registration; SHS; Swiss Health Survey.

*Causes of death and disability are often “categorized according to cause of injury (i.e., falls), not nature of injury (i.e., fracture)”.[40]

Note: Citations are provided at the first mentioning of each distinct source. For osteoporosis, incidence, prevalence and disease-specific mortality were all adjusted for the proportion of falls resulting in fractures, using the estimates provided in the meta-analysis by Morrison et al.[41]. Alternative scenarios with higher parameter values than the corresponding (GBD) base case values are in bold type. Alternative scenarios with lower parameter values than the corresponding (GBD) base case values are underlined. Alternative scenarios where values were not consistently higher or lower than the corresponding (GBD) base case values are in italics.

We also accounted for disease incidence trends based on GBD estimates for incidence rates across all ages, separately for women and men, for the last 15 years (Table 2).[18] Based on these data, we estimated average annual percentage changes (AAPCs). AAPCs were applied in the first 15 years of the model as simple multiplicative factors affecting incidence. After 15 years, we assumed no further changes in disease incidence.

Table 2 AAPCs for disease incidence between 2003 and 2017

Disease	sex	AAPC (%)	95% CI LB (%)	95% CI UB (%)
Breast cancer	women	-0.919	-2.033	0.194
Colorectal cancer	men	-0.450	-2.321	1.421
	women	-0.579	-2.651	1.493
Coronary heart disease	men	0.513	-0.303	1.329
	women	-0.571	-1.517	0.374
Ischemic stroke	men	1.179	-0.089	2.447
	women	0.951	-0.451	2.354
Type 2 diabetes mellitus	men	0.971	0.369	1.573
	women	0.654	-0.028	1.337
Osteoporosis (falls)	men	-2.125	-2.305	-1.945
	women	-1.299	-1.456	-1.142
Low back pain	men	0.576	0.408	0.744
	women	0.351	0.201	0.500
Depression (major depressive disorder)	men	-0.645	-0.917	-0.372
	women	-0.651	-0.873	-0.430

Source: Own calculations based on data from GBD Results Tool.[33]
Abbreviation: AAPC, Average Annual Percentage Change; CI, Confidence Interval; GBD, Global Burden of Disease; LB, Lower Bound; UB, Upper Bound.
Explanation: For women, low back pain incidence increased, on average, by 0.351% per year between 2003–2017.

2.2 Intervention model

2.2.1 Overview

The population prevalence of each physical activity category was estimated based on the Swiss Health Survey.[29] Energy expenditure in MET-minutes per week was assigned to each physical activity category according to the Swiss Health Survey and the compendium of physical activities (see sections 2.2.2 and 2.2.3).[42] The relationship between energy expenditure and RRs was modelled based on published meta-analyses.[43-46]

Measures of intervention effects from the trials were standardized as MET-minutes gained per week.[47] To estimate fixed and variable intervention costs, we used a bottom-up approach with current Swiss prices. Resource consumption was as reported in the trials where available; otherwise, we made assumptions (see section 2.2.4). For the language-region-specific analyses, we assumed a separate implementation and, therefore, that half of the fixed intervention costs would be incurred in the German-speaking region and a quarter each in the French- and Italian-speaking regions of Switzerland.

Two specific modelling aspects requiring attention are time lag between increased physical activity and observed health benefits as well as the decay of intervention effects. While energy expenditure might change quickly in response to a physical activity intervention, health effects might occur with some delay.[13,21] However, there is no robust evidence regarding the length of the time lag between increased physical activity and observed health benefits.[2] Some evidence suggests that this time lag may be relatively short[48,49], while older evidence indicates that time lags may be shorter for cardiovascular diseases and longer for cancers[50,51]. Most previous physical activity modelling studies did not consider time lags. Two studies mentioned, but did not model, them.[13,52] One study included time lags in scenario analyses and showed that no time lags resulted in increased estimates of health benefit.[2] We applied intervention effects from the second year onwards, accounting for the fact that estimates of intervention effects were based on 12-month follow-up data. Furthermore, we assumed a relative annual decay rate of 50% for all intervention effects, which is in line with previous models.[11,13] Other models assumed full intervention effects over a time period of 5 to 10 years.[8]

2.2.2 Prevalence of physical activity categories

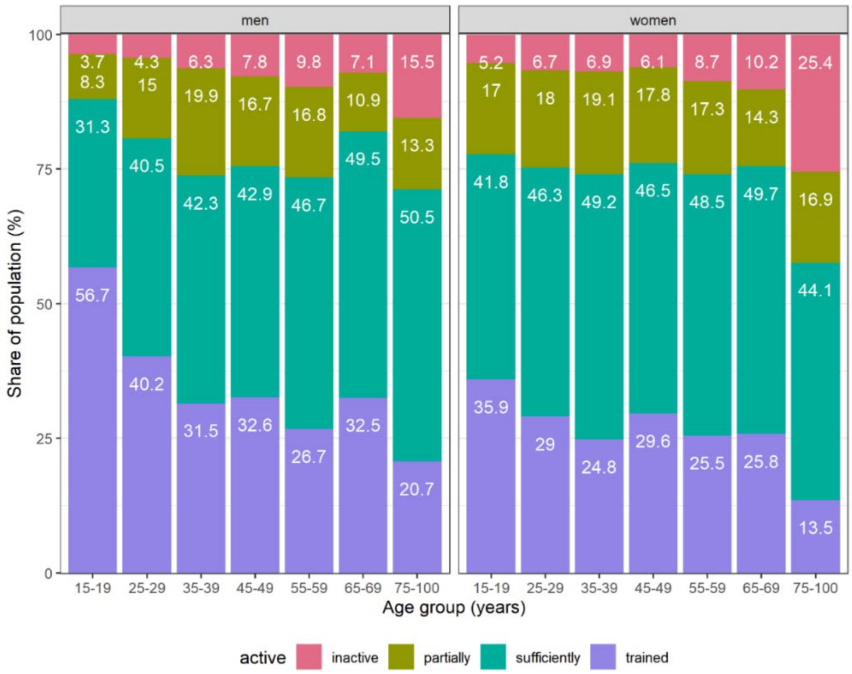
The 2017 prevalence of the different physical activity categories in Switzerland and each language region was sourced from the Swiss Health Survey [SHS].[29] In the SHS, respondents reported if and how often they engaged per week in physical activity that made them sweat. Respondents also supplied estimates of how long, on average, they were active on their "active days" (for a discussion of the potential underestimation of physical inactivity prevalence due to self-reporting, see [53]).

Based on these answers, we estimated the proportions of the Swiss population who were:[29]

- *Inactive*: Less than 30 minutes of moderate physical activity or engaging in intense physical activity less than once per week
- *Partially active*: 30–149 minutes of moderate physical activity or engaging in intense physical activity once per week
- *Sufficiently active*: At least 150 minutes of moderate physical activity or engaging in intense physical activity twice per week
- *Trained*: Engaging in intense physical activity at least three times per week

Prevalences were calculated for 5-year age groups and for both sexes separately (Figure 1). Data were available up to age 75 years. We assumed that the prevalence reported for age 75 years applied to all higher age groups. Regarding the prevalence of each physical activity category in 5-year age groups and by sex in the language regions, we observed small numbers of respondents for some age and sex-specific physical activity categories in some language regions (e.g. the Italian-speaking region). In order to get more robust estimates, we therefore assumed that age and gender distribution within each physical activity category did not differ between language regions.

Figure 1 Prevalence of physical activity categories in Switzerland 2017



Source: Swiss Health Survey 2017.[29]
Explanation: Proportions of self-reported levels of physical activity for women and men. For both sexes, the proportion of "trained" people declined with age. The largest share of "inactive" people was in the highest age group for both sexes.

2.2.3 Mapping MET-minutes to physical activity categories

MET-minutes per week were assigned to each physical activity category (Section 3.2.1) according to data from the Swiss Health Survey 2017.[29] The International Physical Activity Questionnaire [IPAQ] had previously been included in the Swiss Health Survey but was not part of the 2017 wave.[54] Therefore, we had to estimate the MET-minutes per week with another method.

We first evaluated the days per week with activities that lead to at least some sweating (low- to moderate-intensity physical activity) (TKOBW09: "Anzahl Tage pro Woche mit Aktivitäten, wo Sie zumindest ein bisschen ausser Atem kommen, aber nicht unbedingt ins Schwitzen. Das sind zum Beispiel zügiges Laufen, Wandern, Tanzen, Gartenarbeiten oder verschiedene Sportarten").

In the next step, we analyzed the average duration per day with low- to moderate-intensity physical activity (TKOBW11: "Durchschnittliche Dauer in Minuten pro Tag der oben beschriebenen Aktivität"). Values lower than 10 minutes were set to 0 in accordance with the IPAQ scoring guidance as the scientific evidence indicates that episodes or bouts of at least 10 minutes were required to achieve health benefits. We then took the days of low- to moderate-intensity physical activity per week and multiplied it by the average duration per day of low- to moderate-intensity physical activity to get the median minutes of low- to moderate-intensity physical activity per week. The minutes of low- to moderate-intensity physical activity per week were then multiplied by 3 METs to get to the MET-minutes per week of low- to moderate-intensity physical activity.[47] Four METs instead of 3 METs were included in the scenario analysis.

The minutes of high-intensity physical activity per week were analyzed based on the answers given in the Swiss Health Survey regarding "minutes per week of gymnastics, fitness and sports" (SKOBW12: "Minuten pro Woche Gymnastik, Fitness, Sport"). Values lower than 10 minutes were set to 0 with the same rationale as for the low- to moderate-intensity physical activity. The minutes of high-intensity physical activity per week were then multiplied by 6 METs to get the MET-minutes per week of high-intensity physical activity.[55] Eight METs instead of six METs were included in the scenario analysis.

Total MET-minutes per week of physical activity were estimated by adding the MET-minutes per week of high-intensity physical activity to the MET-minutes per week of low- to moderate-intensity physical activity. This approach allowed us to calculate sex-specific (but not age-specific) MET-minutes for each physical activity category (Table 1). We further assumed that MET-minutes per physical activity category do not differ between language regions.

Table 3 Mapping MET-minutes to physical activity categories

Sex	PA level	Scenario	MET-minutes per week
Women	Inactive	Base case (3 METs for light, 6 METs for vigorous PA)	0
	Partially active		360
	Sufficiently active		1,620
	Trained		2,514
	Inactive	Alternative scenario (4 METs for light, 8 METs for vigorous PA)	0
	Partially active		480
	Sufficiently active		2,160
	Trained		3,352
Men	Inactive	Base case (3 METs for light, 6 METs for vigorous PA)	0
	Partially active		360
	Sufficiently active		1,620
	Trained		2,610
	Inactive	Alternative scenario (4 METs for light, 8 METs for vigorous PA)	0
	Partially active		480
	Sufficiently active		2,160
	Trained		3,480

Source: Mattli et al.[47,53] using the Swiss Health Survey [29,53] and the Ainsworth Compendium [42,56].
Abbreviation: MET, Metabolic Equivalent; PA, Physical Activity.

2.2.4 Intervention costs

Intervention set-up and delivery costs were estimated with a bottom-up approach using information from the original studies[57-60] and current tariffs/prices for Switzerland (Table 2). Standard deviations [SDs] for each cost were assumed to be 10% of the mean. We applied the same intervention costs to both sexes and all ages, for the first modelled year.

Table 4 Overview on intervention costs

Intervention type	Set-up costs (fixed costs, CHF, 2018)	Delivery of intervention (variable costs, per participant, CHF, 2018)
Pedometer [60]	2,200,000	42.10
GP referral [58]	1,010,000	295.40
Individualized advice [59]	3,100,000	8.60
Exercise prescription [57]	1,010,000	253.45

Source: Own calculation, see subsequent sections for details
Abbreviation: CHF, 2018 Swiss francs

<u>Pedometer with individualized goal setting</u>

Set-up costs (fixed costs): CHF 2,200,00

- Transferring intervention to Swiss setting: The intervention has already been designed. Relevant information has been published open access and can be unrestrictedly used, distributed and reproduced in any medium provided the original work is properly cited.[60] Therefore, costs are mainly related to translation into German, French and Italian. We assume that these costs would be approximately CHF 100,000.
- Participants have to be aware of intervention: One option would be that GPs recruit participants. In order to do this, GPs would need to be aware of the intervention (this is related to costs). Afterwards, GPs need time to identify the right participants. We assume that this would take at least 10 minutes. According to TARMED (position 00.0010 + 00.0030), this would yield costs of CHF 24.85 (27.92 tax points; 0.89 tax point value for the canton of Zurich).[61,62] Another option could be a big public campaign (similar to what has been done for smoking cessation). We assume that such a campaign would be related to costs of approximately CHF 2 million. As the costs for a public campaign are higher than if the GPs recruited the participants, we further consider only the costs for the public campaign
- Staff coordinating and delivering intervention: CHF 100,000

Delivery of intervention (variable costs; per participant): CHF 42.10

- Pedometer: CHF 40.00
- Handbook including step count diary: CHF 1.00
- Envelope for posting pedometer and handbook: CHF 0.10
- Stamps for posting: CHF 1.00

<u>GP referral to telephone-based counselling</u>

Set-up costs (fixed costs): CHF 1,010,000

- Transferring intervention to Swiss setting: Designing a referral letter template that afterwards can be easily personalized by the GP. We assume that these costs would be approximately CHF 10,000.
- GPs have to be aware of intervention: We assume that creating awareness including some “training” would be related to costs of approximately CHF 1 million.

Delivery of intervention (variable costs; per participant): CHF 295.40

- Referral costs: We assume 15 minutes consultation time (including writing the referral letter). TARMED positions 00.0010 + 00.0020 + 00.0030: CHF 41.40 (46.53 tax points; 0.89 tax point value for the canton of Zurich).[61,62]

- Costs for exercise physiologist: 4.4 consultations or 134 minutes total consultation time (this is approximately 30 minutes per consultation). Physio tariff 7301 (48 tax points per consultation). Plus for one time position 7350 (24 tax points). Total: CHF 254.00 ((4.4 x 48 tax points + 1 x 24 tax points) x 1.08 tax point value for the canton of Zurich).[63]

N.B.: No such profession as "exercise physiologist" currently exists in Switzerland. We do not take into consideration the costs related to "building such a profession". We assume that such a profession does exist, those professionals know what to do and are reimbursed similar to a physiotherapist or a nutritionist.

Individualized physical activity advice

Set-up costs (fixed costs): CHF 3,100,000

- Transferring intervention to Swiss setting: A computer-tailored intervention requires:[64] (1) a questionnaire collecting characteristics of the participant; (2) a data warehouse containing the intervention messages that may be needed; (3) decision rules selecting messages matched to the characteristics of the participant; (4) a letter delivering the messages to the participant. All these aspects have already been designed. However, it is unknown if the information, including the software, could be purchased. The purchasing (and tailoring, including translation, in order to adapt it to the Swiss setting), or otherwise the Swiss-specific re-development, would be related to costs. Cost assumption: CHF 1 million
- Participants have to be aware of intervention: One option could be a big public campaign (similar to what has been done for smoking cessation). We assume that such a campaign would be related to costs of approximately CHF 2 million
- Staff coordinating and delivering intervention: CHF 100,000

Delivery of intervention (variable costs; per participant): CHF 8.60

- Questionnaires for participants (print-out; includes first and second questionnaire): CHF 0.50
- Envelope for posting questionnaires: CHF 0.10
- Stamps for posting: CHF 1.00
- Pre-stamped return envelope (envelope plus stamp): CHF 1.10 x 2 (first and second questionnaire)
- Advice letter for participant (print-out): CHF 0.50 x 3 (tailored physical activity advice at three time points)
- Envelope for posting advice letter: CHF 0.10 x 3 (tailored physical activity advice at three time points)
- Stamps for posting: CHF 1.00 x 3 (tailored physical activity advice at three time points)

Exercise prescription with telephone-based counselling

Set-up costs (fixed costs): CHF 1,010,000

- Transferring intervention to Swiss setting: Translating exercise/lifestyle script that afterwards can be easily personalized by the primary care nurse. We assume that these costs would be approximately CHF 10,000
- GPs/primary care nurses have to be aware of intervention: We assume that creating awareness including some "training" would be related to costs of approximately CHF 1 million

Delivery of intervention (variable costs; per participant): CHF 253.45

- Initial brief advice: 10 minutes, includes time for personalizing written exercise/lifestyle script. TARMED positions 00.0010 + 00.0030: CHF 24.85 (27.92 tax points; 0.89 tax point value for the canton of Zurich).[61,62]
- Written exercise script (print-out): CHF 0.50
- 6-month follow-up visit with primary care nurse: 30 minutes. TARMED positions 00.1430 + 00.1440: CHF 72.60 (81.56 tax points; 0.89 tax point value for the canton of Zurich).[61,62]
- Telephone support from exercise specialist: five calls per participant lasting 15 min each. Physio tariff 7301 divided by two because one call only lasts 15 minutes instead of 30 minutes (24 tax points per call; this value is also very close to the 22 tax points for position 7340). Plus one time position 7350 (24 tax points). Total: CHF 155.50 ((5 x 24 tax points + 1 x 24 tax points) x 1.08 tax point value for the canton of Zurich).[63]

N.B.: No such profession as "exercise specialist" currently exists in Switzerland. We do not take into consideration the costs related to "building such a profession". We assume that such a profession does exist, those professionals know what to do and are reimbursed similar to a physiotherapist or a nutritionist

2.3 Model outcomes

To estimate DALYs, the total number of YLD were divided by the total number of prevalent cases in order to get an average (across all sequela) disability weight for the Swiss population with a specific disease (Table 5). Estimates for both parameters were available from GBD, for the same time period.[33]

Table 5 Disability weights

Disease	Mean disability weight	Standard deviation of disability weight
Breast cancer	0.0763	0.015
Colorectal cancer	0.0906	0.016
Type 2 diabetes mellitus	0.0681	0.015
Coronary heart disease	0.0391	0.008
Ischemic stroke	0.1545	0.027
Osteoporosis	0.0456	0.009
Low back pain	0.1127	0.020
Depression	0.1996	0.039

Source: GBD Results Tool [33,65]

Health care costs related to the medical treatment of diseases were derived from the literature (Table 6).[53,66-68] For breast and colon cancer, we used different annual costs for different treatment phases: for the first year, for subsequent years, and for the last year before death.[66,67] For all other diseases, we had to use constant costs along the disease pathway due to data availability. Where needed, costs were transferred to Swiss francs (CHF), first adjusting for different amounts of healthcare resources used according to purchasing power parity per capita health care spending, and second adjusting for different price levels in the reference country compared to Switzerland.[69] Furthermore, costs were inflated to 2018 values based on changes in per capita healthcare spending in Switzerland.[70] We further estimated age-standardized per capita healthcare spending for each language region based on the statistics of the Swiss risk compensation scheme to allow for regional differences in health care spending.[71]

Table 6 Annual direct medical costs per patient by region in CHF and USD for 2018

Disease	Region	Costs, 2018 CHF	Costs, 2018 USD
Breast cancer, incident	Switzerland	43,959.87	36,941.07
Breast cancer, prevalent		5,215.89	4,383.10
Breast cancer, terminal		62,303.28	52,355.70
Colorectal cancer, incident		73,017.82	61,359.52
Colorectal cancer, prevalent		6,484.21	5,448.91
Colorectal cancer, terminal		145,753.73	122,482.12
T2DM		7,770.37	6,529.72
Coronary heart disease		6,617.99	5,561.33
Ischemic stroke		23,686.49	19,904.61
Low back pain		9,360.94	7,866.33
Osteoporosis		2,506.91	2,106.65
Depression		5,740.96	4,824.33
Breast cancer, incident	French-speaking region	47,580.81	39,983.87
Breast cancer, prevalent		5,645.52	4,744.13
Breast cancer, terminal		67,435.15	56,668.19
Colorectal cancer, incident		79,032.24	66,413.65
Colorectal cancer, prevalent		7,018.31	5,897.74
Colorectal cancer, terminal		157,759.34	132’570.87
T2DM		8,410.41	7,067.57
Coronary heart disease		7,163.10	6,019.42
Ischemic stroke		25,637.52	21,544.14
Low back pain		10,131.99	8,514.28
Osteoporosis		2,713.41	2,280.17
Depression		6,213.84	5,221.71
Breast cancer, incident	German-speaking region	42,482.43	35,699.52
Breast cancer, prevalent		5,040.59	4,235.79
Breast cancer, terminal		60,209.34	50,596.09
Colorectal cancer, incident		70,563.78	59,297.30
Colorectal cancer, prevalent		6,266.28	5,265.78
Colorectal cancer, terminal		140,855.12	118,365.64
T2DM		7,509.21	6,310.26
Coronary heart disease		6,395.56	5,374.42
Ischemic stroke		22,890.41	19,235.64
Low back pain		9,046.33	7,601.96
Osteoporosis		2,422.66	2,035.85
Depression		5,548.01	4,662.19
Breast cancer, incident	Italian-speaking region	46,212.36	38,833.92
Breast cancer, prevalent		5,483.15	4,607.69
Breast cancer, terminal		65,495.68	55,038.39
Colorectal cancer, incident		76,759.23	64,503.56
Colorectal cancer, prevalent		6,816.46	5,728.12
Colorectal cancer, terminal		153,222.10	128,758.07
T2DM		8,168.52	6,864.30
Coronary heart disease		6,957.09	5,846.29
Ischemic stroke		24,900.17	20,924.52
Low back pain		9,840.59	8,269.40
Osteoporosis		2,635.37	2,214.60
Depression		6,035.12	5,071.53

Source: Cost data derived from literature [53,66-68]. Inflation from 2013 to 2018 values based on nominal healthcare cost changes in Switzerland [70].
Abbreviations: CHF, Swiss francs; T2DM, Type 2 Diabetes Mellitus.

Annual productivity losses due to morbidity and informal care for each disease were derived from literature (Tables 7-9).[53,68] Productivity losses due to mortality before the age of retirement (65 years in Switzerland) were estimated by applying sex- and region-specific median salaries for 2018. Median salaries were sourced from the Swiss Earnings Structure Survey 2016 and extrapolated using the nominal wage index.[72] We also considered the proportion of people employed and the degree of employment based on the Swiss Labor Force Survey.[73] Fifteen percent was added to the median salary to account for the mandatory social contributions paid by employers in Switzerland. Future effects and costs were discounted at 3% per annum.

Table 7 Annual productivity losses due to morbidity and informal care per patient by region in CHF and USD for 2018

Disease	Region	Costs, 2018 CHF	Costs, 2018 USD
Breast cancer	Switzerland	24,103.67	20,255.18
Colorectal cancer		26,921.77	22,623.34
T2DM		2,916.99	2,451.25
Coronary heart disease		2,970.04	2,495.83
Ischemic stroke		7,452.76	6,262.82
Low back pain		16,442.82	13,817.50
Osteoporosis		n/a	n/a
Depression		6,316.86	5,308.28
Breast cancer	French-speaking region	24,092.65	20,245.93
Colorectal cancer		26,909.47	22,613.00
T2DM		2,915.66	2,450.13
Coronary heart disease		2,968.68	2,494.69
Ischemic stroke		7,449.35	6,259.96
Low back pain		16,435.31	13,811.18
Osteoporosis		n/a	n/a
Depression		6,313.97	5,305.86
Breast cancer	German-speaking region	24,312.98	20,431.07
Colorectal cancer		27,155.55	22,819.79
T2DM		2,942.32	2,472.54
Coronary heart disease		2,995.83	2,517.50
Ischemic stroke		7,517.48	6,317.21
Low back pain		16,585.61	13,937.49
Osteoporosis		n/a	n/a
Depression		6,371.71	5,354.38
Breast cancer	Italian-speaking region	20,622.52	17,329.85
Colorectal cancer		23,033.62	19,355.98
T2DM		2,495.70	2,097.23
Coronary heart disease		2,541.09	2,135.37
Ischemic stroke		6,376.40	5,358.32
Low back pain		14,068.08	11,821.92
Osteoporosis		n/a	/na
Depression		5,404.55	4,541.64

Source: Productivity losses derived from the literature.[53,68]
Abbreviations: CHF, Swiss francs; T2DM, Type 2 Diabetes Mellitus; n/a, not applicable as all patients older 65 years

Table 8 Productivity losses due to presenteeism, absenteeism, early retirement and informal care per patient per disease for Switzerland in CHF for 2018

Disease	Presenteeism	Absenteeism	Early retirement	Informal care	Sum
Breast cancer	nr	11,341.95		12,753.65	24,103.67
Colorectal cancer	nr	12,668.01		14,244.75	26,921.77
T2DM	nr	525.52	2,391.46	nr	2,916.99
Coronary heart disease	nr	1,410.21	nr	1,559.82	2,970.04
Ischemic stroke	nr	3,538.67	nr	3,914.09	7,452.76
Low back pain	7'260.41	2,770.59	6,411.82	-	16,442.82
Osteoporosis	n/a	n/a	n/a	n/a	n/a
Depression	nr	5,625.64	691.22	nr	6,316.86

Source: Productivity losses derived from the literature.[53,68]

Abbreviations: CHF, Swiss francs; T2DM, Type 2 Diabetes Mellitus; n/a, not applicable as all patients older 65 years; nr, not reported

Table 9 Median annual region-specific salaries used in SPACE

Sex	Region	Salary, 2018 CHF	Salary, 2018 USD
Women	Switzerland	35,412	29,764
Women	French-speaking region	35,400	29,748
Women	German-speaking region	35,725	30,021
Women	Italian-speaking region	30,304	25,466
Men	Switzerland	59,695	50,164
Men	French-speaking region	59,661	50,135
Men	German-speaking region	60,210	50,597
Men	Italian-speaking region	51,074	42,919

Source: Swiss Earnings Structure Survey[72]

Abbreviations: CHF, Swiss francs; USD, US dollars.

3 Sensitivity analysis

We conducted multiple scenario analyses and a probabilistic sensitivity analysis. The values of the following input parameters were varied as part of the scenario analyses:

- population age (35 to 80 years)
- discount rate (0% and 6%)
- disease incidence trend (none)
- health care costs and productivity losses (70% and 130%)
- intervention effects and costs (70% and 130%)
- duration of intervention effect (1 year and 5 years)
- population reached (GP referral and exercise prescription: 5% and 15%; pedometer and individualized advice: 1% and 5%)
- METs assigned (4 instead of 3 METs to low/moderate physical activity and 8 instead of 6 to high intensity physical activity)

Furthermore, we investigated the impact of considering the additional three diseases compared to the five "core" diseases.

A probabilistic sensitivity analysis (PSA) was also conducted. We used the following distributions for key input variables: normal distributions for intervention effects, beta distributions for the annual decay of intervention effect and disability weights, gamma distributions for health care cost and productivity losses, and lognormal distribution for RRs. Whenever possible, we used the lower and upper bounds of the 95% confidence interval or the standard error to characterize uncertainty. Where information on the uncertainty was unavailable, we assumed a standard error of 10% of the reported point estimate. A total of 2,000 simulations were run.

4 Results

Figure 2 Cost-effectiveness planes, societal perspective

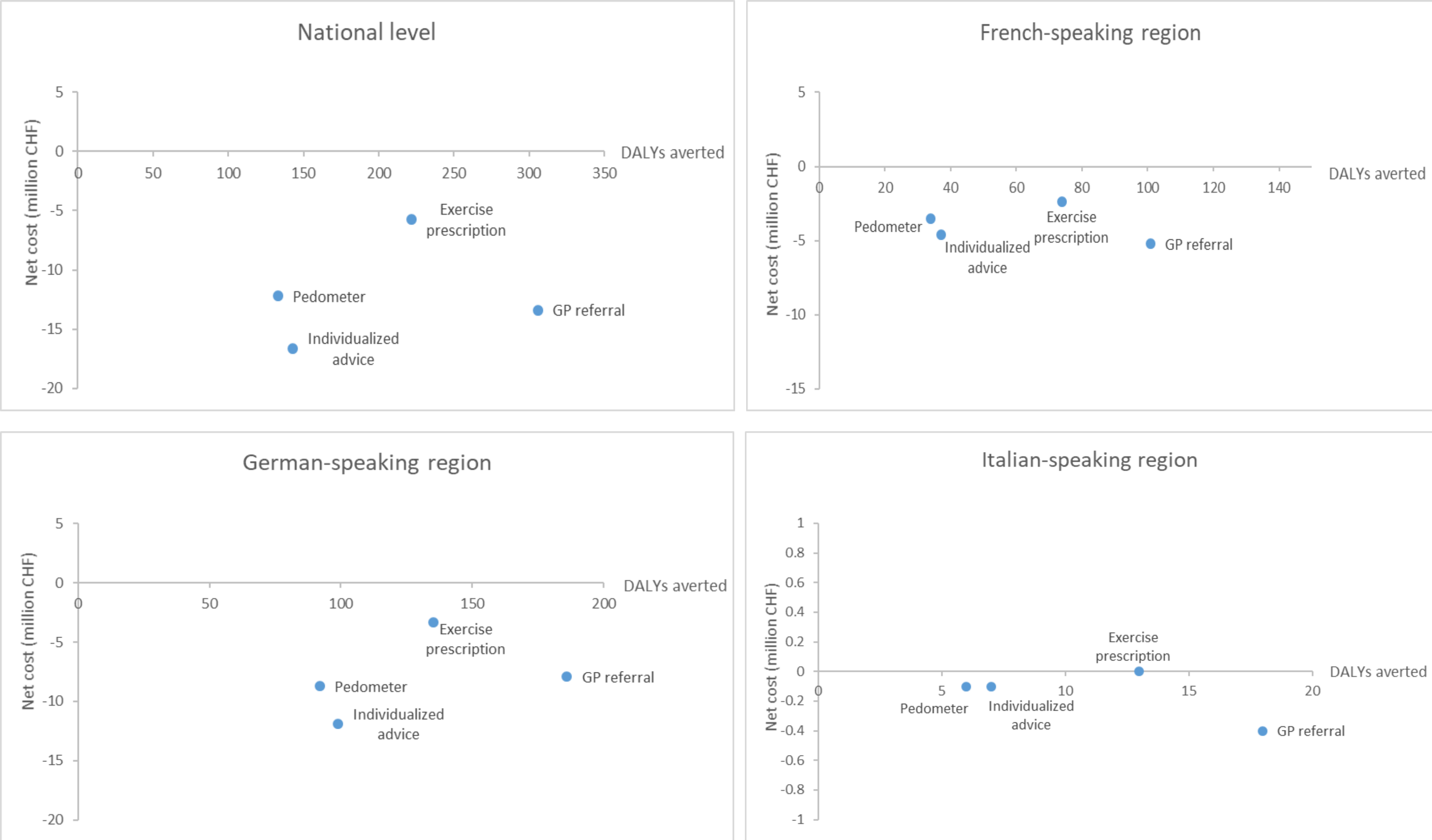


Figure 3 Cost-effectiveness planes, health care payer perspective

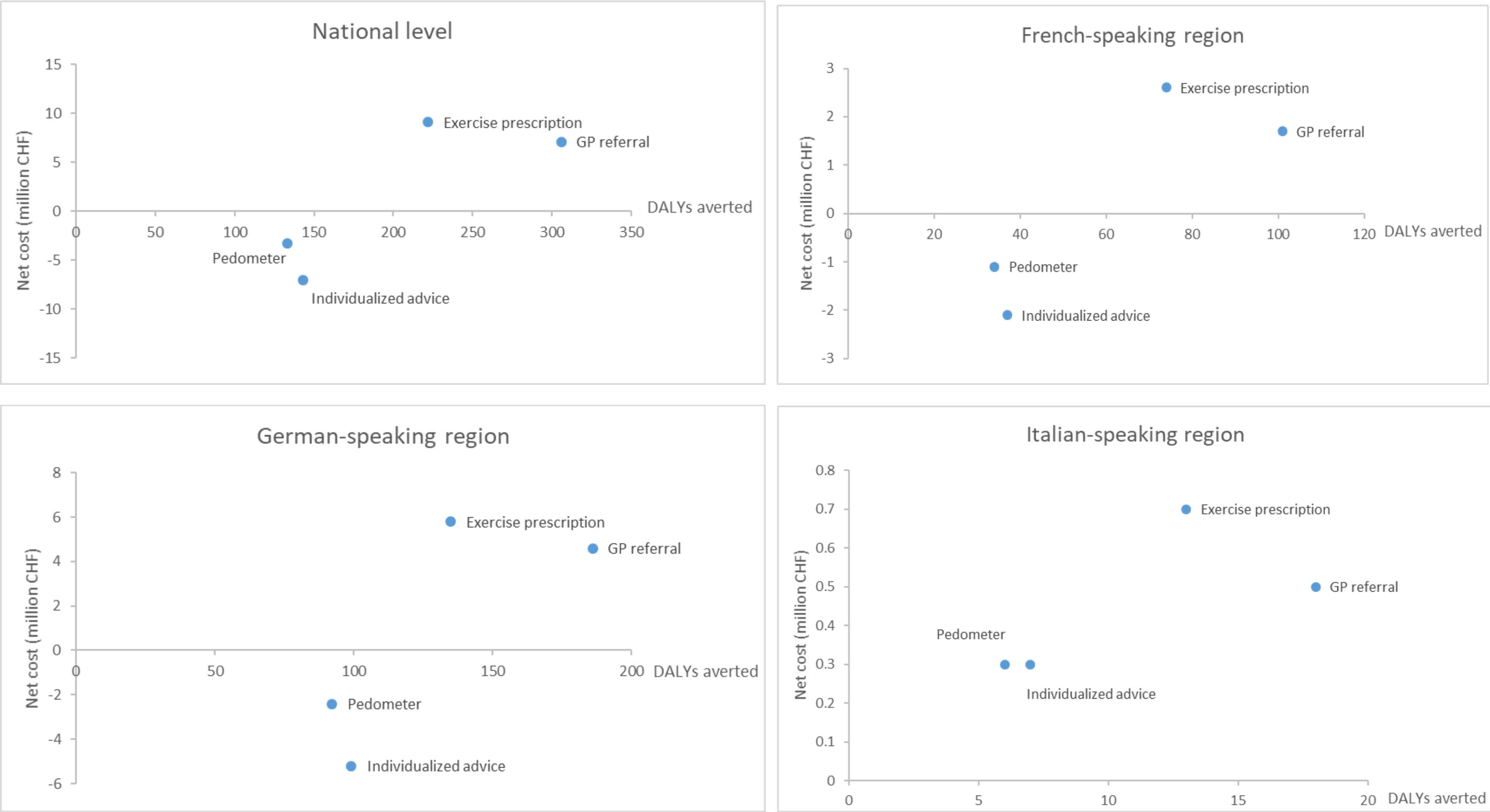
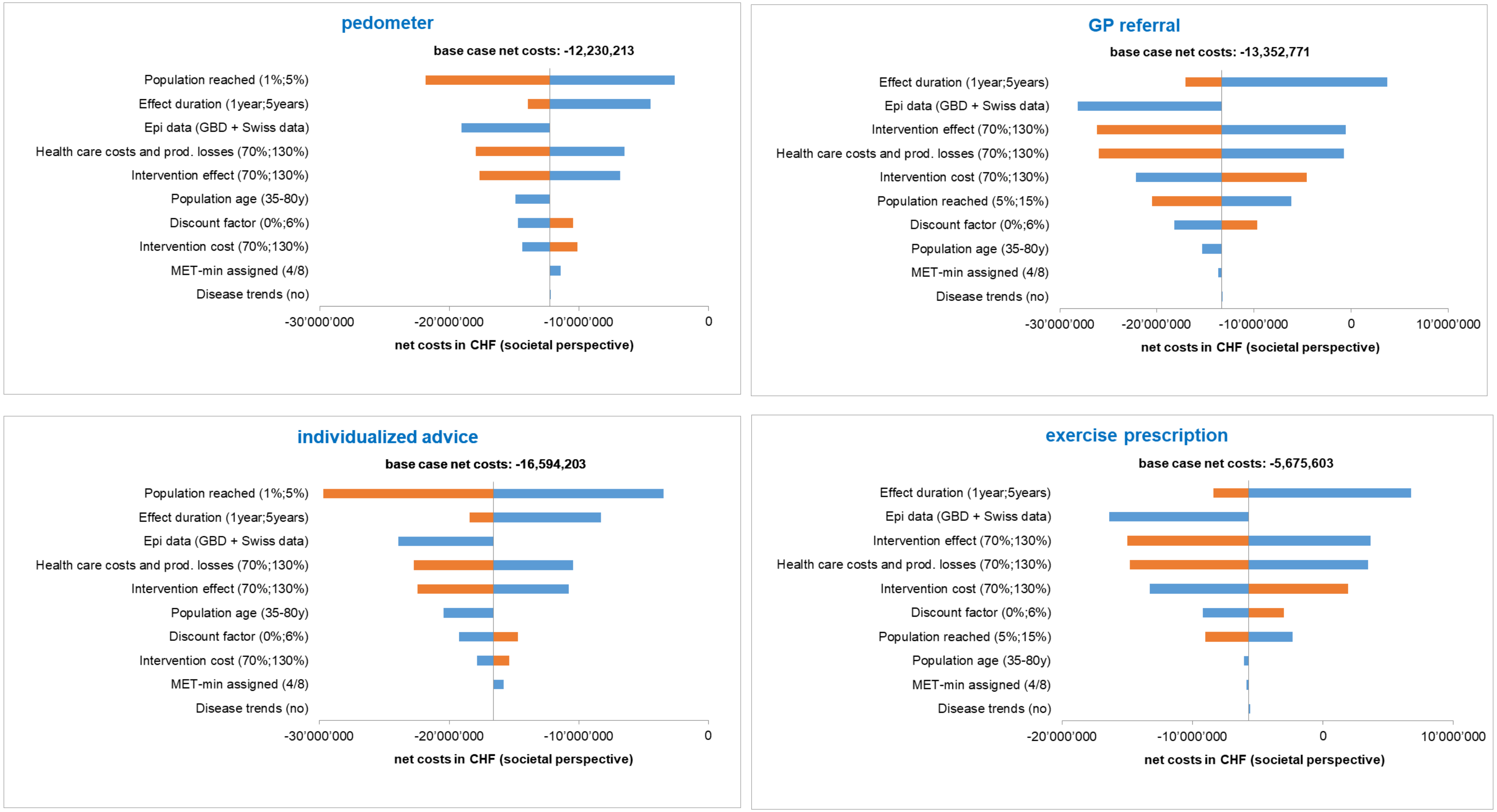
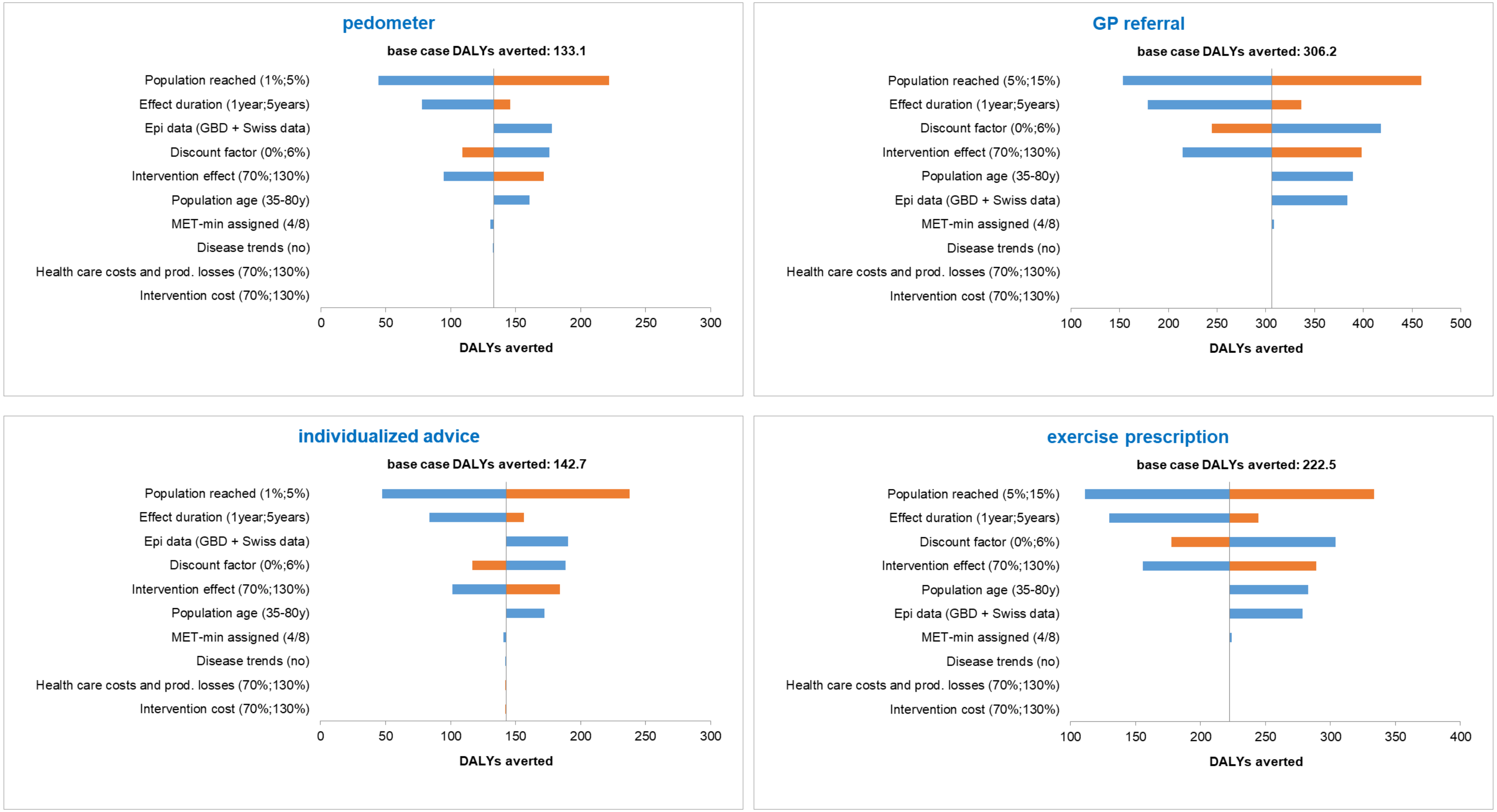


Figure 4 Net costs tornado diagrams for the scenario analysis for all four interventions, national level, societal perspective



Blue bars indicate the impact of parameter values lower than the corresponding base case values; red bars indicate the impact of higher parameter values.

Figure 5 DALYs tornado diagrams for the scenario analysis for all four interventions, national level, societal perspective



Blue bars indicate the impact of parameter values lower than the corresponding base case values; red bars indicate the impact of higher parameter values.

Table 10 Detailed results scenario analysis

	DALYs averted	Net cost, societal perspective (in CHF)	Net cost, health care payer perspective (in CHF)
Pedometer			
Base case	133.1	-12,230,213	-3,297,857
Population age (35-80y)	160.6	-14,910,170	-4,237,074
Discount factor (0%)	175.8	-14,691,616	-5,088,978
Discount factor (6%)	108.8	-10,457,127	-2,093,706
Effect duration (1year)	78.0	-4,475,514	963,366
Effect duration (5 years)	146.0	-13,927,178	-4,275,038
MET-min assigned (4/8)	130.7	-11,412,096	-3,001,141
Population reached (1%)	44.4	-2,610,071	367,381
Population reached (5%)	221.8	-21,850,354	-6,963,095
Health care costs and prod. losses (70%)	133.1	-6,494,170	-175,721
Health care costs and prod. losses (130%)	133.1	-17,966,256	-6,419,993
Epi data (GBD + Swiss data)	177.8	-19,079,718	-6,560,689
Disease trends (no)	132.9	-12,178,234	-3,266,402
Intervention cost (70%)	133.1	-14,362,992	-5,430,636
Intervention cost (130%)	133.1	-10,097,434	-1,165,078
Intervention effect (70%)	94.6	-6,801,602	-340,237
Intervention effect (130%)	171.7	-17,668,496	-6,261,427
Diseases included (only 5 "core")	58.0	2,474,153	3,343,685
GP referral			
Base case	306.2	-13,352,771	7,056,219
Population age (35-80y)	389.0	-15,310,004	9,202,980
Discount factor (0%)	418.0	-18,219,776	3,698,812
Discount factor (6%)	244.4	-9,678,901	9,443,635
Effect duration (1year)	178.9	3,755,776	16,194,193
Effect duration (5 years)	336.5	-17,084,255	4,957,494
MET-min assigned (4/8)	308.5	-13,653,912	6,900,667
Population reached (1%)	153.1	-6,171,386	4,033,110
Population reached (5%)	459.3	-20,534,157	10,079,329
Health care costs and prod. losses (70%)	306.2	-746,162	13,753,302
Health care costs and prod. losses (130%)	306.2	-25,959,381	359,136
Epi data (GBD + Swiss data)	383.6	-28,130,916	81,952
Disease trends (no)	305.6	-13,222,612	7,133,523
Intervention cost (70%)	306.2	-22,166,720	-1,757,729
Intervention cost (130%)	306.2	-4,538,823	15,870,167
Intervention effect (70%)	214.5	-527,716	13,751,957
Intervention effect (130%)	398.0	-26,192,479	353,876
Diseases included (only 5 "core")	151.1	19,488,443	21,435,834
Individualized advice			
Base case	142.7	-16,594,203	-7,043,899
Population age (35-80y)	172.2	-20,439,956	-9,028,765
Discount factor (0%)	188.6	-19,234,034	-8,966,522
Discount factor (6%)	116.6	-14,693,526	-5,751,889
Effect duration (1year)	83.6	-8,294,160	-2,479,256
Effect duration (5 years)	156.5	-18,410,797	-8,090,837
MET-min assigned (4/8)	140.5	-15,808,643	-6,766,414
Population reached (1%)	47.6	-3,464,734	-281,300
Population reached (5%)	237.8	-29,723,672	-13,806,498
Health care costs and prod. losses (70%)	142.7	-10,455,832	-3,699,876
Health care costs and prod. losses (130%)	142.7	-22,732,574	-10,387,921
Epi data (GBD + Swiss data)	190.5	-23,922,087	-10,535,713
Disease trends (no)	142.5	-16,538,601	-7,010,205
Intervention cost (70%)	142.7	-17,825,056	-8,274,751
Intervention cost (130%)	142.7	-15,363,350	-5,813,046
Intervention effect (70%)	101.3	-10,757,893	-3,864,178
Intervention effect (130%)	184.3	-22,443,556	-10,231,712
Diseases included (only 5 "core")	62.3	-880,069	54,725
Exercise prescription			
Base case	222.5	-5,675,603	9,138,849
Population age (35-80y)	282.6	-6,071,797	11,721,564
Discount factor (0%)	303.7	-9,212,450	6,698,141
Discount factor (6%)	177.5	-3,006,461	10,873,946
Effect duration (1year)	130.0	6,744,182	15,774,192
Effect duration (5 years)	244.4	-8,385,153	7,614,597
MET-min assigned (4/8)	224.0	-5,888,691	9,030,113
Population reached (1%)	111.2	-2,332,802	5,074,424

	DALYs averted	Net cost, societal perspective (in CHF)	Net cost, health care payer perspective (in CHF)
Population reached (5%)	333.7	-9,018,405	13,203,273
Health care costs and prod. losses (70%)	222.5	3,477,330	14,002,496
Health care costs and prod. losses (130%)	222.5	-14,828,537	4,275,202
Epi data (GBD + Swiss data)	278.6	-16,390,838	4,081,423
Disease trends (no)	222.0	-5,581,151	9,194,969
Intervention cost (70%)	222.5	-13,280,905	1,533,547
Intervention cost (130%)	222.5	1,929,698	16,744,150
Intervention effect (70%)	155.7	3,639,511	14,005,125
Intervention effect (130%)	289.1	-14,988,509	4,276,705
Diseases included (only 5 "core")	109.9	18,157,126	19,573,849

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6. Discussion

Before this PhD project started, evidence showed that physical inactivity causes a substantial health and economic burden globally [47, 49]. For Switzerland, there was research available investigating the burden of physical inactivity [22]. However, this research estimated the burden for the entire country without differentiating between sub regions although the prevalence of physical inactivity varies significantly between Swiss language regions [8]. Therefore, the aim of the first publication forming part of this PhD thesis was to estimate the burden of physical inactivity in Switzerland separately for the German-, French- and Italian-speaking regions [1]. As this first PhD publication showed a substantial burden of physical inactivity in the Swiss language regions, we investigated interventions aiming to increase physical inactivity in a systematic review that underlies the second publication forming part of this PhD thesis [2]. We then moved on and used findings from the first two PhD publications to develop a health economic model that investigates the cost-effectiveness of physical activity interventions in Switzerland and its three language regions [3]. The cost-effectiveness model has recently been submitted for publication. This chapter summarizes the main findings of the two publications forming part of this PhD thesis and the paper that has been submitted for publication, discusses them and provides prospects for future research.

6.1 Summary of findings

6.1.1 Aim 1: Burden of physical inactivity in Swiss language regions [1]

We estimated the burden of physical inactivity in Swiss adults from a societal perspective with a prevalence-based top-down approach using population attributable fractions (PAFs) and the latest data available for Switzerland. The following nine diseases related to physical inactivity were included in the analysis: coronary heart disease, hypertension, ischemic stroke, type 2 diabetes mellitus, breast cancer, colorectal cancer, osteoporosis, low back pain, and depression. Total DALYs, health care costs, and productivity losses of these diseases were then retrieved from the global burden of disease (GBD) study and a recent study of the costs of NCDs in Switzerland. In order to analyze the fraction of this total burden that is attributable to physical inactivity, we combined estimates of the prevalence of physical inactivity stemming from the Swiss Health Survey in 2012 with literature-based estimates of disease incidence in the presence vs. absence of physical inactivity and resulting relative risks (RRs). The combination of these two types of parameters allowed us to estimate PAFs, which describe the proportion of disease occurrence that can be attributed to a certain risk factor.

The burden of physical inactivity in Switzerland in 2013 was estimated at CHF 1.610 billion (95%CI CHF 1.413-1.827 billion) plus 40,433 (95%CI 34,935-46,487) DALYs. The DALYs lost due to physical inactivity represented 2.0% (95%CI 1.7%-2.2%) of total DALYs lost in Switzerland. Osteoporosis contributed 34.4% of the DALYs, low back pain 17.7%, cardiovascular diseases 21.9%, and depression 8.3%. Health care costs caused by physical inactivity were estimated at CHF 0.802 billion (95%CI CHF 0.684-0.934 billion) or at 1.2% (95%CI 1.0%-1.3%) of total health care expenditures. This was equivalent to CHF 116 (95%CI CHF 99-135) per capita. Of these health care costs, 35.4% were attributed to cardiovascular diseases (coronary heart disease, ischemic stroke, and hypertension), 20.9% to low back pain, 17.5% to depression, and the remaining 26.2% to osteoporosis, type 2 diabetes mellitus, colorectal cancer, and breast cancer. Productivity losses were valued at CHF 0.808 billion (95%CI CHF 0.653-0.983 billion) or CHF 117 (95%CI CHF 94-142) per capita and were mainly caused by low back pain (38.2%), depression (20.0%), and cardiovascular diseases (17.9%).

Furthermore, we found that the French- and Italian-speaking regions, which are home to 30% of the Swiss population, contribute more than 45% to the burden of physical inactivity. Reasons include a higher prevalence of physical inactivity, higher per capita health care spending, and higher disease prevalence than the German-speaking region. In addition, the per capita burden was twice as high in the French- and Italian-speaking regions compared to the German-speaking region. In the German-speaking region, we estimated per capita health care costs due to physical inactivity at CHF 87, productivity losses at CHF 96, and DALYs per 1,000 persons at 4.5. Health care costs in the French-speaking region were estimated at CHF 179 per capita, productivity losses at CHF 164, and DALYs at 8.9 per 1,000 persons. In the Italian-speaking region, per capita health care costs were valued at CHF 172, productivity losses at CHF 153, and DALYs per 1,000 persons at 8.6.

In conclusion, this study showed that physical inactivity causes a substantial health and economic burden in Swiss adults and that the French- and Italian-speaking regions are over-proportionally affected. Investments in interventions aiming to increase physical activity should therefore be considered. Such interventions should be cost-effective and this study indicates that regional differences likely influence the cost-effectiveness of physical activity interventions. Furthermore, this study showed that low back pain and depression substantially add to the burden of physical inactivity. Consequently, future studies should consider these two diseases when estimating the burden of physical inactivity.

6.1.2 Aim 2: Systematic review of cost-effectiveness of physical activity interventions [2]

In this systematic review, we aimed to summarize evidence from RCT-based economic evaluations of primary prevention physical activity interventions in adult populations outside the workplace setting. We included cost-effectiveness analyses in which all data (except unit costs) came from one RCT. As the studies reported different physical activity outcomes, effect measures were standardized in metabolic equivalent of task (MET)-hours gained per person per day. We further calculated the mean differences in costs and outcomes between intervention and control as a basis for estimating the ICER in US$ per MET-hour gained. A benchmark between US$0.44 and US$0.63 per MET-hour gained, which was based on the health care costs and productivity losses of physical inactivity in Switzerland, was used to assess the cost-effectiveness of interventions.

Twelve studies published between 2000 and 2018 were included in the final analysis. In these twelve studies, 22 interventions were investigated. Interventions were based on advice, goal setting and follow-up support, exercise classes, financial incentives or teaching on behavioral change. The effects and the costs of the interventions varied widely and so did the ICER. Four interventions showed an ICER below the applied benchmark. These four interventions were based on individualized advice delivered in four different ways: print (postal mail) or web (website and email) and in a basic form (standard advice) or with additional environmental components (e.g., walking and cycling routes and physical activity possibilities and initiatives in participants' own neighborhood and home exercises). One other intervention that was based on behavior change counseling by telephone had an ICER of US$0.64 per MET-hour gained. One pedometer-based individualized step-related goal setting intervention had an ICER of US$0.67 per MET-hour gained [39]. Another intervention was based on face-to-face advice, goal setting, follow-up face-to-face meeting and follow-up telephone counseling [36]. This intervention had an ICER of US$0.85 per MET-hour gained. All other interventions had an ICER above US$1.00 per MET-hour gained.

In conclusion, we found evidence from RCTs indicating cost-effectiveness of some physical activity interventions for primary prevention in adults. However, cost-effectiveness results varied widely among interventions and the majority of interventions would not be cost-effective according to the benchmark applied. Four interventions that delivered individualized advice via print or web showed best value (physical activity gains) for money (intervention costs). Our study also showed that trial-based evidence on the cost-effectiveness of physical activity interventions is relatively scarce. Therefore, we recommend that future studies investigating the efficacy or effectiveness of interventions aimed at increasing physical activity consider costs as an additional outcome and assess cost-effectiveness.

6.1.3 Aim 3: Cost-effectiveness model of physical activity interventions [3]

The cost-effectiveness model of physical activity interventions was built as a proportional multistate life table model for the Swiss adult population over their lifetime. We named it the

Swiss Physical Activity Cost-Effectiveness (SPACE) model. In the model, a comprehensive set of diseases was included, namely breast cancer, colorectal cancer, type 2 diabetes mellitus, coronary heart disease, ischemic stroke, osteoporosis, low back pain and depression. The effect of interventions on diseases was modelled with data from recent meta-analyses. Interventions analyzed were individualized physical activity advice, pedometer with individualized goal setting, general practitioner (GP) referral for telephone-based counseling and exercise prescription. Intervention effects were taken from RCTs and intervention costs were based on a bottom-up approach with Swiss prices. Cost-effectiveness in terms of cost per DALY averted compared to "doing nothing" as well as cost-effectiveness between interventions were analyzed on the national level and separately for the French-, German- and Italian-speaking language regions. The frequently assumed tentative willingness-to-pay threshold of CHF 100,000 per DALY was used to assess the cost-effectiveness of interventions. Interventions that led to better health and were at the same time cost-saving were categorized as "dominant".

From a societal perspective and irrespective of language region, all four interventions were cost-saving and more effective compared to "doing nothing". At the national level and in the German-speaking region, individualized advice was the preferable intervention followed by GP referral. These two interventions dominated pedometer and exercise prescription. In the French- and Italian speaking regions, GP referral was the preferable intervention that dominated the three others. From a health care payer perspective, however, individualized advice was the preferable intervention followed by GP referral. The uncertainty underlying key model input parameters led to substantial variation in the modelled results, according to the probabilistic sensitivity analysis.

In conclusion, we hope to inform efficient resource allocation and evidence-based decision-making in primary prevention in Switzerland. We recommend that individualized advice and GP referral be further evaluated as interventions and that decision-making considers the specifics of the Swiss language regions. Furthermore, we judge the SPACE model to be not only relevant for Switzerland but also for other multicultural countries. Based on similar data availability, the SPACE model has the potential to be applied beyond Switzerland, primarily to high-income countries with a comparable background, as a tool to guide societal efforts in primary prevention of physical-inactivity-related diseases.

6.2 General discussion

6.2.1 Diseases related to physical inactivity

The following five diseases can be considered the “core set of diseases related to physical inactivity” as they are frequently used in health economic studies investigating physical activity [96, 97, 100]: breast cancer, colorectal cancer, type 2 diabetes mellitus, coronary heart disease and ischemic stroke. Osteoporosis, low back pain and depression have been taken into account less frequently [94, 122, 123]. However, it has recently been shown that physical activity reduces incidence of these three diseases [31, 32, 122]. Consequently, we included them in the first PhD paper (burden of physical inactivity) as well as in the third (cost-effectiveness model of interventions). In the first paper, we showed that all three diseases substantially add to the burden of physical inactivity. In the third paper, these three diseases had a substantial influence on the cost-effectiveness of interventions. Consequently, it can be suggested that future studies investigating the burden of physical inactivity include osteoporosis, low back pain and depression. In addition, the inclusion of the three diseases can be recommended for cost-effectiveness models investigating physical activity interventions.

While we included hypertension in the first PhD paper, we no longer considered it in the third paper. Hypertension is modelled as a disease in its own right in some studies [97, 124] or as part of cardiovascular diseases [125] or as a risk factor for cardiovascular diseases [126]. As the impact of hypertension on the burden of physical inactivity was rather small in the first PhD paper and we did not specifically model other risk factors for the diseases included, we did not consider hypertension in the cost-effectiveness model.

Obesity was also not included as a specific primary disease in either the first or the third PhD paper, as the main burden related to obesity was considered to be caused by cardiovascular diseases and type 2 diabetes mellitus. Therefore, obesity was considered a risk factor rather than a disease on its own. This is in line with many other health economic studies investigating physical inactivity [90-97, 99, 100, 102].

Although we tried to be comprehensive with diseases related to physical inactivity, there may be other diseases for which physical inactivity will be established as a risk factor such as dementia and Alzheimer’s disease [127-130]. Due to conflicting evidence, however, these diseases were not included in our work [131]. A recently-published, very extensive scientific report also found strong evidence that greater amounts of physical activity are associated with reduced risk of developing bladder cancer, endometrial cancer, esophageal cancer, gastric cancer, renal cancer, and anxiety disorders [24]. These diseases may be included in future studies investigating the health economic aspects of physical inactivity.

6.2.2 Cost-effectiveness evaluation of physical activity interventions

The cost-effectiveness evaluation of physical inactivity interventions is subject to several challenges. For example, the ICER benchmark applied in the second PhD paper (between US$0.44 and US$0.63 per MET-hour gained, which is equal to CHF 0.53 and CHF 0.76 per MET-hour gained for 2018) was based on 2.5 hours of moderate intensity physical activity (at 3 METs) per week and the per capita costs of physical inactivity in Switzerland. As approximately one quarter of the Swiss population is physically inactive, the cost per capita for the physically inactive ones is four times higher than for the total population. Therefore, the benchmark for an intervention targeting specifically the inactive people would be approximately four times higher, i.e. between CHF 2 and CHF 3 per MET-hour gained. Consequently, there is no particular benchmark to use for the cost-effectiveness evaluation of physical activity interventions. Furthermore, the outcome will depend on the different types of costs considered for the intervention under evaluation (intervention costs, health care costs offset, productivity losses offset). Further aspects that influence the cost-effectiveness include: the target population (e.g. general population or specifically the inactive ones), the population reached (e.g. 1%, 3%, 5%), and the time horizon considered. As some of these aspects cannot be evaluated in trials, health economic modelling will always play an important role for the evaluation of the cost-effectiveness of physical activity interventions. Therefore, the combination of within-trial cost-effectiveness analysis and beyond-trial modelling, as recently published by Harris et al. [132], may become a widely used method in the future. Modelling also allows for a relatively simple estimation of DALYs averted (or QALY gained). Such more generic outcomes, in comparison to a physical activity specific outcome like MET-hours gained, make it possible to compare interventions between different risk factors for NCDs (e.g. smoking, diet, etc) or compare interventions with other treatments for primary or secondary prevention.

6.2.3 Cost-effectiveness studies run the risk of favoring interventions that only add small benefit

Wu et al. [88] showed previously that some interventions that increased physical activity levels only by small amounts, such as stair climbing prompts, may be very cost-effective due to the very low intervention costs. This finding was supported by the results from the second PhD publication where the intervention investigated by Golsteijn et al. [133] that provided individualized advice delivered via web and included additional environmental components was the most cost-effective. The intervention itself had a negative effect of -0.06 MET-hours gained per person per day when comparing physical activity at the one-year follow-up with baseline. However, compared to the “doing nothing” control group, the incremental effect was 0.26 MET-hours gained per person per day, which is equivalent to approximately 5 min of moderate physical activity per person per day. Although this is a positive effect, it can be considered a relatively low incremental physical activity gain that is not sufficient to lead to substantial health benefits [35]. The annual intervention costs were US$25.14 per person. This led to an ICER of US$0.27 per MET-hour gained, which was below the benchmark of between US$0.44 and US$0.63 per MET-hour gained applied in this study. Therefore, the intervention was considered cost-effective although the physical activity gain can be considered insufficient to lead to substantial health benefits. These findings were also confirmed in the third PhD paper, where we also included the intervention by Golsteijn et al. [133]. Consequently, relying on cost-effectiveness alone might favor interventions that are unable to add substantial health benefits. Therefore, we recommend that the specifics of each intervention should be considered and additional criteria such as minimal clinically-relevant effectiveness thresholds might be used in future physical activity policy decision-making.

6.2.4 Regional differences in physical inactivity and their consequences for policy making

In Switzerland, 24.3% of the population over the age of 15 is physically inactive [8]. However, the prevalence of physical inactivity shows significant regional differences: 21.0% of the adult population in the German-speaking region is physically inactive whereas 32.6% are physically inactive in the French-speaking region and 31.5% in the Italian-speaking region [8]. Due to this difference in the prevalence of physical inactivity and other differences such as per capita health care spending and disease prevalence, we showed in the first PhD paper that the per capita burden of physical inactivity is twice as high in the French- and Italian-speaking regions as in the German-speaking region [1]. Furthermore, the cost-effectiveness of physical activity interventions differed between language regions, as investigated in the third PhD paper [3]. In this paper, we showed that in regions with higher prevalence of physical inactivity, more costly interventions can still be cost-effective. These findings suggest that physical inactivity is tackled language-region specifically in Switzerland. This may also be the case for other risk factors for NCDs as they also show substantial regional variation [8].

6.2.5 Summary of strength and limitations

This PhD thesis has a number of strengths, but also some limitations that should be considered. One major strength is the societal perspective chosen for the cost assessment, i.e. the incorporation of productivity losses. Previous studies mainly focused on health care costs, while Briggs et al. [99] also included social care costs for ages above 75 years. A further strength of this thesis was the comprehensive set of diseases included. Besides the “core set of diseases related to physical inactivity” (breast cancer, colorectal cancer, type 2 diabetes mellitus, coronary heart disease and ischemic stroke), we also considered osteoporosis, low back pain and depression. These three additional diseases substantially added to the burden of physical inactivity and influenced the cost-effectiveness of interventions. An additional strength of the thesis is the language-region-specific analyses made. While the study by Roux et al. [112] analyzed cost-effectiveness separately for different age groups, many other models investigating physical activity interventions focused on entire countries without analyzing subgroups. In Switzerland, where the prevalence of physical inactivity substantially differs between language regions, the regional analysis was shown to be crucial to allocate resources efficiently. Furthermore, we considered fixed and variable intervention costs separately when assessing the cost-effectiveness of physical activity interventions to account for the fact that the use of certain resources is independent from the number of people receiving the intervention [115]. Our findings showed that the separation of fixed and variable intervention costs may substantially influence cost-effectiveness when the scale of the intervention substantially differs.

The main limitation of the thesis is the uncertainty arising from the use of secondary data sources. For example, the RR we used for our calculations are not based on a standardized definition and measurement of physical activity and a standardized assessment of confounding. We also assumed equal RR across gender and age-groups. In addition, intervention effect measures were standardized to MET-hours gained per person per day. Although this method was used in previous studies, it may have some limitations when applied to broad outcomes such as step gains or proportions of populations meeting physical activity guidelines [88, 134]. Moreover, many studies did not report sufficient statistical detail and, therefore, we were not able to properly address the uncertainty of effect measures.

A further limitation is that response in the Swiss Health Survey was non-random. For instance, responders were of higher average socioeconomic status and reported better subjective health than non-responders [135]. This may have affected our estimates of prevalence of physical activity categories as well as MET-minutes assigned to each physical activity category. Furthermore, we may have underestimated the prevalence of physical inactivity as the Swiss Health Survey investigates self-reported activity levels. According to a recent study from Switzerland, time spent physically active was 4.2 times higher when self-reported compared to measurements with accelerometers [136]. Several other studies also showed substantial differences between self-reported physical activity and objective measurements [137]. Our estimates are consistent in at least the sense that both prevalence and RR were based on self-reported physical activity levels.

As a further limitation, the productivity losses estimated were based on limited data available from the literature. For some domains such as presenteeism, early retirement and informal care, values were not reported in the literature. Therefore, we likely underestimated the true productivity losses due to morbidity and informal care.

Regarding the language-region-specific analyses, the following aspects were considered in the model: population counts, prevalence of physical activity categories, disease costs, productivity losses and fixed intervention costs. Other aspects were assumed to be the same, mainly due to lack of region-specific data: intervention effect, variable intervention costs, disease incidence, disease-specific mortality and disability weights.

Furthermore, we focused on interventions that can be implemented on a population-level and therefore excluded studies investigating the workplace setting. However, some interventions focusing on the workplace setting have been previously shown to be cost-effective [138]. By limiting the study design to RCTs, we also excluded interventions targeting the built environment [88, 134, 139, 140]. As we excluded studies that did not report specific physical activity outcomes, we did not include studies only reporting quality-adjusted life-years as part of pure cost-utility analyses [125, 141, 142]. These studies showed varying results in terms of cost per quality-adjusted life-years gained by physical activity interventions.

In regard to the burden of physical inactivity, it is also noteworthy that we only investigated the impact of physical activity on primary prevention. There are several diseases in which physical activity is an effective modifier of the course of clinical disease, and one could argue that there is an additional burden related to inactive patients [143]. In addition, we did not consider costs of myocardial infarctions occurring during physical activity and costs of sport injuries. However, there is evidence that sport injuries especially happen to people that are not regularly active [144].

6.3 Prospects for future research

First of all, Switzerland would benefit from a Swiss burden of disease study. Such a study is suggested as we detected discrepancies between GBD data and data coming directly from Switzerland. Alternatively, Switzerland could further develop the collaboration with the GBD study to increase data consistency. However, the understanding of the true burden of disease in Switzerland is considered fundamental to adequately assess the burden of risk factors for diseases and the cost-effectiveness of interventions tackling those risk factors. Furthermore, DALYs have been confirmed as a very valuable complementary measure to number of deaths (mortality) and money (economic burden). In a society where quality of life is a very important good, it is time to make this measure more common. Another measure that goes even beyond morbidity, mortality and economic burden is well-being [145]. Well-being may be investigated as an additional, separate outcome in future studies.

In addition, it is recommended to refine SPACE in such a way that it allows for a cost-effectiveness evaluation of all behavioral risk factors for NCDs (i.e. smoking, alcohol abuse, dietary risks and physical inactivity) in Switzerland. Multistate life table models like SPACE have already been used to assess interventions against smoking and unhealthy diet [146-155]. This would allow for a comprehensive understanding of NCDs and the cost-effectiveness of interventions tackling their risk factors. Such future models may not only address single risk factors but also multiple risk factor behavior [156-158].

The SPACE model currently contains data for the population from 15 to 100 years old. Consequently, children are excluded and the model does not allow for a holistic life course approach. Although different physical activity trajectories have been observed, the majority of the population seems to follow a persistent one [159]. In addition, better cardiovascular health indicators have been found in children who engage in higher levels of physical activity during early childhood [160]. This may influence cardiovascular health in adulthood. A holistic life course perspective may be taken in future models, which then would allow us to also analyze the cost-effectiveness of interventions targeting children.

Although there is currently no agreement over the most appropriate approach, several studies suggest the consideration of equity in the economic evaluations of public health interventions [161]. Therefore, future versions of SPACE may also implement equity considerations.

Last but not least, the SPACE model could serve as a template for estimating the cost-effectiveness of physical activity interventions from a societal perspective in other multi-cultural countries.

6.4 Conclusions

This thesis had three aims:

1. Estimating the health and economic burden of physical inactivity in Switzerland and for the French-, German- and Italian-speaking language regions separately
2. Systematically reviewing trial-based economic evaluations of interventions to reduce physical inactivity
3. Developing a health economic model that investigates the cost-effectiveness of physical activity interventions in Switzerland and its three language regions

The thesis showed that the burden of physical inactivity in Switzerland is substantial and that the French- and Italian-speaking regions are over-proportionally affected. These two regions distinguish themselves from the German-speaking region as they have a higher prevalence of physical inactivity, higher per capita health care spending, and higher disease prevalence. Due to the substantial burden of physical inactivity, interventions aiming to increase physical activity should be considered. In the systematic review we conducted, we found evidence from RCTs indicating the cost-effectiveness of some physical activity interventions for primary prevention in adults. These interventions were then further evaluated in a cost-effectiveness model built for the Swiss setting. This model showed that Swiss policy makers have cost-effective options of physical activity promotion. We recommend that individualized advice and GP referral be further evaluated as interventions and that decision-making considers the specifics of the Swiss language regions. Furthermore, we judge the cost-effectiveness model to be not only relevant for Switzerland but also for other multicultural countries. Based on similar data availability, our model has the potential to be applied beyond Switzerland, primarily to high-income countries with a comparable background, as a tool to guide societal efforts in primary prevention of physical-inactivity-related diseases.

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Appendix: Curriculum vitae

Personal information

Date of birth	8 October 1981
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Education

2016 - to date	PhD student, University of Basel Topic: "Scaling up cost-effective physical activity interventions in a culturally diverse setting" Supervisors: Prof. Nicole Probst-Hensch, Prof. Arno Schmidt-Trucksäss, Prof. Matthias Schwenkglenks, Prof. Simon Wieser PhD programs: PhD Program Health Sciences (PPHS) University of Basel, SSPH+ PhD Program in Public Health, PhD Program in Public Health Sciences for Universities of Applied Sciences (SSPH+ UAS)
2013	Certificate of Advanced Studies in Health Economics, Zurich University of Applied Sciences (ZHAW), Winterthur
2011	Master of Advanced Studies in Business Administration, Zurich University of Applied Sciences (ZHAW), Winterthur
2006	Master in Human Movement Science, Swiss Federal Institute of Technology (ETH), Zurich

Employment history

2018 - to date	Head of the HTA and Health Economic Evaluation Group, Zurich University of Applied Sciences (ZHAW), Winterthur Institute of Health Economics, Winterthur
2017 - to date	Lecturer and Project Manager, Zurich University of Applied Sciences (ZHAW), Winterthur Institute of Health Economics, Winterthur

2014 - 2018	Deputy head of the Health Economics Research Group, Zurich University of Applied Sciences (ZHAW), Winterthur Institute of Health Economics, Winterthur
2012 - 2016	Research Associate, Zurich University of Applied Sciences (ZHAW), Winterthur Institute of Health Economics, Winterthur
2011 - 2012	Market Access and Health Economics Manager, Zimmer GmbH, Winterthur
2008 - 2011	Clinical Research Associate, Zimmer GmbH, Winterthur
2006 - 2007	Human Movement Scientist, Sport Clinic, Sport Biomechanics, Zurich

Institutional responsibilities

Zurich University of Applied Sciences (ZHAW): Head of HTA and Health Economic Evaluation at Winterthur Institute of Health Economics

Approved research projects (selected)

Projects assessing costs and epidemiology of diseases in Switzerland:

- Physical inactivity / tobacco / cystic fibrosis / schizophrenia
- Economic impact of levothyroxine dose adjustments in Switzerland
- Inpatient costs and reimbursement of patients with acute myelotic leukemia
- Inpatient hospital costs of febrile neutropenia as a consequence of chemotherapy for breast cancer and Non-Hodgkin lymphoma

Projects assessing cost-effectiveness and cost-benefit of interventions / health technology assessments (HTA) in Switzerland:

- Economic evaluation of oral versus parenteral iron therapy for iron deficiency without anemia
- HTA on Dynamic Intraligamentary Stabilization (DIS) for the rupture of the anterior cruciate ligament: Implant system Ligamys®
- HTA on four spinal implant procedures for Switzerland
- HTA on interspinous process devices for Switzerland

Projects developing payment systems for Switzerland:

- Prospective payment system for inpatient rehabilitation

Supervision of junior researchers at graduate and postgraduate level

Supervision of MAS theses in health economics: Ueli Peter, Flurina Meier

Teaching activities

- Health Economic Evaluations
- Health Technology Assessment
- Health Economic Modelling

Prizes, awards, fellowships

2017	SSPH+ PhD Abstract Award «Disability and early deaths attributable to physical inactivity in Switzerland in 2015»

Journal publications

Mattli R, Farcher R, Syleouni ME, Wieser S, Probst-Hensch N, Schmidt-Trucksäss A, Schwenkglenks M. Physical Activity Interventions for Primary Prevention in Adults: A Systematic Review of Randomized Controlled Trial-Based Economic Evaluations [published online ahead of print, 2019 Nov 21]. Sports Med. 2019;10.1007/s40279-019-01233-3. doi:10.1007/s40279-019-01233-3

Mattli R, Wieser S, Probst-Hensch N, Schmidt-Trucksäss A, Schwenkglenks M. Physical inactivity caused economic burden depends on regional cultural differences. Scand J Med Sci Sports. 2019;29(1):95–104. doi:10.1111/sms.13311

Pletscher M, Mattli R, von Wyl A, Reich O, Wieser S. The Societal Costs of Schizophrenia in Switzerland. J Ment Health Policy Econ. 2015;18(2):93–103.

Oral conference presentations

Mattli R, Wieser S, Probst-Hensch N, Schmidt-Trucksäss A, Schwenkglenks M. The burden of physical inactivity in Switzerland in 2017. 12. SGS-Jahrestagung, Sportwissenschaftliche Gesellschaft der Schweiz. 2020. Basel, Switzerland

Mattli R, Farcher R, Dettling M, Syleouni M, Wieser S. Die Krankheitslast des Tabakkonsums in der Schweiz: Schätzung für 2015 und Prognose bis 2050. 17. Deutsche Konferenz für Tabakkontrolle. 2019. Heidelberg, Germany

Mattli R, Wieser S, Probst-Hensch N, Schmidt-Trucksäss A, Schwenkglenks M. Disability and early deaths attributable to physical inactivity in Switzerland in 2015. Swiss Public Health Conference, The Swiss Society for Public Health. 2017. Basel, Switzerland

Mattli R, Wieser S, Schwenkglenks M. The burden of physical inactivity in Switzerland and the influence of cultural differences. 12th World Congress on Health Economics, International Health Economics Association. 2017. Boston, USA

Mattli R, Schmidt M, Wirz M, Dettling M, Wieser S. Design of a prospective payment system for inpatient rehabilitation in Switzerland. 12th World Congress on Health Economics, International Health Economics Association. 2017. Boston, USA

Mattli R, Hess S, Maurer M, Eichler K, Pletscher M, Wieser S. The social cost of physical inactivity in Switzerland in 2011. 11th World Congress on Health Economics, International Health Economics Association. 2015. Milan, Italy

Mattli R, Hess S, Maurer M, Eichler K, Pletscher M, Wieser S. The social cost of physical inactivity in Switzerland in 2011. Active Living Research Annual Conference. 2015. San Diego, USA

Mattli, R.; Hess, S.; Maurer, M.; Eichler, K.; Pletscher, M.; Wieser, S. The social cost of physical inactivity in Switzerland in 2011. 10th Annual Meeting and 5th Conference of HEPA Europe. 2014. Zurich, Switzerland

Mattli R, Pletscher M, von Wyl A, Reich O, Wieser S. The social cost of schizophrenia in Switzerland. Swiss Public Health Conference, The Swiss Society for Public Health. 2014. Olten, Switzerland

Poster presentations

Hess S, Brunner B, Mattli R, Bruegger U, Eichler K. Dynamic intraligamentary stabilisation for the treatment of the anterior cruciate ligament rupture: A health technology assessment for Switzerland. HTAi 12th Annual Meeting. 2015. Oslo, Norway

Mattli R, Pletscher M, Eichler K Wieser S. Inpatient hospital costs of febrile neutropenia as a consequence of chemotherapy for breast cancer and Non-Hodgkin lymphoma in Switzerland. ISPOR 16th Annual European Congress. 2013. Dublin, Ireland

Mattli R, Balliere A, Menzie AM. Comparing the economic impact of prosthesis choice in unicompartmental knee arthroplasty procedures: development of an economic model. ISPOR 15th Annual European Congress. 2012. Berlin, Germany

Graduate education

Course	Institution	ECTS
Epidemiology		
Systematic Reviews and Meta-Analysis: a Practical Approach	SSPH+, University of Bern	1
GIS in public health	SSPH+, University of Basel	1
Biostatistics	University of Basel	2
Advanced methods in (Network) Meta-Analysis – A Practical Course in R (Swiss Epidemiology Winter School)	SSPH+, University of Bern	2
Social and Behavioral Science in Health Research		
Evidence-based Public Health using the GRADE approach	SSPH+, University of Bern	2
Ein Public-Health-Problem erkennen und lösen	SSPH+, University of Zürich	2
Health System Research		
Gesundheitsökonomische Modellierung – Hands-on	SSPH+, University of Basel	3
Ökonomische Evaluation im Gesundheitswesen	SSPH+, University of Zurich	3
Health Economics for Public Health Decision-Making (SSPH+ International Doctoral Courses and Seminars in Health Economics and Policy)	SSPH+, University of Lausanne	3
Other (Soft Skills etc.)		
Writing a Journal Article – and Getting it Published	SSPH+, University of Bern	1
Introduction to the Statistical Software R	SSPH+, University of Basel	1
Raus mit der Sprache! - Stimme und Körpersprache als Erfolgsfaktoren (Transferable Skills)	University of Basel	1
Self-Branding and Self-Promotion (Transferable Skills)	University of Basel	1
Storytelling for Science (Transferable Skills)	University of Basel	-

Active participation at an international conference with presentation, 1 ECTS in total (applicable for SSPH+): Mattli, R.; Wieser, S.; Schwenkglenks, M. (2017). The burden of physical inactivity in Switzerland and the influence of cultural differences. Oral presentation at the 12th World Congress on Health Economics, International Health Economics Association. (7-11 July). Boston, USA	1
Total ECTS	**24**